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# What is the best time for postoperative radiation therapy in pN1 prostate cancer?

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We retrospectively compared long-term biochemical recurrence rates (BCR) in pN1 PCa patients that underwent adjuvant radiotherapy (aRT) vs. no aRT/early salvage (esRT) after robot-assisted radical prostatectomy and extended pelvic lymphadenectomy. All PCa pN1 M0 patients treated at a single high-volume center between 2010 and 2020 were analyzed. Patients with <10 LNs yield, or >10 positive LNs, or persistently detectable PSA after RARP were excluded. Kaplan-Meier (KM) plots depicted BCR rates. Multivariable Cox regression models (MCRMs) focused on predictors of BCR. The cumulative incidence plot depicted BCR rates after propensity score (PS) matching (ratio 1:1). 220 pN1 patients were enrolled, 133 (60.4%) treated with aRT and 87 (39.6%) with no-aRT/esRT. aRT patients were older, with higher rates of postoperative ISUP grade group 4-5, and higher rates of pT3b stage. The actuarial BCR was similar (aRT 39.8% vs. no-aRT/esRT 40.2%; p=1). Median time to BCR was 62 vs. 38 months in aRT vs. no-aRT/esRT patients (p=0.001). In MCRMs, patients managed with no-aRT/esRT were associated with higher rates of BCR over time (hazard ratio [HR]: 3.27, p<0.001). ISUP grade group 5 (HR: 2.18, p<0.01) was an independent predictor of BCR. In PS-matched cumulative incidence plots, the BCR rate was significantly higher in the aRT group (76.4 vs. 40.4%; p<0.01). Patients managed with no-aRT/esRT experienced BCR approximately two years before the aRT group. Despite, the important BCR benefit after aRT, this treatment strategy is underused in daily practice.

*Key words: prostate cancer; radiation therapy; prostatectomy; adjuvant radiotherapy; early salvage radiotherapy; biochemical recurrence*

Patients with lymph node (LN) invasion after robot-assisted radical prostatectomy (RARP) represent a heterogeneous population with different survival rates [1–4]. Particularly, in up to 15% of patients affected by localized PCa, LN invasion at final pathology after RARP and extended pelvic LN dissection (ePLND) could be detected [5]. Moreover, LN invasion represents one of the most important prognostic factors for disease recurrence and cancer-specific mortality (CSM) [6].

Today, the European Association of Urology (EAU) guidelines recommend three different management strategies according to the burden of nodal invasion, in pT0-pT4 pN1 patients: 1) observation (microscopic involvement of ≤2 lymph nodes, with PSA <0.1 ng/ml and absence of extranodal extension); 2) adjuvant androgen deprivation therapy (ADT); 3) external beam radiation therapy (EBRT) with concomitant ADT. Specifically, in those patients treated with EBRT, the radiation field should include both prostatic fossa and pelvic LN [7, 8].

Whereas there is no substantial evidence to support one approach over the others, therapeutic decisions in the management of these patients are driven by physicians' preferences or dictated by institutional protocols. Nowadays, the role of adjuvant radiotherapy (aRT) on survival rates remains controversial. Despite several authors reported prolonged survival with aRT administration vs. no treat-

ment, the magnitude of the aRT survival benefit appears to be influenced by several tumor features [9–11]. Specifically, men with low-volume nodal disease (<3 positive LNs), International Society of Urological Pathology (ISUP) grade groups 2-5 and pT3-4 or R1 PCa, as well as those with 3–4 positive LNs appear to be the ideal candidates for aRT [1, 12].

This said, all previously mentioned studies were biased by their retrospective nature and included a really heterogeneous population of patients that were treated with EBRT alone vs. EBRT+ADT. In consequence, differently from the pN0 setting where high-level evidence [13–15] is available in the literature, we lack good quality data supporting the use of aRT in all pN1 patients, as well as its use in some specific pN1 subgroups. Lastly, the role of early salvage RT (esRT) has been poorly investigated [8].

In this scenario, the optimal management strategy of pN1 patients after RARP remains undefined [16–18]. Specifically, an important unmet need is to find the ideal candidates for aRT, in order to reduce overtreatment of some patient categories, while avoiding dangerous delays in treatment administration. To address these voids, we retrospectively compared long-term biochemical recurrence rates (BCR) in pN1 patients who underwent aRT vs. no-aRT/esRT after RARP.

## Patients and methods

**Patients' selection and characteristics.** We retrospectively identified all patients treated with RARP and ePLND at a single high-volume center (European Institute of Oncology-IEO) between 2010 and 2020. A subset of the included cohort has already been included in a previous mono-institutional publication [19]. Specifically, the ePLND template consisted of the removal of all external iliac, internal iliac, and obturator LN. Additional removal of common iliac or presacral LNs was performed according to the clinician's preference and, mainly, preoperative disease characteristics. All patients underwent preoperative staging, according to the EAU guidelines.

Inclusion criteria were: histological diagnosis of PCa; RARP+ePLND; pN1 disease; postoperative PSA ≤0.1 ng/ml; no detectable metastases at preoperative staging. For the purpose of this analysis, we excluded all patients with an inadequate number of LNs removed at ePLND (number of LN yield <10) or patients with the high-burden nodal disease (number of positive LNs >10). Moreover, patients with persistently detectable PSA after RARP and patients with missing data were not considered (n=19). With aRT were considered all treatments administered within 6 months from RARP. Conversely, as esRT were considered all treatments administered after more than 6 months after RARP. All patients that underwent aRT or esRT received ADT for 9–12 months as a standard practice in our institution for this setting of patients [19]. Lastly, the population was divided according to the treatments received: the first group encompassed all the patients who underwent adjuvant radiotherapy (aRT) vs. the second group which encompassed all the patients who did not receive RT or received just salvage radiotherapy (no-aRT/esRT).

Follow-up after surgery consisted of repeated PSA testing and urologic examination, which was scheduled according to the EAU guidelines [20]. Biochemical recurrence-free survival (RFS) was calculated from the date of surgery for those who received only surgery. On the contrary, RFS was calculated from the date of aRT for those who received this treatment after surgery. Specifically, the BCR definition was consistent with both the American Urological Association and the American Society for Radiation Oncology (ASTRO) recommendations: two consecutive PSA tests ≥0.2 ng/ml performed consecutively [20].

**Ethical approval.** All procedures performed in studies involving human participants were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was conducted within the notification presented to the Ethics Committee of IRCCS European Institute of Oncology (Milan, Italy), CE notification no. 79.

**Radiation therapy treatment planning and delivery.** All patients were treated at the Division of Radiotherapy of the European Institute of Oncology, with three-dimensional (3D) conformal RT or with intensity-modulated RT (IMRT). Clinical target volumes, contoured according to the guidelines of the Radiation Therapy Oncology Group [20–22], included the prostatic fossa and pelvic lymph nodes. Regarding 3D conformal RT treatments, a total dose of up to 70.4 Gy was administered: 50.4 Gy in 28 fractions to the pelvis and a sequential boost of 20 Gy in 10 fractions to the prostatic fossa. The IMRT dose prescribed to the prostatic fossa ranged from 66 to 69 Gy, delivered in 30 fractions equivalent to 70 Gy in 35 fractions, considering an $\alpha/\beta$ of 1.5 Gy. Pelvic doses were 51 and 54 Gy in 30 fractions to the negative and positive lymph node areas, respectively. For the prostatic fossa, a margin of 5 mm in all directions was added to create the planning target volume (PTV), while for the pelvis PTV, an isotropic margin of 5 mm was added to the lymph nodes CTV.

All patients underwent a planning CT scan (2.5 mm slicing) in the supine position with leg immobilization (Combifix; SinMed, Reeuwijk, The Netherlands). Patients were asked to have a full bladder and empty rectum before the acquisition of the planning CT, and each treatment session, in order to minimize daily variations in prostatic fossa location and hence reduced the risk of missing the target.

In 2010, image-guided IMRT was implemented at our institution with Rapidarc™ volumetric-modulated arc therapy technology (Varian Medical System, Palo Alto, CA, USA); therefore, most patients treated from 2010 onwards underwent volumetric-modulated arc therapy image-guided-IMRT, while all those treated before 2010 underwent 3D conformal RT.

**Statistical analyses.** We relied on two analytical steps. First, we evaluated the overall BCR rates. Univariable and multivariable Cox regression models focused on predictors

of BCR over time. BCR rates over time were plotted with the Kaplan-Meier method.

Second, cumulative incidence plots depicted BCR rate differences after propensity score (PS) matching (ratio 1:1), which was used to minimize potential differences that might exist in patients' characteristics according to aRT vs. no-aRT/esRT (i.e., selection bias). Matching was performed according to the following variables: age at diagnosis, iPSA, pT-stage, and postoperative ISUP group.

All statistical tests were two-sided with a level of significance set at p<0.05. Analyses were performed using the R software environment for statistical computing and graphics (version 3.4.1; http://www.r-project. org/).

## Results

**Descriptive analysis of the study population.** Overall, 220 (44 %) pN1 patients with 1–10 positive LNs represented the study population. Of those, 133 (60.4%) vs. 87 (39.6%) were treated with aRT vs. no-aRT/esRT, respectively (Table 1). Median PSA at baseline was 8.2 (IQR: 5.8–13.8) for the whole cohort and 8.5 (IQR: 6.0–15.6) and 8.1 (IQR 5.7–11.0) for aRT and no-aRT/esRT cohort, respectively. Specifically, 26 of 220 (11.8%) patients initially managed with observation developed BCR and were subsequently treated with esRT. The median time from RARP to esRT was 40 months (IQR: 17–62). aRT patients were older (67 vs. 63 yrs., p<0.001), relative to their no-aRT/esRT counterpart. Moreover, higher rates of postoperative pathological ISUP grade group 4–5 PCa were observed in aRT patients (51.2 vs. 25.2 %; p<0.001).

A statistically significant difference was recorded between aRT and no-aRT/esRT regarding pT stage (5 vs. 14 patients in stage pT2; 43 vs. 40 in stage pT3a and 85 vs. 33 in stage pT3b, p<0.001). No statistically significant difference was found between groups for the median number of nodes removed (17 vs. 16; p=0.3) and the median number of positive nodes (1 vs. 1; p=0.7). The median follow-up time was 61 (IQR: 17–87) months.

**Analyses predicting the rates of BCR.** The actuarial BCR was virtually the same between the two categories (aRT 39.8% vs. no-aRT/esRT 40.2%; p=1). The median time to

**Table 1. Descriptive characteristics of 220 non-metastatic prostate cancer patients treated with robot-assisted radical prostatectomy, stratified according to management strategies: aRT vs. no-aRT/esRT.**

| | | Overall cohort (n=220)‡ | aRT (n=133)‡ | No-aRT/esRT (n=87)‡ | p-value |
|---|---|---|---|---|---|
| **Age at diagnosis** | Median | 63 | 67 | 63 | **<0.001** |
| | Interquartile range | 58–68 | 62–70 | 58–68 | |
| **iPSA** | Median | 8.2 | 8.5 | 8.1 | 0.14 |
| | Interquartile range | 5.8–13.8 | 6.0–15.6 | 5.7–11.0 | |
| **cT-Stage** | 1 | 54 (24.5) | 32 (24.1) | 22 (25.3) | 0.9 |
| | 2 | 77 (35.0) | 46 (34.6) | 31 (35.6) | |
| | 3 | 72 (32.7) | 45 (33.8) | 27 (31) | |
| | Not determined | 17 (7.7) | 10 (7.5) | 7 (8.0) | |
| **Preoperative ISUP score** | 1 | 35 (15.9) | 18 (13.5) | 17 (19.5) | **0.04** |
| | 2 | 56 (25.5) | 27 (20.3) | 29 (33.3) | |
| | 3 | 56 (25.5) | 34 (25.6) | 22 (25.3) | |
| | 4 | 41 (18.6) | 30 (22.6) | 11 (12.6) | |
| | 5 | 32 (14.5) | 24 (18.0) | 8 (9.2) | |
| pT-stage | 2 | 19 (8.6) | 5 (3.8) | 14 (16.1) | **<0.001** |
| | 3a | 83 (37.7) | 43 (32.3) | 40 (46.0) | |
| | 3b | 118 (53.6) | 85 (63.9) | 33 (37.9) | |
| **Postoperative ISUP score** | 2 | 95 (43.2) | 54 (40.6) | 41 (47.1) | **<0.001** |
| | 3 | 35 (15.9) | 11 (8.3) | 24 (27.6) | |
| | 4 | 43 (19.5) | 32 (24.1) | 11 (12.6) | |
| | 5 | 47 (21.4) | 36 (27.1) | 11 (12.6) | |
| **Number of removed lymph nodes** | Median | 16 | 17 | 16 | 0.3 |
| | Range | 13–21 | 13–22 | 13–20 | |
| **Number of positive lymph nodes** | Median | 1 | 1 | 1 | 0.7 |
| | Range | 1–2 | 1–2 | 1–2 | |
| **Number of positive lymph nodes (categories)** | 1 | 139 (63.2) | 78 (58.6) | 61 (70.1) | 0.1 |
| | ≥2 | 81 (36.8) | 55 (41.4) | 26 (29.9) | |

Note: ‡column percentage; Abbreviations: aRT-adjuvant radiotherapy; esRT-early salvage radiotherapy; iPSA-initial PSA; ISUP-International Society of Urological Pathology

BCR was 62 vs. 38 months, respectively, in aRT vs. no-aRT/esRT patients (p=0.001; Figure 1).

Since the vast majority of the population harbored only 1 metastatic LN at ePLND, we stratified the overall cohorts into 2 subgroups: 1) patients with only 1 positive LN (n=139; 63.2%) vs. 2) patients with positive LNs ≥2 (n=81; 36.8%). No statistically significant difference was observed in median BCR-free survival rates (58 vs. 53 months; p=0.7) respectively in LN=1 vs. LNs ≥2 patients (Figure 2).

In multivariable Cox regression models, patients managed with no-aRT/esRT were associated with higher rates of BCR over time (hazard ratio [HR]: 3.27, p<0.001), compared to their aRT counterparts. Moreover, the ISUP grade group 5 (HR: 2.18, p<0.01) was an independent predictor of BCR. No statistically significant association was identified between BCR rates and age, iPSA, pT stage, or a number of positive LNs (Table 2).

Last, we focused on the association between aRT vs. no-aRT/esRT and BCR rates over time, after PS matching (ratio 1:1; aRT-57 vs. no RT/ESRT = 57; Supplementary Table S1). In PS-matched cumulative incidence plots depicting the association between aRT vs. no-aRT/esRT and 5-year BCR

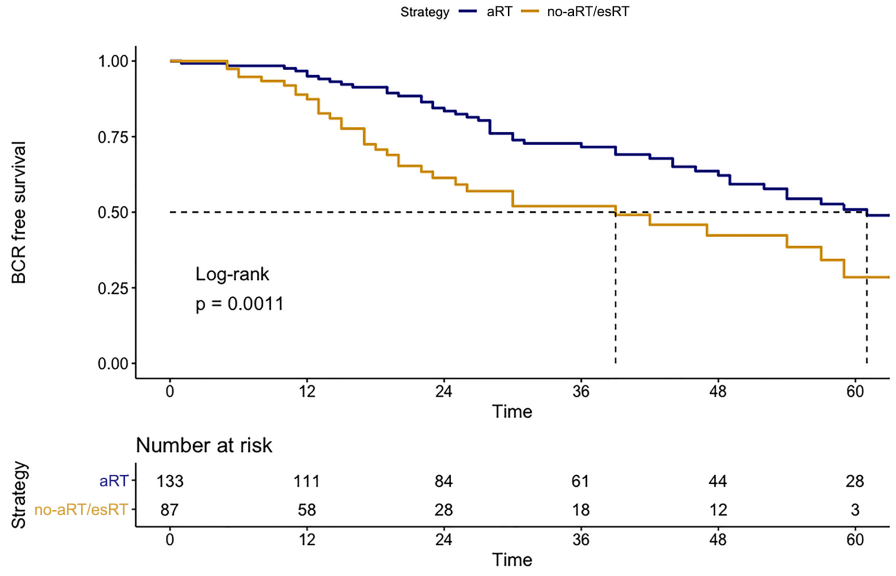


**Figure 1. BCR-free survival according to the two strategies aRT vs. no-aRT/esRT.**

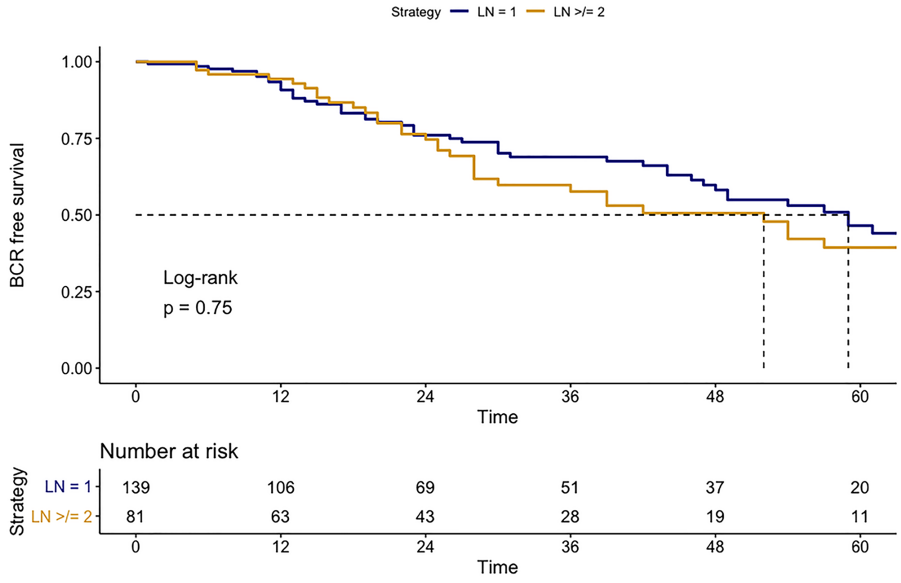


**Figure 2. BCR-free survival according to the number of positive LNs.**

rates, a significant difference was observed (respectively, 40.4 vs. 76.4%; p<0.01) (Figure 3).

## Discussion

The literature lacks strong evidence to recommend one therapeutic strategy over the others (aRT vs. ADT vs. no-aRT/esRT) in pN1 patients after RARP. Nowadays, the choice of treatment to be administered strongly depends on clinical preference or institutional protocols. Moreover, only sporadic series addressed the role of esRT in patients with positive LN [23, 24]. These unmet needs represented the aim of the current study. We retrospectively analyzed the BCR rates in patients with positive LN that were treated with aRT vs. no-aRT/esRT between 2010–2020 at a single high-volume center. Our results showed several important findings.

**Table 2. Univariable and multivariable Cox regression models predicting biochemical recurrence.**

| | | Univariable HR | CI (2.5-97.5%) | p-value | Multivariable HR | CI (2.5-97.5%) | p-value |
|---|---|---|---|---|---|---|---|
| **Treatment strategy** | | | | | | | |
| | aRT | Ref. | | | Ref. | | |
| | no RT/esRT | 2.07 | (1.33–3.25) | **< 0.01** | 3.27 | (1.95–5.47) | **< 0.001** |
| **Age** | | | | | | | |
| | Continuously coded | 1.01 | (0.97–1.04) | 0.7 | 0.98 | (0.94–1.01) | 0.7 |
| **iPSA** | | | | | | | |
| | Continuously coded | 0.99 | (0.99–1.01) | 0.7 | 1.00 | (0.99–1.02) | 0.6 |
| **pT stage** | | | | | | | |
| | pT2 | Ref. | | | Ref. | | |
| | pT 3a | 1.32 | (0.55–3.18) | 0.5 | 1.69 | (0.65–4.36) | 0.3 |
| | pT 3b | 1.79 | (0.77–4.16) | 0.2 | 2.49 | (0.94–6.58) | 0.06 |
| **ISUP grade** | | | | | | | |
| | Grade 2 | Ref. | | | Ref. | | |
| | Grade 3 | 0.84 | (0.42–1.66) | 0.6 | 0.67 | (0.32–1.40) | 0.3 |
| | Grade 4 | 0.84 | (0.47–1.50) | 0.6 | 0.94 | (0.53–1.69) | 0.8 |
| | Grade 5 | 1.95 | (1.16–3.29) | **0.01** | 2.18 | (1.266–3.79) | **< 0.01** |
| **Number of positive LN** | | | | | | | |
| | LN=1 | Ref. | | | Ref. | | |
| | LN≥2 | 1.07 | (0.70–1.65) | 0.7 | 0.94 | (0.59–1.49) | 0.8 |

Abbreviations: aRT-adjuvant radiotherapy; esRT-early salvage radiotherapy; LN-lymph node; HR-hazard ratio; CI-confidence intervals; Ref-reference

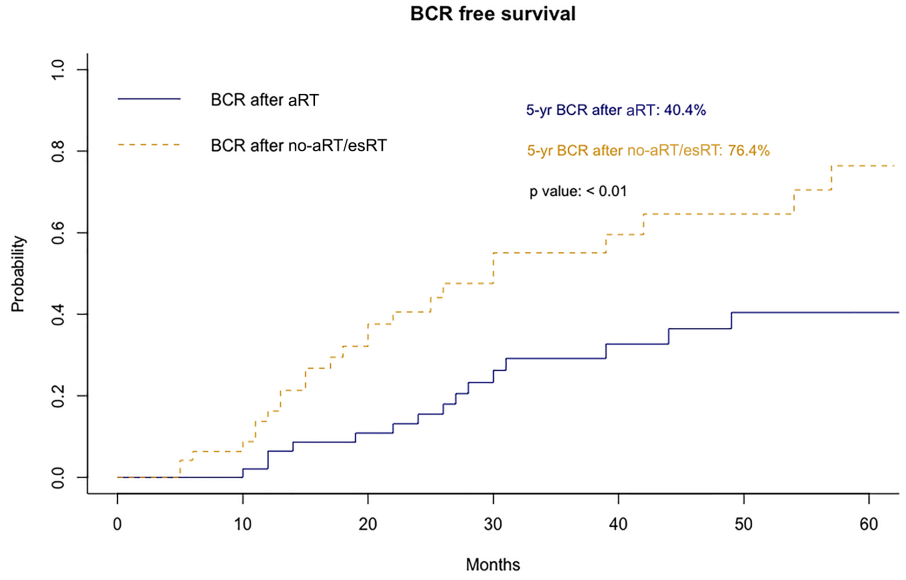


**Figure 3. Cumulative BCR in aRT vs. no-aRT/esRT after PS matching.**

First, aRT was administered to 60.4% of the entire population. Specifically, older patients (67 vs. 63 yrs) and patients with more advanced primary tumors (pT3b and/or ISUP grade group 4–5) were more frequently treated with aRT. Our findings are consistent with those of Abdollah et al. who reported a rate of aRT administration that ranged from 42 to 50.7% in North American patients [12, 25], and indicates that approximately half of the population was not immediately treated with radiation therapy after RARP. Several hypotheses could justify the mentioned findings. First, clinicians may prefer not to treat patients with aRT in order to maximize urinary continence and/or erectile function recovery after surgery. Second, patients may be scared of radiation therapy and concomitant ADT side effects. In consequence, a part of them may prefer to be treated only in case of BCR (esRT) vs. to be preventively treated after RARP (aRT), without evidence of BCR. Due to the retrospective nature of the current analysis, we are unable to validate or reject any of the mentioned hypotheses. In consequence, reasons for aRT underuse in daily clinical practice, despite evident survival benefits with the use of aRT in pN1 patients (Table 3), should be tested in other multi-institutional series with, ideally, a prospective design.

Second, we observed similar rates of BCR in patients that were treated with aRT vs. no-aRT/esRT (aRT 39.8% vs. no-aRT/esRT 40.2%; p=1). However, the median time to BCR was significantly lower in no-aRT/esRT vs. aRT group (38 vs. 62 months; p=0.001). Last, in multivariable Cox regression models that were fully adjusted for all available pre- and postoperative patients and tumor characteristics, no-aRT/esRT was associated with higher rates of BCR over time (HR: 3.27, p<0.001), compared to their aRT counterparts. These findings are consistent with those previously reported by Tilki et al. [8]. The mentioned authors compared BCR rates over time in a less contemporary (2005–2013) cohort of pN1 patients managed with initial observation (receiving salvage RT after BCR) vs. aRT+/–ADT. Tilki et al. reported inferior BCR-free survival rates in men managed with initial observation vs. those treated with aRT. Specifically, the 4-year BCR-free survival was 43.0% vs. 57.5% in no-aRT/esRT vs. aRT patients, respectively.

Taken together, our findings and those of Tilki et al. indicate a BCR benefit over time in pN1 patients immediately treated with RT after RARP, compared to those managed with initial observation. These results should encourage the immediate use of RT in all pN1 patients after radical prostatectomy. This said, the oncological benefit of aRT should be balanced with the adverse side effects of both aRT and concomitant ADT administration. In consequence, despite a significant BCR benefit of aRT vs. no-aRT/esRT, more studies focusing on

**Table 3. Summary of the available evidence on aRT in pN1 patients.**

| Author | Year | Treatment type | Endpoint(s) | Cohort size | Groups Stratification | Main findings |
|---|---|---|---|---|---|---|
| Gupta et al. [20] | 2019 | RP+/–HT+/–aRT | OS | 8,074 | Group 1 (observation): 4489<br>Group 2 (ADT): 2065<br>Group 3 (ADT+aRT): 1520 | ADT+aRT improved OS in the majority of patients.<br>Adjuvant therapy did not confer significant OS benefit in up to 30% of patients without high-risk features. |
| Abdollah et al. [21] | 2018 | ADT+/–aRT within 1 year from RP+ePLDN | OS | 5,498 | Group 1 – very low risk*:<br>13 (ADT alone), 6 (ADT+aRT)<br>Group 2 – low risk*:<br>520 (ADT alone);<br>265 (ADT+aRT)<br>Group 3 – intermediate risk*:<br>1740 (ADT alone);<br>1536 (ADT+aRT)<br>Group 4 – high risk*:<br>531 (ADT alone);<br>289 (ADT+aRT)<br>Group 5 – very high risk*:<br>396 (ADT alone);<br>202 (ADT+aRT) | Intermediate and high-risk groups (3 and 4) are the ones that get major benefits from aRT;<br>in the remaining patients (25% of the cohort), aRT had no significant survival benefit. |
| McDonald et al. [22] | 2018 | RP+/–ADT+/–aRT | CSM, OS, MFS | 90 | Group 1 (RP): 17<br>Group 2 (RP+ADT): 35<br>Group 3 (RP+aRT+ADT): 38 | First post-operative PSA ≥ 0.2 ng/ml may help risk stratify pN1 patients who harbor systemic disease compared to patients with a first postoperative PSA of 0.2 ng/ml. |

**Table 3.** ***Continued ...***

| Author | Year | Treatment type | Endpoint(s) | Cohort size | Groups Stratification | Main findings |
|---|---|---|---|---|---|---|
| Kim et al. [23] | 2017 | RP+/–aRT | CSS | 3,548 | Group 1 (RP alone): 2643<br>Group 2 (aRT): 905 | aRT after RP showed a CSS benefit in prostate adenocarcinoma with 4 or more involved LNs irrespective of LNR.<br>In prostate adenocarcinoma with up to 3 involved LNs after RP, aRT may provide CSS benefits when the LN ratio is 7% or higher. |
| Jegadeesh et al. [24] | 2017 | RP+HT+RT | OS | 906 | | 5 y OS was 87% for RT+HT vs. 82% for only HT. ≥ 3 LNs involved were associated with poorer OS |
| Zareba et al. [25] | 2017 | RP+/–ADT+/–aRT | OS | 7,791 | Group 1 (observation): 4489<br>Group 2 (RP+ADT): 1571<br>Group 3 (RP+aRT): 355<br>Group 4 (RP+aRT+ADT): 976 | ADT+aRT was associated with significantly lower all-cause mortality compared to both observation and ADT alone.<br>Adjusted 10 y OS probabilities conditional on surviving at least 1 y after RP for patients managed with observation, ADT alone, aRT alone, and ADT+aRT were 69%, 67%, 75%, and 77%, respectively. |
| Poelaert et al. [26] | 2017 | RP+PLND+aRT+HT | bRFS, cPFS, CSS | 154 | | bRFS was 67%, cPFS was 71%, and CSS was 96% at 5 y.<br>The number of pN1 was prognostic for CSS and OS. |
| Moschini et al. [2] | 2016 | RP+PLND+/–aRT | Identifying predictive factors for BCR metastasis, OS and CSM | 1,101 | | ≥3 pN1, GS, R1, aHT were significant predictors of BCR, metastasis, CSM, and OM.<br>aRT was associated with decreased CSM. |
| Wong et al. [27] | 2016 | RP+/–ADT+/–aRT | OS | 7,225 | Group 1 (RP): 3636<br>Group 2 (RP+ADT): 2041<br>Group 3 (RP+aRT): 350<br>Group 4 (RP+aRT+ADT): 1198 | Patients treated with multimodal aRT+aHT had significantly higher OS rates than patients treated without adjuvant therapy or with aHT/aRT alone. |
| Abdollah et al. [28] | 2014 | RP+ePLND+/–aRT | CSM-free survival, OM-free survival | 1,107 | Group 1 (ADT alone): 721<br>Group 2: (ADT+aRT): 386 | aRT addition to ADT was associated with a more favorable CSM rate at 10 y. The 10 y CSM-free rate was 83.6% in the entire cohort, 86.7% in patients treated with aRT+ADT, and 82.3% in patients treated with ADT alone. |
| Briganti et al. [29] | 2011 | RP + ePLND+ and adjuvant treatments | CSS and OS | 703 | Group 1 (ADT+aRT): 171<br>Group 2 (ADT only): 532 | Higher CSS and OS in Group 1.<br>No differences between groups according to the number of pN1. |
| Da Pozzo et al. [9] | 2009 | RP+PLND+adjuvant treatments (HT+/–aRT) | BCR-free and CSS | 250 | Group 1 (aRT+ADT): 129<br>Group 2 (ADT alone): 121 | Comparing Group 1 vs. 2, BCR-free survival at 10 y was 51% vs. 41.7%; CSS at 10 y was 70.3% vs. 71.8% respectively.<br>In multivariable analysis, only the number of positive LNs represented an independent predictor of BCR-free survival. |

Notes: *Very Low Risk (1-2 pN1, GS 2-6); Low Risk (1-2 pN1, GS 7-10, pT2/pT3a, R0); Intermediate Risk (1-2 pN1, GS 7 - 10, pT3b/pT4 or R1); High Risk (3-4 pN1); Very High Risk (> 4 pN1). Abbreviations: ADT-androgen deprivation therapy; aRT-adjuvant radiotherapy; BCR-biochemical recurrence; CSM-cancer-specific mortality; CSS-cancer-specific survival; DSS-disease-specific survival; ePLND-extended pelvic lymph node dissection; LN-lymph node; GS-Gleason Score; OM-overall mortality; OS-overall survival; pN0-negative LN; pN1-positive LN; R0/1-negative/positive surgical margins; RFS-recurrence-free survival; RP-radical prostatectomy

oncological outcomes and treatment side effects of aRT are needed before changing EAU guidelines recommendations in pN1 patients.

Third, the observed BCR benefit of aRT vs. no-aRT/esRT remained consistent after 1:1 PS matching (5-year BCR rates: 40.4 vs. 76.4%; p<0.01). This further analysis revealed that the observed findings are not a product of confounding factors due to selection bias. To the best of our knowledge, only 1 previous author [8] reported both unadjusted, multivariable adjusted as well as PS adjusted comparison between aRT and no-aRT/esRT patients. This analytic strategy is necessary in these retrospective series since important differences exist between aRT vs. no-aRT/esRT patients (as previously said, older patients and patients with more advanced primary tumors were more frequently treated with aRT). These differences were probably related to the lack of strong and clear recommendations in the EAU guidelines for pN1 patients and, probably, reflected clinicians' preferences. This said, our comparisons are still limited by their retrospective nature. Moreover, even the strictest form of matching for patients' imbalances does not represent a substitute for a prospective randomized comparison between aRT vs. no-aRT/esRT patients that are, in consequence, urgently needed.

Taken together, we provided the most contemporary analysis that evaluated BCR differences between pN1 patients treated with aRT vs. no-aRT/esRT. Our findings indicate that aRT is underused in this patient category since approximately half of them benefit from immediate RT. Moreover, aRT is associated with lower BCR rates, compared to no-aRT/esRT strategy. These results were validated after PS matching that was fully adjusted for patients' imbalances between the two study groups (aRT vs. no-aRT/esRT).

Despite its novelty, our study has several limitations. First, as previously stated, the data are retrospective and influenced by inherent selection bias that was only partially reduced by multivariable adjustment or PS matching. Second, due to the nature of the study, we lack structural information about ADT administration, its duration, and its possible weight on the oncological outcomes. Third, treatment adherence and patients' compliance are unavailable information within our dataset. Fourth, we lack some important pathological findings that were previously associated with BCR rates over time, such as microscopic or extranodal LN involvement. Fifth, other important oncological outcomes (castration resistance and metastatic progression) and treatment side effects should be systematically recorded and analyzed in future trials.

In conclusion, our data confirmed that aRT should be considered for the treatment of pN1 patients, as previously reported. Specifically, patients managed with no-aRT/esRT experienced BCR approximately two years before their aRT counterparts. Despite, the important BCR benefit of aRT administration, this treatment strategy is dramatically underused in daily practice.

**Supplementary information** is available in the online version of the paper.

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