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Original Article

Radiotherapy for node-positive prostate cancer: 2019 Recommendations of the Australian and New Zealand Radiation Oncology Genito-Urinary group

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ABSTRACT

The management of node-positive prostate cancer is highly variable, with both locoregional and systemic treatment options available. With the increasing use of novel imaging techniques such as PSMA-PET and MRI, combined with the increasing use of surgery for high-risk prostate cancer, clinical and pathological regional nodal disease is being detected at a higher rate and at an earlier stage than previously. This creates a window for a potentially curative management approach. The role of radiotherapy including optimal radiation target volumes and dose, as well as the timing and duration of accompanying systemic therapy remains uncertain. At a workshop in 2017, the Australian and New Zealand Faculty of Radiation Oncology Genito-Urinary Group (FROGG) identified variations in the management of node-positive prostate cancer identified on primary staging or on histopathology at radical prostatectomy. FROGG reviewed the literature and developed a set of evidence-based recommendations on the appropriate investigation and management of clinically and pathologically node-positive prostate cancer. These recommendations encompass imaging techniques, radiation treatment target volumes and doses, as well as the use of androgen deprivation therapy.

The 8th edition of the American Joint Commission on Cancer prostate cancer staging system defines N1 disease as regional nodal metastases located below the aortic bifurcation [1]. Thus, for the purpose of this paper, we define node-positive prostate cancer as N1 disease. The management of newly diagnosed N1 prostate cancer continues to evolve, alongside advances in the early detection of regional and metastatic disease using imaging modalities such as prostate-specific membrane antigen- (PSMA) and choline-positron emission tomography (PET) scans, as well as multiparametric magnetic resonance imaging (MRI). There is some evidence demonstrating the potential benefit of a combination of curative intent pelvic radiotherapy (RT) and androgen deprivation therapy (ADT) in the setting of de novo as well as pathologically node-positive disease [2–9], however, there are no randomised trials specifically investigating the role of RT for patients with involved lymph nodes. Of the studies that have been undertaken, most utilise conventional staging investigations, often without modern RT techniques such as intensity-modulated radiotherapy (IMRT), image-guidance, or dose-escalation.

In order to provide guidance on the radiotherapeutic management of newly diagnosed N1 prostate cancer, the Australian and New Zealand Faculty of Radiation Oncology Genito-Urinary Group (FROGG) has developed a set of recommendations.

Materials and methods

A wide variation in the management of node-positive and recurrent prostate cancer was identified by FROGG, prompting the development of evidence-based recommendations. A working party of FROGG members reviewed the current literature, and

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drafted an initial set of recommendations. In April 2017, a two-day workshop was held by FROGG, addressing the management of node-positive prostate cancer, as well as the management of recurrent prostate cancer [10]. Workshop participants included sixty-two specialists in radiation oncology, medical oncology, urology, radiology and nuclear medicine from Australia, New Zealand and the United States. During the workshop, the draft recommendations were presented, discussed, and modifications were made. Following the workshop, the FROGG working party reviewed and finalised the recommended guidelines on node-positive prostate cancer, incorporating evidence from recent relevant publications.

Results

The FROGG executive committee approved the final recommendations which include the levels and grades of evidence as described by the Oxford Centre for Evidence-based Medicine [11], and supporting references (Tables 1 and 2). Given that many of these recommendations are based on lower level of evidence, when considering management of node-positive prostate cancer, individual patient circumstances and preference should be taken into consideration, and patients should be encouraged to participate in a clinical trial, if available.

Discussion

Clinically node-positive prostate cancer at initial diagnosis

Recommended staging investigations

Approximately 5–10% of patients with newly diagnosed prostate cancer will have synchronous nodal metastases based on conventional staging with computed tomography (CT) [12]. This proportion has increased with the use of more recent imaging techniques, such as PSMA-PET/CT and MRI scans. Compared to conventional CT scans, Gallium-68 PSMA-PET/CT is more accurate for nodal staging prior to both primary and salvage lymph node dissection [13,14]. A meta-analysis of the diagnostic accuracy of CT and MRI staging of pelvic lymph nodes for prostate cancer reported per-patient pooled sensitivity of approximately 40% and specificity of 82% [15]. Systematic reviews and meta-analyses of Gallium-68 PSMA PET/CT for primary staging report patient-based analysis pooled sensitivity for lymph node detection of 61–77% and specificity of 97% [16,17].

Staging Gallium-68 PSMA-PET/CT prior to primary treatment of advanced prostate cancer has been shown in a meta-analysis to be positive for disease outside the prostate in 32% of cases [17,18]. A study of Gallium-68 PSMA PET/CT scans as a staging test prior to definitive RT of 109 men with intermediate- or high-risk prostate cancer documented that PSMA PET/CT resulted in the upstaging of 6.4% of patients to M1 disease, 15% from N0M0 to N1M0, and downstaged 2.8% from M1 to M0 [19]. Similar findings were described in another study of PSMA PET/CT, with a change of management intent in 21% of cases [20]. A review of various prostate cancer-specific PET tracers for recurrent disease, demonstrated higher rates of disease detection with Gallium-68/Fludeoxyglucose-18 PSMA tracer compared to choline and fluciclovine-based tracers [21]; with similar findings also reported in prospective studies directly comparing PSMA and choline [22,23].

PSMA-PET/CT scans are a relatively new technology with caveats previously outlined in the FROGG paper on relapsed prostate cancer such as false-positive, false negative and indeterminate results [10]. We recommend that patients being considered for curative intent treatment for N1 prostate cancer be offered a PSMA-PET/CT, if available, in order to provide further information on the extent of their disease and help in the accurate delivery of RT. PSMA-PET/CT scans should be performed and interpreted by experienced nuclear medicine physicians, and be reviewed in a multidisciplinary team meeting.

Table 1
Summary of recommendations for the use of radiotherapy for newly diagnosed clinically node-positive (cN1) prostate cancer.

Recommendation	Level of evidence	Grade of evidence	References
Staging with PSMA-PET/CT, if available, should be offered to patients with clinically suspicious lymph nodes on conventional imaging	5	D	[13–23]
RT to the prostate and pelvic lymph nodes, combined with ADT is associated with improved disease-free and overall survival, compared to ADT or RT alone	2b	B	[2–7,25–28]
The preferred RT target volume includes the prostate and bilateral pelvic lymph nodes, delineated in accordance with published guidelines	5	D	[35–36]
Elective pelvic lymph nodes should be treated to doses of at least 45–54 Gy EQD2	5	B	[25,36,41–46]
Gross nodal disease should be treated to a higher dose while maintaining safe normal tissue dose constraints. Using appropriate image-guidance and where safe, doses of at least 60 Gy EQD2 are recommended	5	D	–
Long term ADT of 18 months to 3 years is recommended	5	B	[41,60–61]

Abbreviations: PSMA-PET = prostate-specific membrane antigen-positron emission tomography. RT = radiotherapy. ADT = androgen deprivation therapy. EQD2 = equivalent dose in 2-Gy fractions.

Table 2
Summary of recommendations for the use of radiotherapy for pathologically node-positive (pN1) prostate cancer post-prostatectomy.

Recommendation	Level of evidence	Grade of evidence	References
Observation, ADT, or ADT with RT are possible treatment options, and treatment decisions should be individualised according to risk of recurrence and patient preference	1b	A	[8–9,68–69,72,79–81]
RT to the pelvic lymph nodes and prostate bed combined with ADT should be discussed with patients by a radiation oncologist	2b	B	[8–9,72,79–81]
The optimal duration of ADT when given concurrently with RT is not known. A duration of 6 months to 3 years of ADT is recommended	5	D	–
The preferred RT target volume includes the prostate bed, the known involved nodal regions and bilateral pelvic lymph nodes, delineated in accordance with published guidelines	5	D	[35,36]
Elective pelvic lymph nodes should be treated to doses of at least 45–54 Gy EQD2	5	B	[25–26,41–46]

Abbreviations: ADT = androgen deprivation therapy. RT = radiotherapy. EQD2 = equivalent dose in 2-Gy fractions.

The significance and clinical benefit of detecting additional metastases using PSMA-PET/CT over conventional imaging is unclear, and FROGG recommends that any major changes in management based on PSMA-PET/CT imaging are undertaken with caution. If additional disease is detected beyond the pelvis, this should not necessarily preclude a patient who is staged as M0 on conventional imaging from being treated with definitive doses of RT. Pelvic nodal RT doses and volumes may be modified based on PSMA-PET/CT findings, however, there is no current evidence that this will result in improved clinical outcomes. There is therefore a need for well-designed controlled trials evaluating the impact on patient outcome of treatment decisions based on PSMA-PET/CT imaging compared to conventional imaging [24].

Role of definitive RT with ADT

There is no prospective randomised data specifically examining the role of RT for patients with clinically node-positive (cN1) prostate cancer. Evidence supporting its use is derived from non-randomised analyses (Table 3) and extrapolation from the proven benefit seen in randomised studies of locally advanced disease [2–7,25–28].

In men with high-risk or locally advanced prostate cancer, two large randomised controlled trials (RCTs) have demonstrated the addition of RT to ADT approximately halves the risk of prostate-cancer specific mortality and improves 10-year overall survival (OS) by 6–10% [25–28]. Unlike SPCG-7 which mandated node-negative disease [27,28], the PR.3/PR07/Intergroup RCT included almost 20% of patients without pelvic lymph node staging, as well as 25% of patients with PSA > 50 ng/mL, a large proportion of whom were likely to be harbouring pelvic lymph node metastases [25,26].

Radiation Therapy Oncology Group (RTOG) 96–08 has been the only RCT specifically designed to evaluate the combination of RT and ADT in patients with N1 prostate cancer, but the study closed prematurely due to poor accrual. An RCT of men with locally advanced prostate cancer treated with RT versus RT and orchiectomy included 39 men (43% cases) with surgically lymph node-staged N1 disease [29]. The addition of immediate orchiectomy resulted in a statistically significant difference in OS in the N1 cohort that was not demonstrated in node-negative cases. A retrospective unplanned analysis of 173 men with biopsy-proven involved lymph nodes in the RTOG 85–31 RCT of RT versus RT combined with ADT, reported that combined therapy resulted in higher rates of OS (9-year OS 62% vs 38%) and biochemical control, with a lower incidence of distant metastases and disease-specific failure [2]. A retrospective single institution study of 255 patients with subclinical biopsy-proven N1 disease also found that combination RT and ADT resulted in improved OS, freedom from distant metastases and freedom from biochemical relapse, compared to ADT alone [4].

Exploratory analysis of the control arm in the STAMPEDE trial [3] and several registry analyses [5–7], have shown improved outcomes with the addition of RT to ADT in cN1 prostate cancer patients. Of the 157 cN1 non-metastatic prostate cancer cohort in the STAMPEDE trial, the addition of RT to ADT was associated with improved 2-year failure-free survival (89% vs 64%), even after adjusting for Gleason score, PSA, age and performance status [3]. However, the heterogeneous and non-randomised nature of these analyses limits the drawing of firm conclusions from this data [30]. Two separate analyses of cN1 prostate cancer patients in the Surveillance, Epidemiology, and End Results (SEER) database reported that local treatment with RT was associated with significantly improved overall and prostate-cancer specific survival compared to no RT [5,6]. However, these studies lacked information regarding the use of ADT. Lin et al's series of 636 matched samples of cN1 patients from the National Cancer Data Base (NCDB) found the addition of RT to ADT was associated with a significant improvement in OS (5-year OS 72% vs 53%) [7]. Another observational analysis of the NCDB of cN1 prostate cancer, found that the addition of local therapy with either radical prostatectomy (RP) or RT improved OS, with no difference in survival between RP and RT [31].

Several existing guidelines recommend pelvic RT combined with ADT in patients with newly diagnosed cN1 prostate cancer. The 2018 National Comprehensive Cancer Network (NCCN) guidelines recommend nodal irradiation and dose-escalation to positive nodes "as dose-volume histogram parameters allow" [32]. Long-term ADT given concomitantly with RT is recommended unless medically contraindicated. Surgery is not included as a treatment option for cN1 disease in the NCCN guidelines. The 2017 EAU/ESTRO/SIG guideline recommends that patients who are cN1 at diagnosis be offered pelvic external beam radiation combined with long-term ADT, although RP and extended pelvic lymph node dissection may be offered in selected patients as part of multimodal therapy [33]. However, there are differing recommendations from other relevant organisations. For example, the Cancer Council Australia's Prostate Cancer Guidelines from 2010 state that the role of RT in node-positive disease is yet to be defined, although these older guidelines may not be relevant to today's practice in light of more recent evidence. [34].

The role of surgical management with RP and lymphadenectomy is beyond the scope of this paper. Nonetheless, surgery is a

Table 3
Studies of definitive radiotherapy for clinically node-positive (cN1) prostate cancer.

Reference	Study design	Patient cohort	Outcomes	No RT	RT	RT volume
Zagars, 2001 [4]	Retrospective series	Biopsy-proven N1, *n* = 255, all received ADT	10-year FFR	25%	80%	Prostate
			10-year LC	49%	89%	
			10-year FFDM	56%	85%	
			10-year OS	46%	67%	
Tward, 2013 [6]	Retrospective SEER database analysis	cN1, *n* = 1100, no information on ADT	10-year PCSS	50%	63%	Not described
			10-year OS	29%	44%	
Rusthoven, 2014 [5]	Retrospective SEER database analysis	cN1, *n* = 796, no information on ADT	10-year PCSS	53%	67%	Not described
			10-year OS	29%	45%	
Lin, 2015 [7]	Retrospective NCDB analysis	cN1, *n* = 3540, all received ADT	5-year OS	49%	72%	Not described
James, 2016 [3]	Prospective RCT, unplanned cohort analysis	cN1, *n* = 177, all received ADT	2-year FFS	53%	81%	Majority prostate + pelvis

Abbreviations: RT = radiotherapy. N1 = node-positive. ADT = androgen deprivation therapy. FFR = freedom from relapse. LC = local control. FFDM = freedom from distant metastases. OS = overall survival. SEER = Surveillance, Epidemiology, and End Results. PCSS = prostate cancer-specific survival. NCDB = National Cancer Data Base. RCT = randomised control trial. FFS = failure-free survival.

local therapy that may be considered in highly selected men with cN1 prostate cancer [31,33]. However, these men should be counselled that adjuvant or salvage RT following surgery may still be required.

A Korean phase 3 trial (NCT03241537) is currently investigating the role of adding pelvic and prostate RT to 2–3 years of ADT in men with cN1 prostate cancer. The ENZARAD trial (NCT02446444) evaluating the additional benefit of enzalutamide to RT and ADT for men with high-risk and/or cN1 prostate cancer has recently closed to accrual. ENZARAD allowed for staging PSMA-PET/CT scans, although the trial based enrolment on conventional imaging. This trial provision will allow interrogation of the data in order to determine the additional value of this imaging modality compared to conventional staging investigation.

Based on the consistent benefit seen for locoregional therapy in RCTs of men with locally advanced disease, as well as retrospective series of patients with node-positive disease, we recommend patients with cN1 disease at diagnosis should be considered for a multimodal treatment approach. An informed discussion of management options, including curative intent RT to the prostate and pelvis combined with ADT, should be undertaken between the patient and a radiation oncologist. Discussions may also involve multidisciplinary team members including a urologist and medical oncologist.

Recommended RT target volume

Definitive RT for cN1 prostate cancer should encompass the prostate and pelvic lymph nodes, ensuring inclusion of known regional nodal metastases. Contouring guidelines detailing delineation of pelvic nodal volumes have been published by the RTOG and PIVOTAL trial groups [35,36]. These guidelines include delineation of the obturator, external and internal iliac, and presacral lymph nodes. Although the common iliac lymph nodes have been shown in small series to be involved on PET imaging in up to 18% of cases during primary staging [37], as well as account for up to 20% of positive lymph nodes during investigation of biochemical relapse [38,39], routine inclusion of the entire region results in an increased treatment volume and potential for increased bowel toxicity. Spratt et al. reported patterns of failure after prostate only RT and found extending the pelvic field superior border to L4/L5 would have covered 93% of patients with isolated nodal failure, and on multivariate analysis, ≥T3a disease predicted for the presence of common iliac and superior promontory lymph nodes [40]. These data suggest not all patients will benefit from inclusion of the common iliac lymph nodes, and the extent of elective nodal irradiation should therefore be individualised, taking into consideration the location and level of nodal involvement, prognostic features, dose to organs at risk, and patient factors such as age and comorbidity.

Recommended RT dose

When treating the prostate and pelvic lymph nodes with definitive RT, dose-escalation to the clinically involved nodes should be considered in order to potentially eradicate gross disease. In the published RCTs of definitive RT, elective nodal irradiation doses ranged from 45–50.4 Gy equivalent dose in 2 Gy fractions (EQD2) [25,26,41–46]. Non-randomised studies have utilised higher elective nodal doses up to 56 Gy EQD2 [47,48]. A number of small studies have described the role of dose-escalation using a simultaneous integrated boost technique with IMRT, volumetric modulated arc therapy or tomotherapy, to macroscopic lymph node metastases, and report a low incidence of Grade 3 acute toxicity [48–50]. The only study reporting late toxicity at 3 years, treated the prostate to 69.3 Gy, elective pelvic nodes to 45 Gy and gross nodal disease to 65 Gy in 25 fractions using a simultaneous integrated boost technique [49]. The 3-year actuarial risk of late grade 2 genitourinary and gastrointestinal toxicity was 34% and 20%, respectively.

The NCCN guidelines recommend dose-escalation to clinically positive nodes as dose-volume parameters allow [32]. Guidelines from a Singapore group recommend a dose range of 54–79.2 Gy to involved nodes, depending on the proximity of the nodes to neighbouring normal tissue [51]. We recommend dose-escalation to more than 60 Gy EQD2 to the involved nodal gross tumour volume, while respecting dose constraints of adjacent organs at risk. We recommend the elective nodal region be treated to doses of at least 45–54 Gy EQD2. The majority of published RCTs of prostate and pelvic nodal RT have utilised conventional fractionation, and this approach is recommended. The RCTs demonstrating equivalency of moderate hypofractionation are applicable to prostate only RT, and the recently published ASTRO guidelines regarding moderate and ultra-hypofractionation specifically identified radiation to the pelvic nodes as out of scope [52–56]. However, in experienced centres using image-guidance and IMRT, moderate hypofractionation to the prostate ± nodal region may be considered [57–59].

Duration of ADT with definitive RT

The optimal duration of ADT combined with RT for cN1 prostate cancer is unknown, and recommendations are based on extrapolation from studies of high-risk prostate cancer. With the increasing utilisation of PSMA-PET/CT for staging of high-risk patients, a proportion of patients considered as cN0 based on conventional imaging are 'upstaged' to cN1 disease. Men with cN1 disease thus represent a heterogenous group, ranging from the presence of a solitary subcentimetre lymph node detected on PSMA-PET/CT alone to multiple macroscopic pelvic lymph nodes.

Most clinical guidelines recommend at least 2–3 years of long-term ADT when combined with pelvic radiation [32,33]. Existing Australian guidelines recommend that if RT is used for cN1 disease, that long-term ADT is recommended [32]. The recent TROG 03.04 RADAR RCT of 18 months versus 6 months of ADT combined with RT for locally advanced prostate cancer demonstrated improved prostate cancer-specific survival (PCSS) but no OS benefit with 18 months' duration [60]. The Nabid RCT of 36 months versus 18 months of ADT for high-risk prostate cancer was unable to demonstrate superiority of 36 months over 18 months with respect to PCSS and OS, nor was it able to demonstrate non-inferiority of 18 months of ADT [61].

Extrapolating from the locally advanced prostate cancer data, we recommend 18 months to 3 years of ADT for men receiving RT for cN1 disease, with duration of ADT based on assessment of patient's comorbidities, tolerance to ADT and burden of disease.

Pathologically node-positive prostate cancer

Up to 15% of patients are found to have pathological nodal (pN1) metastases at the time of RP [62], although contemporary series report proportions as low as 2% [63]. Historically, these patients were considered to have metastatic disease and therefore be incurable. However, more recently, favourable long-term outcomes have been described in a subpopulation of these patients, with 10-year PCSS rates of 70–80% reported in selected series [8,63].

Adjuvant therapy

Men with pN1 disease represent a heterogeneous population, and as such, an individualised treatment approach accounting for patient and tumour characteristics is recommended. A retrospective series of 369 pN1 patients post-RP and extended pelvic LND who did not receive any adjuvant therapy, reported 10-year biochemical relapse-free rates of 28%, PCSS of 72% and probability of

freedom from distant metastases of 65% [64]. Another series of 1003 men with pN1 disease documented a 10-year biochemical relapse-free rate of 41% in the 108 men who did not receive any adjuvant therapy [65]. Therefore, not all men with pN1 disease will relapse and therefore potentially benefit from adjuvant therapy after RP.

Prognostic variables to guide management include the number of positive lymph nodes, Gleason score, T-stage, and margin status [9,66,67]. Database and retrospective reviews of pN1 patients reported poorer PCSS and OS associated with ≥3 involved lymph nodes, Gleason score ≥8, positive margins, and ≥pT3 disease [9,66]. Briganti et al. had similar findings, but determined a cut-off of ≤2 involved nodes predicting for improved PCSS [67]. All of these studies reported that adjuvant RT was associated with improved PCSS. Moschini et al. developed low-, intermediate- and high-risk categories based on these variables [66], which may serve as a guide for the recommendation of adjuvant therapy, although these have not been prospectively validated.

Role of adjuvant ADT alone

In patients found to have pathological nodal disease, early adjuvant ADT has been shown in the Eastern Cooperative Oncology Group (ECOG) 3886 randomised trial to result in improved overall, prostate-cancer specific and progression-free survival, with median OS of 13.9 years compared to 11.3 years [68,69]. However, this small RCT of immediate ADT versus observation included in its protocol that delayed ADT was to be commenced on development of clinical local or distant progression, and that PSA level was not a criterion for initiation of ADT. As this management approach is not a common practice in the modern era, the study's applicability to contemporary practice is questionable. In the European Organisation for Research and Treatment of Cancer (EORTC) 30846 RCT of immediate versus delayed ADT in men with pN1 prostate cancer who did not undergo RP, there was a non-statistically significant increase in the hazard of death in the delayed arm; the trial was underpowered and unable to demonstrate non-inferiority of delayed ADT [70]. An observational study using the SEER database also did not find any difference in 10-year OS or PCSS with the use of ADT within 120 days of RP in men with pN1 disease [71]. Similarly, both an NCDB analysis and retrospective comparative analysis of pN1 patients were unable to demonstrate an OS benefit with adjuvant ADT alone compared to observation [8,72]. This would suggest there is a cohort of men who will not benefit from immediate lifelong ADT in the absence of RT, and consideration should be given for reserving ADT for patients requiring salvage therapy. However, because of the shortcomings described in the ECOG and EORTC RCTs, and limitations when interpreting population-based studies, the ideal indication and timing of post-operative ADT for pN1 disease remains to be determined.

Role of combined adjuvant ADT and RT

There are no randomised trials comparing ADT alone with ADT and RT post-RP in patients with pN1 disease. All 3 of the adjuvant post-RP RCTs excluded patients with known nodal metastases [73–78].

Isolated local and/or regional recurrences in pN1 patients do occur, with a retrospective review of 800 pN1 men, describing the prostate bed and/or regional lymph nodes as the first of site of recurrence in 31% of the 183 men with radiologically evident disease [65]. Despite clinical recurrence, the 5-year PCSS rate was almost 60%.

Several retrospective series have demonstrated that the addition of adjuvant RT to ADT in patients with nodal metastases detected at prostatectomy results in prolonged biochemical relapse-free, cancer-specific and OS rates [8,9,72,79–81] (Table 4). A matched analysis of pN1 patients post-RP showed that adjuvant RT in addition to ADT was associated with significantly higher OS and PCSS, with 10-year OS rates following tri-modality therapy of up to 74% at 10 years, compared to 55% with adjuvant ADT alone, and 10-year PCSS 86% vs 70% [81]. The benefits of combined adjuvant ADT and RT were maintained regardless of the number of involved nodes. The NCDB retrospective review of post-RP patients found that the addition of RT to adjuvant ADT was associated with a 7% improvement in OS at 5 years (88% vs 81%), again irrespective of the total number of involved nodes, extent of lymph node dissection, margin status, Gleason score or pre-treatment PSA level [9]. Touijer et al. reported outcomes of more than 1300 patients with pN1 disease following RP who were managed with observation, lifelong ADT, or adjuvant RT combined with ADT [8]. In this retrospective series, a combined modality approach with ADT and RT was associated with superior OS and PCSS compared to either ADT alone or to observation. From these data, a risk-adjusted tool based on Gleason score, pathological T-stage, margin status, and the number of positive nodes was developed to assist in quantifying the survival benefit of adjuvant ADT and RT compared to no adjuvant treatment. The study also found that despite more advanced pathological features and the presence of multiple lymph node metastases, adjuvant ADT and RT resulted in a greater magnitude of survival benefit, suggesting the importance of maximal locoregional control. Another cohort of more than 7000 pN1 patients from the NCDB reported significantly higher OS rates with combined adjuvant ADT and RT, compared to adjuvant ADT alone or observation [72]. However, a propensity score model of SEER data for men with pN1 disease found no difference in OS or PCSS

Table 4
Studies of adjuvant radiotherapy for pathologically node-positive (pN1) prostate cancer post-prostatectomy.

Reference	Study design	Patient cohort	Outcomes	No RT	RT	RT volume
Da Pozzo, 2009 [79]	Retrospective series	*n* = 250, all received ADT	10-year BCR-FS 10-year PCSS	42% 72%	51% 70%	Majority prostate bed + pelvis
Briganti, 2011 [81]	Retrospective matched analysis	*n* = 364, all received ADT	10-year PCSS 10-year OS	70% 55%	86% 74%	Majority prostate bed + pelvis
Abdollah, 2014 [80]	Retrospective series	*n* = 1107, all received ADT	8-year PCSS 8-year OS	86% 75%	92% 88%	Not described
Wong, 2016 [72]	Retrospective NCDB analysis	*n* = 7225	5-year OS with ADT 5-year OS without ADT	83% 85%	89% 88%	Majority prostate bed + pelvis
Jegadeesh, 2017 [9]	Retrospective NCDB matched analysis	*n* = 1652, all received ADT	5-year OS	81%	88%	Prostate bed ± pelvis
Touijer, 2018 [8]	Retrospective series	*n* = 1388, majority received ADT	PCSS with ADT OS with ADT	Ref. Ref.	HR = 0.41 HR = 0.46	Prostate bed + pelvis

Abbreviations: RT = radiotherapy. ADT = androgen deprivation therapy. BCR-FS = biochemical relapse-free survival. PCSS = prostate cancer-specific survival. OS = overall survival. NCDB = National Cancer Data Base. Ref. = reference. HR = Hazard ratio.

with the addition of adjuvant RT, despite equivalent use of adjuvant ADT [82].

Abdollah et al. aimed to identify which patients with pN1 disease would benefit from adjuvant RT. In their series of men treated with RP, extended pelvic lymph node dissection, and adjuvant ADT, the addition of RT resulted in an 8-year OS rate of 88% compared to 78% without adjuvant RT, and it also improved PCSS [80]. Men with ≤2 involved nodes but Gleason score ≥7 and locally advanced disease (pT3b/pT4 and/or positive surgical margins), or men with 3–4 positive lymph nodes irrespective of other tumour characteristics were demonstrated to have a higher relative risk reduction in cancer-specific mortality with the addition of RT, from 70% to 79%. Unlike the other reported series, there was no benefit of adjuvant RT for men with ≤2 involved nodes and organ-confined or low-grade disease, nor in those with >4 involved nodes, however, this study included only those men who underwent an extended pelvic lymph node dissection, and its findings may therefore not be applicable to all patients. Nini et al. found pT2b/pT3a disease or shorter time to biochemical recurrence predicted for an increased risk of local recurrence, while predictors for systemic recurrence were Gleason score 9–10 and time to biochemical recurrence [65].

In interpretation of these results, it is important to appreciate that retrospective reviews are limited by selection bias and confounders which can influence outcomes. These limited data suggest that although combined adjuvant RT and ADT is associated with improved survival outcomes in patients with pN1 disease, there may be a cohort of men at low risk of locoregional only recurrence, who may not benefit from adjuvant RT, and could be observed and offered salvage RT with ADT if their PSA rises.

Patient selection for adjuvant therapy should be individualised and tailored. The NCCN guidelines suggest observation, ADT, or ADT and RT are all valid treatment options for men with pN1 disease [32]. The EAU-ESTRO-SIOG guidelines also include observation, ADT, or ADT and RT [33]. They describe a more favourable group where observation or expectant management could be considered (≤2 involved lymph nodes and PSA < 0.1 ng/mL and in the absence of extracapsular extension). In their guidelines, adjuvant ADT may be offered for pN1 disease, with a discussion regarding the addition of RT. A German trial is currently accruing and randomises men with pN1 disease and low tumour burden (defined as micrometastases or ≤2 macrometastases) to adjuvant RT or observation [83].

Based on the limited retrospective evidence demonstrating improved survival with adjuvant RT combined with ADT post-RP, patients with pN1 prostate cancer should be presented in a multidisciplinary meeting with histopathology and imaging reviewed, and discussion amongst the urology, radiation oncology and medical oncology teams. FROGG also recommends these patients be referred to a radiation oncologist to discuss the potential benefits and side effects of adjuvant RT and ADT, to enable informed decision-making regarding adjuvant therapy.

The optimal duration of ADT when given concurrently with adjuvant RT for pN1 disease is not known. In the salvage setting for pN0/Nx disease, the 2 RCTs investigating the role of short-term ADT (4–6 months) in addition to salvage RT to the prostate bed ± lymph nodes reported improved rates of freedom from progression with the addition of short-term ADT [84,85]. An OS benefit was demonstrated in the RTOG 96-01 RCT with the addition of 2 years of anti-androgen therapy, with the greatest benefit on post-hoc analysis in those men with more unfavourable clinical and pathological features [86]. In the setting of intact high-risk prostate cancer, longer durations of up to 36 months of ADT are recommended when combined with RT.

It remains uncertain how the evidence regarding the use of ADT in the intact and salvage setting is applicable to the adjuvant pN1 cohort. In the adjuvant setting, potential microscopic disease, rather than macroscopic disease is being treated, and pN1 disease can also range from a single micrometastatic deposit to multiple pathological involved lymph nodes. Given their high-risk status, in the majority of men with pN1 disease, 18–36 months of concurrent ADT with RT is appropriate. However, for patients with more favourable prognostic features, comorbidities limiting tolerance to ADT, or patient preference, a minimum of 6 months' duration of ADT can be offered.

Recommended RT target volume

Similar to definitive RT for cN1 prostate cancer, if recommending adjuvant RT for pN1 prostate cancer, the known involved nodal regions as well as bilateral pelvic lymph nodes, should be included in the elective nodal volume. The extent of elective nodal irradiation requires an individualised approach.

FROGG recommends inclusion of the prostate bed consistent with the target volume used in the retrospective studies supporting adjuvant RT for pN1 disease (Table 4), as the majority of men with pN1 disease also have adverse prognostic features for local recurrence. Omission of prostate bed RT can be considered in highly select cases of pT2 disease with negative margins in order to minimise morbidity, particularly in those with significant post-operative urinary symptoms.

Recommended RT dose

In the adjuvant setting, we recommend the elective nodal region receive doses of at least 45–54 Gy EQD2, and the prostate bed, a minimum dose of 64–66 Gy EQD2 [10]. The use of IMRT and image-guided RT is highly recommended to ensure adequate target volume coverage, and to minimise dose to organs at risk.

Conclusion

In conclusion, in response to the uncertainties and limited high-level evidence for the management of cN1 and pN1 prostate cancer, FROGG has developed recommendations on the role of RT for this group of patients. This is especially important in an era where new imaging modalities can detect nodal involvement at an earlier stage, and surgery is being performed in a greater percentage of high-risk and potentially node-positive patients. RT has been shown to play a role in improving clinical outcomes in men with cN1 and pN1 prostate cancer. FROGG recommends these men be evaluated in a multidisciplinary setting, with subsequent referral to a radiation oncologist to discuss their RT management options.

Declaration of Competing Interest

None of the authors have any conflict of interest to declare.

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