Adjuvant versus salvage radiotherapy in prostate cancer: multi-institutional retrospective analysis of the Spanish RECAP database

A. Hervás1 · A. Gómez-Caamaño2 · M. Casaña3 · A. Gómez-Iturriaga4 · J. Pastor5 · J. Jove6 · J. L. Mengual3 · C. Gómez-San Segundo7 · J. Muñoz8

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Abstract

Purpose To compare adjuvant radiotherapy (ART) to salvage radiotherapy (SRT) after radical prostatectomy (RP) in a cohort of prostate cancer (PCa) patients. The primary aim was to comparatively assess 2- and 5-year biochemical relapse-free survival (BRFS). A secondary aim was to identify predictors of survival.

Patients and methods Data were acquired from the RECAP database, a population-based prostate cancer registry in Spain. Inclusion criteria included RP (with or without lymphadenectomy) followed by ART or SRT. A total of 702 patients were analyzed. Pre-RT PSA values (>0.5 vs. ≤0.5 ng/ml), pathological stage (T1–2 vs. T3–4), post-surgical Gleason score (≤7 vs. 8–10), margin status (positive vs. negative), hormonal treatment (yes vs. no), and RT dose (≤66 Gy vs. >66 Gy) were evaluated to assess their impact on BRFS.

Results The mean patient age in the ART and SRT groups, respectively, was 64 years (range 42–82) and 64.8 years (range 42–82). Median follow-up after RT in the whole sample was 34 months (range 3–141). A total of 702 patients were included: 223 (31.8%) received ART and 479 (68.2%) SRT. BRFS rates (95% CI) in the ART and SRT groups at months 24 and 60 were, respectively: 98.1% (95.9–100.0%) vs. 91.2% (88.2–94.2%) and 84.5% (76.4–92.6%) vs. 74.0% (67.4–80.7%) (p = 0.004). No significant differences in OS were observed (p = 0.053). The following variables were significant predictors of biochemical recurrence in the SRT group: (1) positive surgical margin status (p = 0.049); (2) no hormonotherapy

1 Department of Radiation Oncology, Hospital Ramón Y Cajal, Madrid, Spain
2 Department of Radiation Oncology, Hospital Clínico Universitario, Santiago de Compostela, Spain
3 Department of Radiation Oncology, Instituto Valenciano de Oncología, Valencia, Spain
4 Department of Radiation Oncology, Hospital Universitario Cruces, Barakaldo, Spain
5 Department of Radiation Oncology, Hospital General de Valencia, Valencia, Spain
6 Department of Radiation Oncology, Hospital Germans Trias i Pujol, Barcelona, Spain
7 Department of Radiation Oncology, Hospital Gregorio Marañón, Madrid, Spain
8 Department of Radiation Oncology, Hospital Infanta Cristina, Badajoz, Spain

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(p = 0.03); (3) total prostate dose ≤66 Gy (p = 0.004); and pre-RT PSA ≥0.5 ng/ml (p = 0.013).

Conclusions This is the first nationwide study in Spain to evaluate a large cohort of PCa patients treated with RP followed by postoperative RT. ART yielded better 2- and 5-year BRFS rates, although OS was equivalent. These findings are consistent with most other published studies and support ART in patients with adverse prognostic characteristics after radical prostatectomy. Prospective trials are needed to compare immediate ART to early SRT to better determine their relative benefits.

Keywords Prostate cancer · Postoperative treatment · Radiotherapy

Introduction

Radical prostatectomy (RP) is a mainstay of treatment in patients with prostate cancer (PCa). However, approximately 40–50% of patients with adverse prognostic features—positive surgical margins, high Gleason scores, extracapsular extension, and seminal vesicle involvement—will eventually develop recurrent disease [1]. Adjuvant radiotherapy (ART) is often administered to these patients to lower the risk of recurrence. Nevertheless, most patients—60 to 90%, depending on the study and patient characteristics [1]—who undergo RP will not develop recurrent disease. Consequently, despite the relatively low morbidity of ART, many authors argue that ART should not be used, except in well-defined cases, because a substantial proportion of patients will be treated unnecessarily [2–10].

Given the low likelihood of local recurrence, it has been argued that close observation is a better approach than ART because salvage radiotherapy (SRT) can be administered if and when biochemical failure occurs, with similar outcomes [10]. The primary argument in favor of this wait-and-see approach is to avoid the potential toxicity of ART, particularly in those patients who will not develop a recurrence. Moreover, although ART has been shown to reduce the risk of biochemical recurrence [11], this does not appear to yield better overall survival rates than SRT [4]. Numerous clinical trials and systematic reviews have been conducted to assess the optimal timing of radiotherapy (RT) and to determine the patient subgroups most likely benefit from ART or SRT [1, 12, 13]. However, the issue remains unresolved and controversial.

The Spanish Prostate Cancer Registry (RECAP) is a large national database of PCa patients created, in part, to help resolve questions such as the one described above. In the present study, we used RECAP data to retrospectively assess outcomes in patients treated with RP for PCa followed by either ART or SRT. The primary aim was to compare the two groups in terms of 2- and 5-year biochemical survival. Secondarily, we sought to identify predictors of survival.

Materials and methods

Data source

The RECAP database, which was initiated in the year 2008, is an observational database accruing data from a total of 88 radiotherapy practice sites over the history of the registry. At the time of our analysis, the database contained information on approximately 13,250 men registered from 1991 through 2011. The retrospective review of medical records was approved by the local ethics committees.

Patient selection

A search for patients in the RECAP database with the following criteria was performed:

Patients who underwent RP (with or without lymphadenectomy) followed by postoperative RT (adjuvant or salvage).

Availability of both biochemical and clinical outcomes.

Outcome measures

The primary end point was time to biochemical failure, defined as nadir plus 0.2 ng/ml, from the completion of RT. After RT, patients with an undetectable or decreasing PSA were considered to have no biochemical evidence of disease (bNED). Patients who died before any evidence of biochemical failure at last follow-up were censored at that final follow-up point. We also assessed overall survival (OS), cause-specific survival (CSS), and disease-free survival (DFS) rates.

Follow-up evaluations after RT consisted of the following: (1) serum PSA testing every 3–6 months, and (2) digital rectal examination every 6–12 months. Additional tests, including computed tomography or bone scans, were performed if clinically necessary.

Pre-RT PSA values (>0.5 vs. ≤0.5 ng/ml), pathological stage (T1–2 vs. T3–4), post-surgical Gleason score (≤7 vs. 8–10), margin status (positive vs. negative), hormonal treatment (yes vs. no), RT dose (<66 Gy vs. ≥66 Gy) and the indication for RT (adjuvant vs. salvage) were analyzed for their impact on biochemical relapse-free survival (BRFS).
**Statistical analysis**

The statistical analysis was performed with the SAS® System, version 9.2 (SAS Institute, Cary, NC; USA). Descriptive analyses were performed and survival estimates were determined using log-rank test. Multivariate analysis was performed with Cox regression modeling with 0.25 as entry criteria and 0.10 as permanence criteria. All statistical tests were two-sided, with the significance level set at \( p < 0.05 \).

**Results**

The patient characteristics are displayed in Table 1. The mean patient age in each group (ART and SRT, respectively) was 62.7 (range 43–75) and 64.8 (42–82) years. Median follow-up after RT was 34 months (range 3–141).

A total of 223 patients (31.8%) received ART while 479 (68.2%) underwent SRT.

As Fig. 1 shows, the time to relapse was significantly greater (log-rank test; \( p = 0.0036 \)) in the ART group. BRFS rates (95% CI) for the ART versus SRT groups were as follows: month 24: 98.1% (95.9–100.0%) versus 91.2% (88.2–94.2%); and month 60: 84.5% (76.4–92.6%) versus 74.0% (67.4–80.7%).

**Overall survival**

No significant between-group differences in OS (Fig. 2) were observed (log-rank, \( p = 0.05 \)). At months 24 and 60, 100% of patients in the ART group remained alive, versus 99.3 and 94.5% in the SRT group.

CSS outcomes were similar, with no significant differences (\( p = 0.331 \), log-rank) between the groups (Fig. 3).

No significant differences were observed for DFS (log-rank test, \( p = 0.587 \)) (Fig. 4). DFS rates (95% CI) for the ART and SRT groups, respectively, were as follows: month 24: 98.5% (96.5–100.0%) versus 97.6% (96.0–99.1%); month 60: 91.3% (85.2–97.5%) versus 88.9% (83.2–94.6%).

On the Cox regression model, several variables were found to be predictive of biochemical recurrence in the SRT group (Table 2).

There were no statistically significant differences between the groups for OS, CSS, or DFS. However, the multivariate Cox proportional regression analysis (Table 2) shows that several factors were significant predictors of biochemical recurrence in the SRT group: (1) positive surgical margin status; (2) no hormonotherapy; (3) total dose to prostate \( \leq 66 \) Gy vs. \( > 66 \) Gy; and (4) pre-RT value PSA \( \geq 0.5 \) ng/ml.

**Discussion**

In the present study, we retrospectively assessed patients included in the RECAP database treated with RP followed by either adjuvant RT or salvage RT. Our main finding was that 2- and 5-year BRFS rates were significantly better in patients who underwent ART compared to those who received SRT. In addition, numerous post-surgical

| Table 1 Patient demographic and clinical characteristics |
|-----------------|-----------|----------|
| Variable         | ART       | SRT       |
|                 | N (%)     | N (%)     |
| Age, mean (range) | 62.7 (43.0–75.0) | 64.8 (42.0–82.0) |
| PSA (pre-RT, ng/ml) | 223 (100.0%) | 70 (14.6%) |
| \( \leq 0.5 \)     | 232 (100.0%) | 70 (14.6%) |
| \( > 0.5–1.0 \) | 0 (0.0%) | 131 (27.4%) |
| \( \geq 1.0–2.0 \) | 0 (0.0%) | 149 (31.1%) |
| \( > 2.0 \)       | 0 (0.0%) | 129 (26.9%) |
| T-stage post-surgery | 83 (40.1%) | 272 (61.3%) |
| T1–2             | 124 (59.9%) | 172 (38.7%) |
| T3–4             | 16      | 35       |
| Missing          | 35       | 51       |
| N-stage post-surgery | 78 (41.5%) | 214 (50.0%) |
| N0               | 6 (3.2%) | 7 (1.6%) |
| N1               | 104 (55.3%) | 207 (48.4%) |
| NX               | 35       | 51       |
| GS (pre-surgical) | 159 (76.1%) | 343 (89.3%) |
| \( \leq 7 \)     | 199 (90.9%) | 393 (89.3%) |
| 8–10             | 20 (9.1%) | 47 (10.7%) |
| Missing          | 4        | 39       |
| GS (post-surgical) | 152 (76.1%) | 343 (82.3%) |
| \( \leq 7 \)     | 199 (90.9%) | 393 (89.3%) |
| 8–10             | 20 (9.1%) | 47 (10.7%) |
| Missing          | 4        | 39       |
| Margin status    | 156 (70.9%) | 214 (47.5%) |
| Positive         | 156 (70.9%) | 214 (47.5%) |
| Negative         | 64 (29.1%) | 237 (52.5%) |
| Missing          | 3        | 28       |
| Hormonal treatment | 153 (68.6%) | 308 (64.4%) |
| Yes              | 70 (31.4%) | 170 (35.6%) |
| No               | 153 (68.6%) | 308 (64.4%) |
| Missing          | 0        | 1        |
| Total dose to prostate | 97 (44.5%) | 145 (30.7%) |
| \( \leq 66 \) Gy | 97 (44.5%) | 145 (30.7%) |
| \( > 66 \) Gy    | 121 (55.5%) | 327 (69.3%) |
| Missing          | 5        | 7        |

ART indicates adjuvant radiotherapy; SRT salvage radiotherapy; GS Gleason score; PSA prostate-specific antigen
variables were predictive of biochemical recurrence in the SRT group. Overall, these findings are consistent with the published literature.

In recent years, many studies [1, 11, 14–16] have investigated the optimal timing of postoperative RT. The general consensus seems to be that ART confers a biochemical survival advantage in well-defined patients with adverse prognostic features (positive surgical margins, high Gleason scores, extracapsular extension, and seminal vesicle involvement). However, the advantage of ART over SRT in terms of OS is less clear, with many authors suggesting that the two approaches are equivalent in this regard [17]. Consistent with the previous reports [1, 15, 18–20], we found that patients who underwent ART presented better 2- and 5-year BRFS rates than those who received SRT. Nonetheless, our data are in line with other studies showing that OS is similar regardless of whether ART or SRT is used.

Bolla et al. in a follow-up study to the European Organization for Research and Treatment of Cancer (EORTC) 22911 trial [16], reported long-term results (>10-year median follow-up) confirming that ART significantly improves BRFS and local control compared to a wait-and-see approach. However, more recent evidence from systematic reviews [21] and clinical guidelines [22] continue to suggest that the controversy between ART and
Fig. 3 Cause-specific survival

![Cause-specific survival graph]

Log Rank Test \( p = 0.3306 \)

Fig. 4 Disease-free survival

![Disease-free survival graph]

Log Rank Test \( p = 0.5871 \)

Table 2  Significant predictors of biochemical recurrence on the definitive COX regression model for patients treated with salvage radiotherapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>( p ) value (Wald Chi Square)</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostatectomy margins</td>
<td>Negative margins versus microscopic/macrosopic involvement</td>
<td>0.0489</td>
<td>0.596</td>
<td>0.356–0.997</td>
</tr>
<tr>
<td>Hormonotherapy</td>
<td>No versus yes</td>
<td>0.0330</td>
<td>1.948</td>
<td>1.055–3.596</td>
</tr>
<tr>
<td>Total dose to prostate</td>
<td>≤66 versus &gt;66</td>
<td>0.0038</td>
<td>2.102</td>
<td>1.271–3.475</td>
</tr>
<tr>
<td>PSA</td>
<td>≤0.5 versus &gt;0.5</td>
<td>0.0158</td>
<td>0.088</td>
<td>0.012;0.633</td>
</tr>
</tbody>
</table>
SRT remains unresolved. Nonetheless, most authors suggest that ART should be strongly considered in patients who present specific adverse characteristics. The systematic review performed by Wallace et al. [21] concluded that there is sufficient evidence to support the use of ART in patients with adverse pathologic findings (i.e., seminal vesicle invasion, positive surgical margins, extraprostatic extension).

**Optimal timing for salvage radiotherapy**

Guidelines published in 2013 by both the American Urology Association and American Society of Therapeutic Radiation Oncology (AUA/ASTRO) [22, 23] recommended offering ART to patients with adverse pathologic findings (seminal vesicle invasion, positive surgical margins, extraprostatic extension) after prostatectomy. A recent study carried out by Gandaglia et al. to validate the AUA/ASTRO criteria [24] found that early radiotherapy (<6 months after RP) improves cancer-specific survival, but only in patients with highly aggressive prostate cancer. These authors found that ART was not associated with lower CSS rates and therefore conclude that the presence of ≥2 pathological features (Gleason score 8–10, stage pT3b/4, presence of nodal invasion) might help to identify the patients most likely to benefit from ART. Stish et al. [25] retrospectively evaluated more than 1100 men who underwent SRT following RP, concluding that outcomes may be better when SRT is performed at lower PSA levels. They suggest that their findings support early initiation of SRT.

The debate between ART and SRT is becoming blurred by a growing trend towards the use of early or “ultra-early” SRT in cases with low but rising PSA levels. Traditionally, SRT was not initiated until relatively high PSA levels (e.g., ≥1.0 ng/ml) were detected. Although recent guidelines recommend starting SRT before PSA exceeds 0.5, more recent data suggest that it would be advantageous to initiate SRT at lower PSA levels. Harris et al. [26], in a study involving 194 patients, found that rising iPSA levels are strongly associated with a higher risk of biochemical failure, even after adjusting for known prognostic factors. Those authors found that, compared to an iPSA of <0.2 ng/ml, slightly higher but still low iPSA values (≥0.2–<0.5) significantly increased the risk (hazard ratio, 2.6; \( p = 0.01 \)) of biochemical failure, thus concluding that waiting for the PSA to rise above 0.2 may significantly compromise biochemical control. However, not all authors support these findings. The recent report (2016) by Taguchi et al. [27] found no survival benefit for ultra-early SRT, leading the authors to conclude that SRT should be administered after two consecutive PSA values ≥0.2 ng/ml and before reaching 0.5 ng/ml.

According to Kang et al. [5], biochemical failure occurs about 8 years prior to distant metastasis, thus underscoring the importance of early detection of biochemical relapse. King et al. [28] conducted a systematic review of all published SRT studies, concluding that SRT should be initiated at the lowest possible PSA because tumor control rates were better when SRT was initiated at lower PSA levels (success decreased by 2.5% with each 0.1 ng/ml increase in PSA). Those findings led the authors to concluded that early SRT may be equivalent to ART. A recent systematic review conducted by Briganti et al. [13] confirmed this finding, emphasizing the need to administer early SRT at low PSA levels to achieve the maximum benefits.

**Importance of dose**

In recent years, several studies have evaluated the dose–response relationship between SRT and biochemical failure. In a multicentre study, Pisanski et al. [29] evaluated 1108 patients who underwent SRT, finding that, at 65.2 months of follow-up, the 5- and 10-year bNED rates (defined as PSA > 0.2 ng/ml and rising) were 63.5 and 49.8%, respectively. A salvage radiation dose of ≥66.0 Gy was associated with a reduced cumulative incidence of biochemical failure, but not of distant metastasis. Therefore, the authors conclude that the use of SRT doses of ≥66.0 Gy are supported. Our data seem to confirm this: doses <66 Gy were significant predictors of biochemical relapse in our SRT group. The systematic review conducted by King et al. [28] also support the use higher doses to obtain better rates of biochemical control.

**Use of androgen-deprivation therapy**

In our study, 34.2% of patients underwent ADT, and the multivariate analysis showed that lack of hormonotherapy was predictive of biochemical relapse in the SRT group but not in the ART group. Although these findings suggest that ADT may improve BRFS, it is still not clear, based on currently available evidence, whether ADT improves OS. According to the expert panel who helped develop the AUA/ASTRO guidelines, methodological weaknesses in the studies that have examined the use of ADT in patients who undergo RP followed by ART or SRT do not allow us to draw any definitive conclusions [22, 23]. However, evidence from two randomized controlled trials [30, 31] points to a benefit for ADT. Shipley et al. [31] randomized 760 men to SRT plus ADT or to SRT plus placebo, finding that the addition of 24 months of ADT significantly increased long-term overall survival while reducing the incidence of metastatic disease and cancer-specific mortality. In another trial, Carrie et al. [30] randomly assigned...
participants to either SRT alone or SRT plus short-term ADT, finding that patients who received ADT were significantly more likely to be free of biochemical or clinical progression at 5 years.

**Predictors of survival**

The original results (year 2005) from the large EORTC 22911 trial involving patients with high-risk disease (positive surgical margins or stage pT3 disease) after RP demonstrated that immediate EBRT improves BRFS and locoregional control compared with a wait-and-see policy [12]. In a subsequent analysis, the investigators demonstrated that pathologic margin status was the strongest predictor of prolonged BRFS after ART [14], thus concluding that ART might not be advisable for patients with negative surgical margins. However, other authors have found that a Gleason score >6 but <7, PSA before RP, tumor stage, and positive surgical margins were predictors of outcome [18]. In the present study, we were unable to identify any significant predictors of survival in the ART group. By contrast, we found four independent predictors in the SRT group: positive surgical margin status, no hormone therapy, total dose to prostate ≤66 Gy, and pre-RT PSA values ≥0.5 ng/ml. These data are largely consistent with the other studies cited here.

**Strengths and limitations**

The main limitation of the present study is its retrospective design. In addition, the specific radiotherapy treatment modalities varied among the participating centers and this could have affected treatment outcomes. The main strength of the current study is the large (>700 patients) cohort.

**Conclusions**

In the present study, we have shown that ART yields better 2- and 5-year BRFS rates than SRT. These findings appear to support the use of ART in patients with adverse prognostic characteristics after radical prostatectomy. Data from recent studies suggest that early SRT, based on low but rising PSA levels, may offer a compromise between ART and delayed SRT. However, prospective RCTs would be valuable to compare immediate ART to early or even ultra-early SRT.

**Compliance with ethical standards**

**Conflict of interest** The authors state that they have no relationships, conditions or circumstances that present potential conflicts of interest with this study.

**Ethical approval** The retrospective review of medical records was approved by the local ethics committees.

**Informed consent** Informed consent was obtained from all live individual participants included in the study.

**References**


