La radiologia medica (2022) 127:206–213
https://doi.org/10.1007/s11547-021-01435-8

RADIOTHERAPY

Dose-escalated pelvic radiotherapy for prostate cancer in definitive or postoperative setting

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Received: 23 July 2021 / Accepted: 16 November 2021 / Published online: 30 November 2021

Abstract

Purpose Given the absence of standardized planning approach for clinically node-positive (cN1) prostate cancer (PCa), we collected data about the use of prophylactic pelvic irradiation and nodal boost. The aim of the present series is to retrospectively assess clinical outcomes after this approach to compare different multimodal treatment strategies in this scenario.

Methods Data from clinical records of patients affected by cN1 PCa and treated in six different Italian institutes with prophylactic pelvic irradiation and boost on pathologic pelvic lymph nodes detected with CT, MRI or choline PET/CT were retrospectively reviewed and collected. Clinical outcomes in terms of overall survival (OS) and biochemical relapse-free survival (b-RFS) were explored. The correlation between outcomes and baseline features (International Society of Urological Pathology-ISUP pattern, total dose to positive pelvic nodes $\leq / > 60$ Gy, sequential or simultaneous integrated boost (SIB) administration and definitive vs postoperative treatment) was explored.

Results ISUP pattern < 2 was a significant predictor of improved b-RFS (HR = 0.3, 95% CI 0.1220–0.7647, $P = 0.0113$), while total dose < 60 Gy to positive pelvic nodes was associated with worse b-RFS (HR = 3.59, 95% CI 1.3245–9.741, $P = 0.01$). Conversely, treatment setting (postoperative vs definitive) and treatment delivery technique (SIB vs sequential boost) were not associated with significant differences in terms of b-RFS (HR = 0.85, 95% CI 0.338–2.169, $P = 0.743$, and HR = 2.39, 95% CI 0.93–6.111, $P = 0.067$, respectively).

Conclusion Results from the current analysis are in keeping with data from literature showing that pelvic irradiation and boost on positive nodes are effective approaches. Upfront surgical approach was not associated with better clinical outcomes.

Keywords Prostate cancer · Radiotherapy · Dose escalation · Boost

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Purpose

Treatment for high-risk and locally advanced prostate cancer (PCa) is still a matter of debate [1], and management of clinically node-positive (cN1) PCa is one of the most challenging issues. A recent systematic review and meta-analysis suggested that local treatment may confer significant advantage in terms of overall survival (OS) and cancer-specific survival (CSS) in cN1 patients, as compared to androgen deprivation therapy (ADT) alone [2]. However, no randomized trial was included, and currently there are no data suggesting the superiority of radical prostatectomy (RP) or radiotherapy (RT) in this setting [3–7]. Several randomized clinical trials established that the addition of definitive RT to long-term ADT significantly improves OS when compared to ADT alone [8–10] in high-risk PCa, while modest evidence supports RP for cN1 patients [11]. Actually, surgery for locally advanced disease is performed as a part of a multimodal treatment approach [12–14], but curative role of pelvic nodal dissection (PLND) remains controversial [15]. Moreover, risk of biochemical persistence/recurrence is significantly higher [16], questioning the oncological radicality of surgery performed in N1 patients. At the same time, regarding the RT approach, no definitive paradigm exists for cN1 patient treated with definitive intent or patients with pelvic persistence/recurrence of disease after RP. Early adjuvant ADT + RT seems to improve oncologic outcomes if compared to surgery and adjuvant ADT alone [17]. On the other hand, whole pelvic radiotherapy (WPRT) did not show significant survival advantages, and its role in PCa is debated [18–22]. The use of different target volumes during the WPRT planning represents another issue in this scenario [23]. Interestingly, the availability of new imaging methods and intensity-modulated RT (IMRT) implementation allowed to refine RT planning in this setting. Given the absence of standardized planning approach in this complex scenario, we collected data about the use of nodal IMRT boost in patients with either cN1PCa treated with ADT + definitive RT or patients with PSA biochemical persistence/recurrence after RP and positive imaging findings for nodal macroscopic disease. The aim of the present series is to retrospectively assess clinical outcomes after this approach to compare different multimodal treatment strategies in this complex scenario.

Methods

Population

Data from clinical records of patients affected by cN1PCa and treated in six different Italian institutes with WPRT were retrospectively reviewed and collected. Both patients undergoing definitive and postoperative treatment were included in the present analysis. Either prostate and seminal vesicles or prostate bed was treated according to these different settings. Prophylactic pelvic irradiation with boost on pathologic pelvic lymph nodes detected with CT, MRI or choline PET/CT was administered in all patients. Long-term concomitant androgen deprivation therapy (ADT), defined as ≥ 18 months of LH-RH analogue administration, was prescribed in all patients.

RT technique

IMRT or volumetric-modulated technique (VMAT) was always used. Either sequential or simultaneous integrated boost (SIB) techniques were allowed, provided that all patients received a boost on pathologic pelvic lymph nodes. Both moderately hypofractionated and conventionally fractionated treatments were allowed. Dose/fractionation schedules administered were different according to clinical setting, with regimens consisting in 70–80 Gy in 28–40 fractions on prostate (definitive setting), 60–78 Gy in 30–39 fractions on prostate bed (postoperative setting). WPRT was always administered, with dose/fractionation schedules ranging between 44 and 54 Gy in 22–35 fractions, and prescribed dose to pathologic pelvic lymph nodes ranged between 54 and 75 Gy in 30–35 fractions. Dose constraints were selected according to treatment schedule and local clinical practice.

Outcomes

Clinical outcomes in terms of overall survival (OS) and biochemical relapse-free survival (b-RFS) were explored with the Kaplan–Meier analysis. OS and b-RFS were defined as the time from RT start to death or biochemical relapse, respectively. Biochemical relapse was defined according to Phoenix definition for patients treated in radical setting [24]. For postoperative patients, biochemical relapse was defined as a PSA increase above 0.2 ng/ml for patients with a PSA nadir ≤ 0.2 ng/ml or 2 consecutive PSA increases > 25% if compared to nadir in patients with a PSA nadir > 0.2 ng/ml, according to our previous work regarding the treatment of macroscopic evidence of disease after surgery [25].

Statistical analysis

Cox proportional-hazards regression was performed to explore the correlation between outcomes and baseline features (ISUP pattern [26], total dose to positive pelvic nodes ≤ / > 60 Gy, sequential or simultaneous boost administration and definitive vs postoperative treatment). Hazard ratio (HR) and 95% confidence interval (95% CI) were reported for each of the above-mentioned factors. Toxicity was reported according to Common Terminology Criteria for Adverse Events (CTCAE) score v.4.03 [27]. Chi-square test was used to explore correlation between adverse events, technique (SIB vs sequential boost administration) and nodal boost dose.

Results

Population

In this multicentric retrospective study, data from 102 patients treated in six different Italian institutes from February 2004 to May 2019 were collected and analyzed. Baseline ISUP Grade Groups were distributed as follows: thirty-nine patients (38.2%) were assigned to ISUP Grade Groups 1–2, while sixty-three patients (61.8%) were assigned to ISUP Grade Groups 3–5. Fifty-two (51%) and 50 (49%) patients were treated in postoperative and definitive settings, respectively. All surgical patients underwent extensive pelvic lymphadenectomy at the time of surgery. Baseline patients' features are summarized in Table 1.

Table 1 Patients' characteristics

Characteristics	
Number of patients	102
Age, median (range)	62.78 (53–77)
Stage	
< T3	47 (46%)
≥ T3	55 (54%)
ISUP grading group	
Group 1–2 (low-risk)	39 (38.2%)
Group 3–5 (intermediate-to-high-risk)	63 (61.8%)
Primary treatment	
Radical prostatectomy	52 (51%)
Radiotherapy	50 (49%)
Dose/fractionation schedules	
Definitive setting (prostate)	70–80 Gy in 28–40 fractions
Postoperative setting (prostate bed)	60–78 Gy in 30–39 fractions
Whole pelvis	44–54 Gy in 22–35 fractions
Positive nodes	54–75 Gy in 30–35 fractions
Total dose to lymph nodes	
> 60 Gy	68 (66.7%)
≤ 60 Gy	34 (33.3%)
Boost delivery technique	
Simultaneous integrated boost (SIB)	51 (50%)
Sequential	51 (50%)
Androgen deprivation therapy	
Yes	91 (89.2%)
No	11 (10.8%)

Clinical outcomes

After a median follow-up of 37.0 months (range 4–163), median OS was not reached. We found that 23 patients (22.5%) developed biochemical recurrence, while seventy-nine (77.4%) did not. Median b-RFS in the overall population was 85 months (95% C.I. 77.27–107.00). Fourteen out of 52 (26.9%) and 9 out of 50 (18%) patients in the postoperative and definitive settings developed biochemical recurrence, respectively. Kaplan–Meier analysis showed a median b-RFS of 98 months (95% C.I. 64–98) versus 85 months (95% C.I. 71–107) in postoperative and definitive setting, respectively [Fig. 1]. The Cox proportional hazards model showed that ISUP pattern < 2 was significant predictor of improved b-RFS (HR = 0.3, 95% C.I. 0.1220–0.7647, $P = 0.0113$), while total dose ≤ 60 Gy to positive pelvic nodes was associated with worse b-RFS (HR = 3.59, 95% C.I. 1.3245–9.741, $P = 0.01$). Conversely, treatment setting (postoperative vs definitive) and treatment delivery technique (SIB vs sequential boost) were not associated with significant differences in terms of b-RFS (HR = 0.85, 95% CI 0.338–2.169, $P = 0.743$, and HR = 2.39, 95% CI 0.93–6.111, $P = 0.067$, respectively) [Fig. 2]. Twenty-two (21.56%) patients developed clinical recurrence (3 local, 2 regional and 17 distant). Of these, 18 patients (17,7%) received ADT, 2 received ADT + SBRT, one patient received ADT + palliative RT and one patient received palliative RT only.

Toxicity analysis

Overall, any grade acute GI toxicity occurred in 55 patients (56.9%), 27 of whom had been treated in postoperative and 28 in definitive setting, respectively; one G2 and 1 G3 toxicities were reported. Thirteen (12.7%) late GI toxicities were recorded (7 in the definitive and 6 in postoperative setting, respectively, all G1). Acute GU toxicities of any grade were reported in 43 patients (42.1%), 27 of whom had been treated in the definitive and 16 in postoperative setting, respectively; among those patients only 2 cases of G2 and 1 of G3 toxicity were reported. Late GU toxicities occurred in 16 patients (15.7%), 7 of whom were treated in the definitive and 9 in the postoperative setting, respectively (15 G1 and 1 G2) (Table 2). Influence of technique (SIB vs sequential

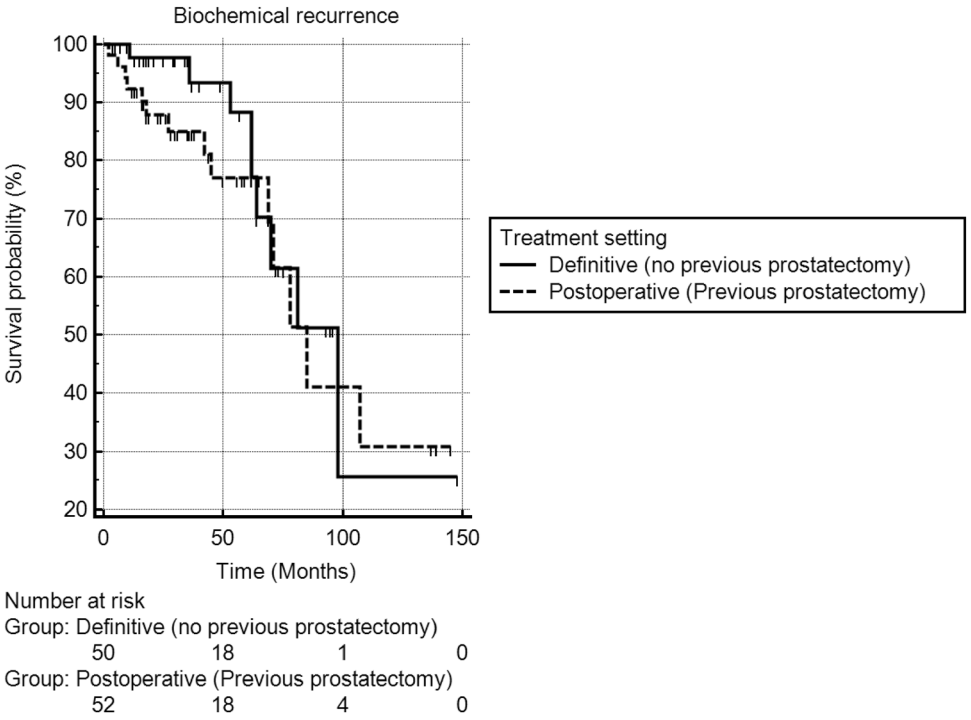

Fig. 1 Kaplan–Meier analysis of b-RFS (Biochemical Recurrence-Free Survival)

boost administration) was negligible regarding acute GI toxicity ($P=0.55$), acute GU toxicity ($P=0.42$), late GI toxicity ($P=0.82$) or late GU toxicity ($P=1$). No significant differences were detected between patients treated with total boost dose $\leq$ or >60 Gy in terms of acute GI toxicity ($P=0.88$), acute GU toxicity ($P=0.32$), late GI toxicity (0.14) or late GU toxicity ($P=0.84$).

Discussion

Overall, data from the present analysis showed promising results after WPRT using and IMRT/VMAT boost on positive pelvic nodes, both in the definitive and postoperative setting. To our knowledge, this is the largest multicentric series assessing clinical outcomes in a similar population. Previous reports from literature showed the technical feasibility and an acceptable tolerability profile of this approach [28–30]. Feasibility of this treatment strategy was demonstrated also in a prospective phase I trial, testing a dose-escalated regimen on the whole pelvis of 79 high-risk or cN1 patients, with a 5 Gy boost to positive nodes [31]. Muller et al. collected data about 39 patients treated with pelvic IMRT to 45–50.4 Gy, 21 of whom received a radiation boost with total doses ranging between 60 and 70 Gy concomitant to ADT. Also in this case, a mixed cohort of postsurgical and radically treated patients was included in the analysis. Authors reported a PSA control and cancer-specific survival of 67 and 97% at 5 years, respectively [32]. Moreover, salvage RT on macroscopic relapse was demonstrated as a valid therapeutic option in patients with macroscopic relapse [33]. Our data are favorably comparable with conventional local therapy in association with ADT in cN1 patients, considering that 5-year OS ranged between 71.5 and 78.8% [6, 7], while reported crude 10-year survival ranged between 45 and 62.7% [3, 4]. Treatment intensification with IMRT/VMAT boost could improve clinical outcome in this population. However, a comparison with the available literature is very difficult, due to the heterogeneity of reported data. In patients with persistence/recurrence of pelvic disease after RP, another interesting issue could be represented by the comparison of elective nodal irradiation and stereotactic body radiation therapy (SBRT). De Bleser et al. recently published a retrospective multicentric comparison of these two approaches in 2019, underlining that SBRT could expose patients to higher risk of nodal recurrences and hypothesizing that elective nodal irradiation should be the treatment of choice [34]. In our opinion, clinical presentation should mainly guide management decisions, reserving a stereotactic approach for indolent disease. Furthermore, SBRT could be an optimal treatment option for patients developing metachronous oligorecurrence after a reasonable time after radical prostatectomy, aiming to delay ADT start [35]. Conversely, this approach could be ineffective when synchronous pathological lymph nodes are present or in the early postoperative setting, suggesting aggressive disease behavior. In these cases, prophylactic pelvic irradiation may improve loco-regional control. In this scenario, the availability of new tracers for metabolic imaging, like Ga-PSMA or 18F-Fluciclovine, may further improve the patient's

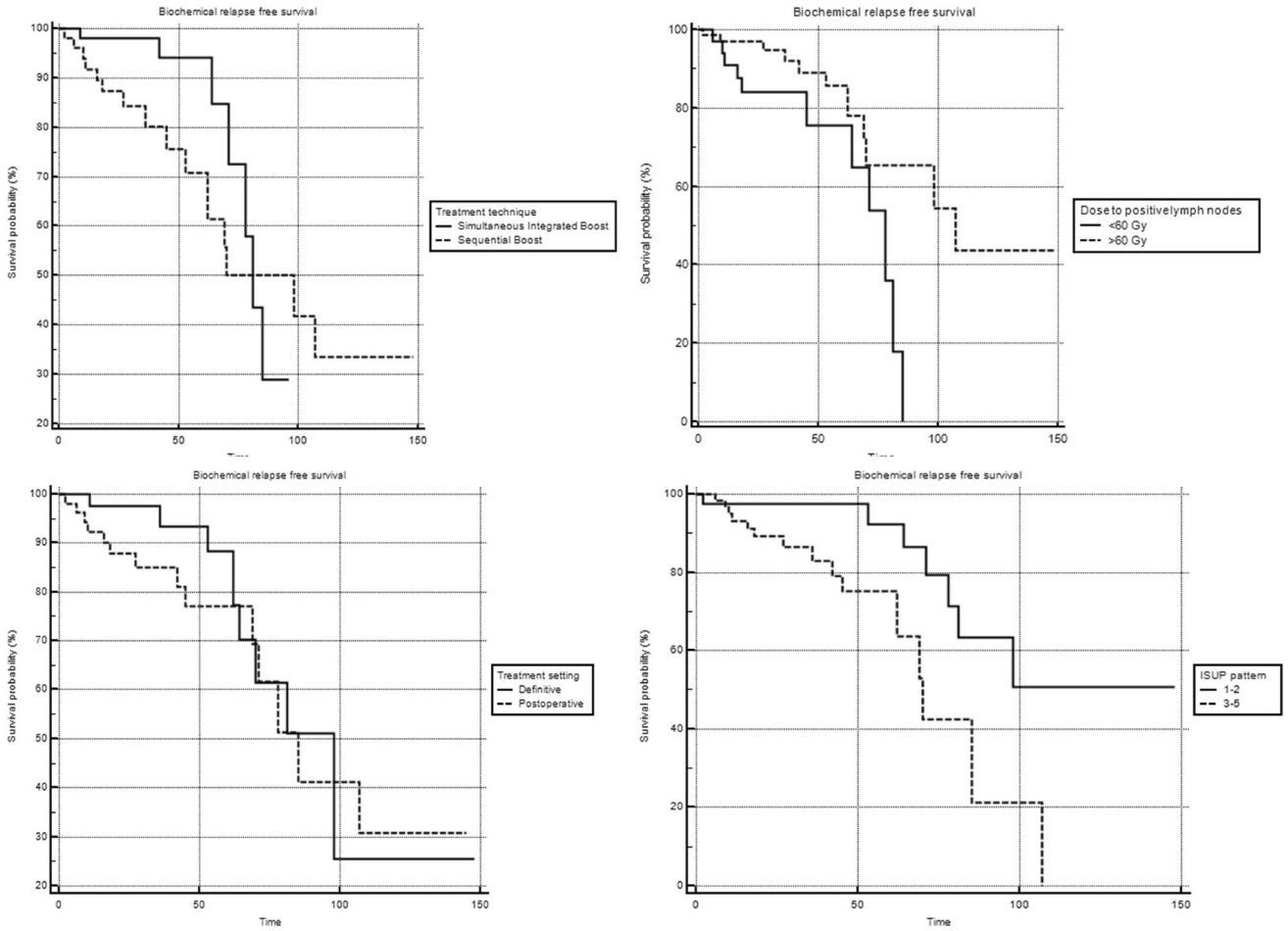

Fig. 2 Cox proportional hazards model. ISUP pattern < 2 and total dose > 60 Gy to positive pelvic nodes were significant predictors of improved b-RFS (HR = 0.3, 95% C.I. 0.1220–0.7647, $P = 0.0113$ and HR = 3.59, 95% C.I. 1.3245–9.741, $P = 0.01$, respectively). Conversely, treatment setting (postoperative vs definitive) and treatment delivery technique (SIB vs sequential boost) were not associated with significant differences in terms of b-RFS (HR = 0.85, 95% CI 0.338–2.169, $P = 0.743$, and HR = 2.39, 95% CI 0.93–6.111, $P = 0.067$, respectively

Table 2 Rate of genitourinary (GU) and gastrointestinal (GI) adverse events reported

Reported toxicities	
GU acute toxicity	43 (42.1%)
Grade ≥ 2	3 (2.9%)
GU late toxicity	16 (15.7%)
Grade ≥ 2	1 (1%)
GI acute toxicity	47 (46.1%)
Grade ≥ 2	2 (1.9%)
GI late toxicity	13 (12.7%)
Grade ≥ 2	0

selection process, also in case of very low PSA values [36]. Of note, inclusion of RP within multimodal treatment strategy was not associated with improved biochemical-free survival in our series. Considering the significant impact of surgery on urinary continence and erectile function if compared to definitive RT [37], the role of RP should be carefully revised in cN1 patients. Surgery should be performed only when reasonable certainty of survival benefit is expected. Furthermore, significant percentage of cN1 patients could harbor subclinical metastatic disease, undetectable with standard imaging, as suggested by recent results of prospective randomized trials, and high-dose RT using tailored boost on positive nodes may obtain even more significant results when recent advanced metabolic diagnostic examinations such as choline or PSMA PET are used [38–40]. Thus, performing upfront RP may not be the treatment of choice in these cases, while the use of RT on primary tumor is supported for low burden metastatic disease, according to STAMPEDE trial [41]. On the contrary, ≤ 60 Gy boost was significantly associated with worse b-RFS in these patients, suggesting that aggressive RT management plays a key role in their clinical outcomes. Main limitations of the present analysis are related to its retrospective nature and the mixed cohort of patients included. Further treatment intensification

in the complex scenario of cN1 patients could consist in new-generation anti-androgen receptors agents (abiraterone acetate, enzalutamide, apalutamide). Many trials are currently ongoing, testing the feasibility and efficacy of concomitant administration of these drugs in the setting of high-risk/locally advanced PCa [42]. However, none of these drugs is currently available for this purpose outside a clinical trial, and definitive data are awaited.

Conclusion

Results from the current analysis are in keeping with data from literature showing that WPRT and IMRT/VMAT boost on positive pelvic nodes are effective and promising approaches, with limited toxicity, both in postoperative and definitive settings. Interestingly, upfront surgical approach was not associated with better clinical outcomes in these patients, while lower RT dose delivered as a boost to macroscopic nodal evidence of disease apparently yielded inferior biochemical control. Finally, cN1 patients would significantly benefit from modern IMRT-based approach tailored on novel diagnostic imaging (e.g., PSMA or choline PET/TC), while upfront RP could be avoided in this setting without compromising main clinical outcomes.

Declarations

Conflict of interest No conflict of interest has to be declared.

Ethical approval Ethical approval was waived by the local Ethics Committees in view of the retrospective nature of the study and all the procedures being performed were part of routine care. The study was performed according to the Declaration of Helsinki, and written informed consent was obtained for all patients.

Informed consent All patients gave consent for the use of their anonymized data for research and educational purposes. All procedures were performed in accordance with ethical standards of institutional ethical committee.

Consent to participate/Consent for publication All patients gave written informed consent for participation in the study.

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