The role of elective pelvic radiotherapy in clinically node-negative prostate cancer: A systematic review

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A B S T R A C T
The role of elective radiotherapy of the pelvic nodal regions in clinically node-negative prostate cancer patients remains highly controversial. This review will address the difficulty of non-invasive nodal staging, even with more advanced imaging techniques, and will show that surgical staging still finds a relatively high percentage of patients with intermediate- or high-risk prostate cancer that have microscopic tumor invasion in the pelvic nodes. Finally, an overview of the current literature on elective pelvic irradiation will be provided.

Prostate cancer (PCa) is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males, accounting for 14% (903,500) of the total new cancer cases and 6% (258,400) of the total cancer deaths in males in 2008 [1]. Although the incidence was already increasing, the introduction of prostate specific antigen (PSA) testing in the early 1990s caused a surge in the diagnosis rate of prostate cancer over the past 20 years and a shift to lower stage and younger age at presentation [2]. The consequence of diagnosing prostate cancer at an earlier stage in younger men is a significant increase in the use of locally aggressive but potentially curative therapies, such as radical prostatectomy (RP) and external-beam radiotherapy (EBRT), possibly resulting in a reduction of mortality rates [3,4].

The clinical behavior of prostate cancer ranges from a microscopic, well-differentiated tumor of little clinical importance, to an aggressive cancer with substantial invasive and metastatic potential. In routine clinical practice, it is paramount to identify those patients who are at risk of dying from their disease. The major prognostic factors of prostate cancer are clinical (TNM) stage, histological grade (i.e. Gleason score), and pre-treatment PSA serum level.

Obviously, locally advanced prostate cancer is by definition an aggressive disease. For instance, in an older surgical series by Epstein et al. with 721 men, only 58.4% and 27.0% of patients with capsular penetration (pT3a) or seminal vesicle invasion (pT3b), respectively, remained progression-free at 10 years follow-up [5]. Moreover, all patients with invasion of adjacent organs (pT4) or lymph node metastases (N1) progressed and ultimately died from their disease.

On the other hand, a significant number of patients with supposed localized disease will also die from prostate cancer. D’Amico et al. stratified these patients into three pre-treatment risk groups, apparently predicting for disease-specific survival [6]. In a study of 7,316 patients with localized PCa, the relative risk of prostate cancer-specific mortality after RP or EBRT was approximately five for intermediate-risk (cT2b or Gleason score 7 or PSA 10–20 ng/mL) and 14 for high risk (cT2c or Gleason score ≥8 or PSA >20 ng/mL) patients versus low-risk (≤cT2a and Gleason score ≤6 and PSA <10 ng/mL) patients. These risk groups correspond to the 2010 version AJCC/UICC prognostic groups [7]. However, there is no definitive consensus on the definition of high-risk disease. Both the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) guidelines define high-risk, localized prostate cancer as cT3a disease or Gleason score ≥8 or PSA >20 ng/mL, and still consider cT2c as intermediate-risk disease [8,9].

Whatever definition is used, intermediate- to high-risk prostate cancer patients, broadly defined as clinical stage ≥cT2b or Gleason score ≥7 or PSA ≥10 ng/mL, clearly benefit from aggressive treatment with surgery and/or radiotherapy [10]. When primary radiotherapy is considered for these patients, there is a consensus that dose-escalation on the prostate improves biochemical disease-free survival (bDFS), while the addition of hormonal treatment...
improves overall survival [11–20]. In contrast, the role of elective radiotherapy on the pelvic nodal regions in clinically node-negative patients remains highly controversial [21,22]. Consequently, enthusiasm for so-called whole pelvic radiotherapy (WPRT) has dwindled. In 1989, still 92% of patients with localized prostate cancer who were treated with EBRT in the United States received WPRT. This number fell to 52% in 1994, and the 1999 patterns of care survey for prostate cancer found that only 23% of cases treated with EBRT received WPRT [23].

This is in marked contrast to other organ sites, such as head and neck cancer, rectal cancer, and gynecological malignancies, where the treatment of lymph node regions is considered standard of care [24–26]. In breast cancer, irradiation to the chest wall and regional lymph nodes after mastectomy significantly improves survival in high-risk patients [27,28]. Moreover, it was recently suggested that axillary dissection might not be necessary in all breast cancer patients with positive sentinel lymph nodes, on condition that they will be treated with adjuvant radiotherapy [29]. On the other hand, elective nodal irradiation has been mostly discredited in lung cancer and Hodgkin’s lymphoma treatment [30,31]. It should be noted that in lung cancer, a possible argument for selective nodal irradiation is the “incidental” irradiation of uninvolved mediastinal areas located in the proximity of the tumor, which effectively amounts to “untended” elective irradiation [32]. In prostate cancer, contemporary highly conformal radiotherapy to the prostate alone results in much less “incidental” radiation dose to the pelvic lymph nodes regions than before. In many cancers, relatively low doses of radiotherapy can successfully eradicate microscopic disease, especially when combined with systemic treatment [24–28]. Ultimately, much depends on the dissemination pattern of each specific cancer: whether it spreads in an orderly and typically contiguous manner from primary organ to lymph nodes and only then to distant metastatic sites, or constitutes a systemic disease from the outset [33]. These questions have not been conclusively answered for prostate cancer, although they have been for other sites.

This review will address the difficulty of non-invasive nodal staging, even with more advanced imaging techniques, and will show that surgical staging still detects a relatively high number of microscopically invaded nodes in patients with intermediate-to high-risk prostate cancer. Finally, an overview of the current literature on elective pelvic irradiation will be provided.

Search strategy and selection criteria

MEDLINE citations were searched for the terms “radiotherapy”, “pelvic”, and “prostate cancer” on June 9th 2013, and this initial search yielded 1679 publications [34]. Only papers published in English since January 1st 1980 were included, resulting in 1438 results. Of those, publications were considered if they either retrospectively or prospectively compared prostate-only radiotherapy versus prostate and pelvic radiotherapy in clinically node-negative patients. Studies on post-operative radiotherapy or lymph-node positive patients were not included. After reviewing titles and/or abstracts, 21 relevant papers were identified. Trial selection results are depicted in Fig. 1.

Lymph node metastasis of prostate cancer

The lymphatic drainage of the prostate follows four major pathways: (1) the lateral pathway along the inferior vesicle vessels to the hypogastric and internal iliac nodes; (2) the posterior pathway from the lower prostate alongside the rectum to the sacral nodes of the promontory; (3) the inferior pathway to the obturator fossa; (4) the ascending pathway from the top of the prostate over the bladder to the external iliac nodes, below the bifurcation of the common iliac artery [35]. The primary drainage area of the prostate therefore consists of at least the internal iliac, obturator, external iliac, and presacral lymphatic nodes. There is no international nomenclature for these lymphatic paths as is the case, for instance, in the head and neck region [24].

Non-invasive nodal staging

Evidently, it is of paramount importance, when deciding on the primary treatment of prostate cancer patients, to accurately detect the presence of pelvic lymph node metastases. Regrettably, non-invasive regional staging for prostate cancer is particularly unreliable. Contrast-enhanced computed tomography (CT) and conventional magnetic resonance imaging (MRI) demonstrate a similarly poor performance in the detection of lymph nodes, with a specificity of at most 40% and a sensitivity of approximately 80% [36]. This can be explained by the fact that conventional imaging relies on nodal size and shape as a diagnostic criterion: only round lymph nodes with a short axis larger than 8 mm and oval nodes with a short axis larger than 10 mm are considered metastatic [37]. Because metastases in prostate cancer are mainly found in lymph nodes with a short axis smaller than 8–10 mm, the use of size and shape criteria is evidently not reliable [36,37].

In an effort to improve staging, positron emission tomography (PET) has been studied, using choline analogs labeled with carbon-11 or fluorine-18 as the radiopharmaceutical. Choline is one of the components of phosphatidylcholine, an essential element of phospholipids in the cell membrane. Malignant tumors show a high proliferation and increased metabolism of cell membrane components that lead to an increased uptake of choline [38]. In one study, this new technique achieved a reported sensitivity and specificity of 80% and 96%, respectively [39]. However, two more recent trials showed a markedly lower sensitivity (of 41% and 56%, respectively), with a comparably high specificity [40,41].

Diffusion-weighted (DW) MRI is an imaging technique able to detect molecular diffusion, i.e. the Brownian motion of water molecules in biologic tissues [42]. DW images are obtained by applying pairs of magnetic field gradients around the refocusing pulse of a T2-weighted sequence. Movement of the tissue water molecules between the two gradients will result in dephasing, depicted as

![Fig. 1. Trial selection.](image-url)
signal loss on the diffusion-weighted images. This signal loss will be proportional to the amount of water molecule movement and the strength of the gradients (b-value). By repeating the sequence with different b-values, the observed signal loss can be quantified using the apparent diffusion coefficient (ADC). DW-MRI appears a promising technique for lymph node staging in squamous cell carcinoma of, for instance, the head and neck or the cervix, although its effectiveness in adenocarcinoma is unknown [43–45].

Our group recently investigated \(^{11}C\)-choline PET-CT and DW-MRI in 36 surgical patients, node negative on CT but with a high estimated risk of lymph node involvement (LNI) [46]. Indeed, almost half of the patients (47%) harbored regional disease, missed on conventional imaging. Disappointingly, sensitivity was extremely low for both investigational techniques (9.4% and 18.8%, respectively), confirming the substantial difficulty of reliably detecting lymph node disease through imaging alone. On the other hand, specificity was high (99.7% and 97.6%, respectively) for both imaging techniques, as well as their negative predictive value (>90%).

Recently, high resolution MRI using lymph node specific contrast agents has been suggested as a novel nodal staging method in prostate cancer. This is called MR lymphography (MRL). The contrast agent used with this technique consists of ultra-small super paramagnetic iron oxide (USPIO) particles, such as ferumoxtran-10, which disrupt the magnetic field and result in signal loss. When these particles are injected intravenously, they are transported by macrophages to normal lymph node tissue. Therefore, normal functioning lymph nodes appear black on MRI 24–36 h after administration of USPIO. In metastatic nodes, however, the signal intensity remains unchanged because of the absence of iron particles. Hari-singhani et al. published a study that presented a sensitivity of 100% and a specificity of 95.7% for MRL on a patient-to-patient basis, with a sensitivity of 90.5% a specificity of 97.8% on a node-to-node analysis [47]. These results were initially confirmed in a large multi-institutional trial from The Netherlands [48]. The high sensitivity (82%) and negative predictive value (96%) of MRL in that study seemed especially promising, suggesting that patients with a negative MRL have a risk of 4% or less of harboring lymph node metastases. In a later study by the same group, MRL detected suspicious lymph nodes in 58 (20%) of 296 patients with intermediate- or high-risk prostate cancer. In 44 patients, the presence of metastatic lymph nodes could be confirmed on pathology; in 14 patients (24.1%) no pathologic nodes were found during routine lymph node dissection, [49]. However, MRL has not yet found its way into routine practice and in most countries it has not even received approval for clinical use [50].

Clearly, imaging is of limited use for the pre-treatment nodal staging of prostate cancer patients. Therefore, clinicians often consult the so-called “Partin tables”, using a combination of clinical stage, Gleason score, and serum PSA levels to predict pathological stage in patients with localized prostate cancer [51,52]. Because of routine PSA screening, patients present at an earlier stage, and consequently, the nomograms have already been updated twice [53,54]. However, these estimates are based on surgical data from radical prostatectomy series with limited lymph node sampling [51–54]. By using the initial Partin tables, Roach et al. have derived a simple equation to approximate the risk of LNI (%) = (2 / \[10^{−5}\])PSA + [(Gleason score – 6) × 10], the so called “Roach equation” [55]. Because this formula has never been updated since its conception in 1994, and has never been rigorously compared to the most recent update of the Partin tables in 2007, its continuing applicability is the subject of much debate [56–58].

Surgical nodal staging

Because of the limited sensitivity and specificity of routine imaging, pelvic LN dissection (LND) remains the most accurate and reliable nodal staging procedure [9]. Surgical series from the PSA era report an incidence of unexpected pelvic metastases in less than 10% of patients who were believed to have localized prostate cancer on imaging [59,60]. However, lymph node involvement is severely underestimated in studies using standard lymphadenectomy, which is limited to the obturator fossa and/or external iliac lymph nodes. For patients with intermediate- to high-risk prostate cancer, extended lymphadenectomy (eLND), including at least the obturator fossa, external iliac, and internal iliac regions, is advised [9,61]. A more extensive dissection not only yields greater numbers of positive nodes but can also identify lymph node involvement when the nodes within a more limited template are negative [62–67]. Table 1 shows the remarkably consistent results from all studies using eLND. Based on these modern series, it can be surmised that occult lymph node metastases will be detected in about 5–6%, 20–25%, and 30–40% of low-, intermediate-, and high-risk prostate cancer patients, respectively [68]. These percentages for intermediate- and high-risk patients are well above the usual threshold for elective nodal irradiation in other cancer types [24–26]. Moreover, these numbers are possibly still an underestimation, given the fact that lymph node metastases are easily missed by conventional pathologic methods [69,70].

Based on the extended lymphadenectomy template, a modern nomogram predicting LNI in patients with clinically node-negative prostate cancer was developed by Briganti et al. [71,72]. This model predicts LNI based on pre-treatment PSA, clinical stage, primary and secondary Gleason grade, and, crucially, the percentage of positive cores [72]. It was not only externally validated by the group from Aachen, but was also proven to be relevant in patients treated between 2006 and 2010 [73,74]. It is to be expected that such an eLND-derived nomogram, including both clinical stage and the percentage of positive cores, can predict LNI more accurately in currently treated intermediate- to high-risk patients than the older nomograms [75].

A promising, and potentially less invasive, alternative to eLND is a sentinel node (SN) procedure. This concept was first introduced by Morton et al. for malignant melanoma in 1992 and has since then been explored in several other solid cancers such as early-stage breast cancer [76]. Usually, a lymphotrophic tracer (often \(^{99m}\)Technetium-nanocolloid) is injected according to an established pattern over the entire prostate under transrectal ultrasound-guidance. The first draining lymph node (i.e. “sentinel” lymph node) can then be detected by single photon emission computed tomography (SPECT), ideally in combination with CT for three-dimensional information. During (open or laparoscopic) surgery, the SN is searched using a gamma probe and resected. The assumption is that if this node is free from cancer cells, the next draining echelons will also be disease-free.

Different institutions have already demonstrated the practical feasibility of the procedure [77,78]. A recent review by Sadeghi et al. reported a high pooled detection rate (93.8%) and low false negative (pooled sensitivity of 94.0%) rate [79]. In our institution, 74 cN0 patients with intermediate- to high-risk prostate cancer received the SN procedure before surgery [80]. In total, 37 patients harbored disease in the lymph nodes, which was detected through a positive SN in 28 patients. Of those 28 patients, 13 patients had metastatic lymph nodes elsewhere in the pelvis, while in 15 patients the SN was the only involved lymph node. It might be interesting to include SN procedure in future randomized trials on elective pelvic radiotherapy; patients with positive SN have probably around 50% chance of still retaining microscopic pelvic disease, and could potentially benefit from pelvic radiotherapy [77–80]. On the other hand, patients with a negative SN have a maximum chance of 15–20% of still harboring pelvic disease and could probably be spared elective radiotherapy [77–80].
Obviously, these SN studies also revealed interesting information on the lymphatic drainage pattern of the prostate [77–80]. Consequently, it has been suggested that even the extended LND template does not cover all possible nodal sites. With an extended LND, probably about two thirds of all primary prostatic lymphatic landing sites are resected, compared with only one third with a limited LND [81,82]. In our institution, intermediate- to high-risk PCA patients are treated with a "superextended" LND, including common iliac (below aortic bifurcation), internal and external iliac region, obturator fossa region, and presacral region [83]. A total of 91 pathologic lymph nodes were found in 34 patients. The predominant site was the internal iliac region (35%), followed by the external iliac region (26%), and the obturator fossa region (25%). Remaining metastases were located in the presacral region (9%), common iliac region (3%), and aortic bifurcation region (1%). A limited LND (external iliac and obturator fossa regions) would have correctly staged 26 of 34 patients, and would have removed all nodal disease in only 10 of 34 patients. An eLND would have correctly staged 32 of 34 patients, but would have removed all pathologic lymph nodes in only 26 of 34 patients. The authors recommend that pelvic lymphadenectomy, or indeed elective pelvic radiotherapy, needs to include the internal iliac and presacral lymph node regions.

These contemporary surgical data suggest that the true incidence of microscopic pelvic disease in clinically node-negative patients is consistently underestimated, rather than overestimated [56–58]. Of course, the prognostic significance of these small tumor deposits can be questioned, but several thorough pathology studies suggest that they can in fact give rise to disease recurrence when left untreated [84–87]. It was also convincingly demonstrated that loco-regional recurrence after radiotherapy will indeed result in late distant metastases [88,89].

Within the urology community, there is a consistent drive for more aggressive management of intermediate- to high-risk patients, with surgical staging evolving from "limited" over "extended" to "superextended" lymphadenectomies [61–68,83]. Moreover, there is increasing evidence of a survival benefit for patients undergoing eLND [90]. Several studies have indicated the possibility of long-term survival in the presence of lymph node involvement, especially in the case of low-volume nodal disease [91–93]. This strongly suggests that patients can benefit from the eradication of (limited) pelvic disease [94]. In conclusion, it can be surmised that the incidence of unsuspected pelvic disease in intermediate- to high-risk prostate cancer patients is common enough to theoretically warrant elective radiotherapy in the absence of surgical removal. These cancer cells in lymph nodes can have clinical significance, but do not necessarily result in distant metastases, provided that adequate loco-regional treatment is delivered.

### Elective pelvic radiotherapy

#### Retrospective analyses

Six retrospective analyses were published in the pre-PSA era, often including patients that would now be considered low-risk [95–101]. The relevance of these studies for current clinical practice is therefore probably limited. In one slightly more recent study by Perez et al. on 963 prostate cancer patients, there was no clinical disease-free survival benefit with WPRT for patients with cT1c or cT2 tumors [102]. However, in patients with poorly differentiated cT3 tumors, WPRT with doses of 50–55 Gy did result in a 50% lower incidence of pelvic (i.e. regional) recurrences (23% vs. 46%, p < 0.01). When whole pelvic doses of only 40–45 Gy were administered, no advantage was seen. PSA levels were available for 317 of 963 patients. For these patients there was a suggestion that WPRT increased biochemical disease-free survival, although the number of patients in this subgroup was too small for the difference to be statistically significant.

All seven contemporary retrospective analyses are summarized in Table 2. The oldest negative study that was conducted in the PSA era was only published as an abstract [103]. Rasp et al. retrospectively evaluated patients with an estimated risk of LNI of greater than or equal to (≥) 15% according to the Roach equation. There was no difference in the Gleason score or pre-treatment PSA between the group that received WPRT and the group that received prostate-only radiotherapy (PORT). However, there was a significant difference in the prostate radiation dose delivered (median 68.4 Gy dose in the WPRT group vs. 63.0 Gy in the PORT group). Patients treated with WPRT also had a significantly more advanced clinical stage than those receiving PORT (p = 0.007), which could explain the higher prostate dose. This discrepancy between the two groups might also explain the apparent lack of benefit from WPRT.

The two retrospective studies by Seaward et al. were conducted in the PSA era [104,105]. Using the Roach equation, they identified 201 patients with an estimated LNI risk ≥ 15% who had undergone either WPRT or PORT. Those who received WPRT had significantly improved bDFS compared to patients who received PORT [104]. Next, they tried to identify a subgroup that benefited most from WPRT. Apparently, intermediate-risk patients (defined as an estimated LNI risk ≥ 15% but <35%) receiving WPRT had significantly improved disease-free survival compared with those receiving PORT (median bDFS 39.5 months vs. 22.5 months, p = 0.0001). Highest risk patients (an estimated LNI risk ≥ 35%) were few in number (n = 71), and although their disease-free survival was longer in the WPRT group (27.2 months vs. 20.8 months), this was not statistically significant [105]. This could suggest that such very high-risk patients may already harbor distant micrometastases and therefore benefit less from WPRT, although the lack of statistical significance might also simply reflect the small number of patients.

Pan et al. retrospectively compared prostate-only, prostate and seminal vesicle, and whole-pelvic treatment [106]. They applied the Partin tables to 1281 patients with clinically localized prostate cancer treated with three-dimensional (3D) conformal radiotherapy (CRT). Three categories of LNI risk were defined: low (<5%), intermediate (5–15%) and high (>15%) risk. Multivariate analysis demonstrated a statistically significant benefit in disease-free survival for the entire population treated with WPRT, with a relative risk reduction of 0.72 (95% confidence interval 0.54–0.97).
beneficial effect was most pronounced within the intermediate-risk group.

A retrospective analysis from the Fox Chase Cancer Center confirmed that radiation dose to the prostate, rather than treatment volume (i.e. elective pelvic radiotherapy or not), is the most important determinant of long-term disease-free survival in intermediate- to high-risk prostate cancer patients [107]. A total of 420 patients with LNI risk estimated >15% were treated with “prostate-only” (n = 48), “partial-pelvis” (periprostatic and obturator fossa lymph nodes, n = 74), and “whole-pelvis” (n = 298) fields. The median prostate dose was 74 Gy for PORT, 82 Gy for PPRT, and 76 Gy for WPRT. The 5-year bDFS rate by dose was 48% for dose <73 Gy, 64% for 73–76.9 Gy, and 74% for > 77 Gy (p = 0.002). Radiation field size was not significantly associated with bDFS. These results obviously endorse the prominence of dose in EBRT for prostate cancer [11–13]. However, because of the limited “whole-pelvis” field size (upper border at the inferior sacro–iliac joints, rather than L5–S1 or common iliac bifurcation), the relevance of pelvic radiotherapy cannot be excluded.

Aizer et al. recently published a large retrospective analysis of 277 patients (LNI risk >15% according to the Roach equation) treated in two referral centers [108]. Although WPRT patients had more advanced and aggressive disease at baseline, the 4-year bDFS rate was 86.3% in the WPRT cohort as compared to 69.4% in the PORT cohort (p = 0.02). Within the entire group, after adjustment for confounding variables, the pre-treatment PSA level (p = 0.001), Gleason score (p < 0.001), use of hormonal therapy (p = 0.002), and use of WPRT (vs. PORT, p = 0.006) predicted for bDFS. Patients undergoing WPRT had increased acute gastro-intestinal toxicity (p = 0.048), but no significant difference in acute genito-urinary toxicity was seen (p = 0.09). No difference in late toxicity was observed.

A Polish analysis retrospectively compared 263 high-risk patients treated with WPRT, combined with neo-adjuvant and long-term androgen deprivation therapy (ADT), versus PORT, combined with long-term androgen deprivation [109]. The results suggest that WPRT, combined with neo-adjuvant androgen deprivation, improves disease-free survival without increasing acute or late side-effects.

The most recent retrospective analysis, by Mantini et al. from Rome, also looked specifically at high-risk prostate cancer patients [110]. Patients were grouped according to LNI risk, as assessed by the Roach formula, using different cutoff levels (15%, 20%, 25%, and 30%). For the entire group, the 4-year bDFS rate was similar between the patients who had undergone WPRT or PORT (90.4% vs. 90.5%, respectively). However, in the cohort of patients with the greatest nodal risk (>30%), a significant bDFS improvement was recorded for the patients who had undergone WPRT. No differences were seen in acute or late toxicity.

As mentioned before, dose-escalation is of paramount importance in the primary radiation treatment of intermediate- to high-risk prostate cancer [11–13]. High dose rate (HDR) brachytherapy boost after a course of EBRT is an elegant way to escalate the dose, while also exploiting the apparent sensitivity of prostate cancer to higher dose rates and shortened overall treatment time [111–114]. Three retrospective analyses looked specifically at the role of WPRT in the context of such a brachytherapy boost. Arguably, these trials again demonstrate that total prostate dose takes precedence over treatment volume (i.e. pelvic radiotherapy or not), but their results are probably not sufficient to discard WPRT altogether.

A retrospective analysis from the H. Lee Moffitt Cancer Center showed an 83% 5-year bDFS in 88 intermediate-risk patients treated with brachytherapy alone, suggesting that excellent results can be achieved without supplemental pelvic radiotherapy [115]. Another recent study retrospectively divided 1357 patients treated in three different hospitals with a combination of EBRT and HDR brachytherapy to an average dose of 100 Gy into three groups, depending on their risk of LNI, based on the Roach equation [116]. Group 1 had a low risk of positive LN (≤15%), group 2 had an intermediate risk (>15% but ≤30%), and group 3 had a high risk (>30%). According to institutional policy the pelvis was treated at two centers, whereas the third center only treated the prostate and seminal vesicles. There were 596 patients with an estimated risk of more than 15% of having LNI. Of these, 284 were treated for the prostate alone and 312 for the whole pelvis. There was no difference in disease-free survival or overall survival between these two groups.

On the other hand, data from Bittner et al. suggest some benefit with WPRT in high-risk patients [117]. They treated 186 patients with brachytherapy and supplemental external beam radiation (EBRT), using either a “mini-pelvis” or a “whole-pelvis” field. With a median follow-up of 6.7 years, the 10-year bDFS was 84.4% vs. 91.7% (p = 0.126), respectively. This non-significant trend was most apparent among ADT-naïve patients, for whom a significant improvement in OS was observed (87.5% vs. 58.8%, p = 0.030).

### Table 2

<table>
<thead>
<tr>
<th>Study</th>
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<th>Field</th>
<th>Median Follow-up (months)</th>
<th>No.</th>
<th>bDFS (%)</th>
<th>p-Value</th>
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<td>52</td>
<td>39 at 5 years</td>
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<td>298</td>
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<td>34</td>
<td>88 at 4 years</td>
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### Randomized trials

To date, only three published prospective randomized trials compared elective pelvic radiotherapy with prostate-only radiotherapy in clinically node-negative, intermediate- to high-risk prostate cancer patients. All three studies are essentially negative.

The Radiation Therapy Oncology Group conducted a prospective randomized trial in the pre-PSA era (RTOG 77-06). Asbell et al. reported on 445 prostate cancer patients with no clinical...
evidence of tumor extension through the capsule (cT1c–2c) treated with primary radiotherapy [118]. Assessment of the regional lymph nodes was mandatory but, at the discretion of the investiga-
tor, lymphangiography or staging lymphadenectomy could be used. Patients were only eligible if either lymphangiogram (75% of patients) or staging laparotomy (25% of patients) had shown no evidence of lymph node involvement. There was no statistically significant difference between the two arms (WPRT vs. PORT) for overall survival, local or regional recurrence, and disease-free sur-
vival. At 12-year median follow-up, there was still no difference between both arms [119].

The other, more recent North-American trial, RTOG 94-13, exam-
ined the role of elective pelvic radiotherapy in patients with an esti-
nated LNI risk >15% based on the Roach equation [120]. Through its 2 x 2 factorial design, this trial attempted to address two major questions in the primary radiation treatment of patients with inter-
mediate- to high-risk prostate cancer simultaneously: (1) WPRT vs. PORT, and (2) the timing of androgen deprivation therapy. The study had four arms: (1) WPRT + NCHT (neo-adjuvant and concurrent ADT); (2) PORT + NCHT; (3) WPRT + AHT (adjuvant ADT immediately following the completion of RT); (4) PORT + AHT.

Initially, WPRT was associated with a 4-year disease-free survival of 54% compared with 47% for PORT (p = 0.022). There was no significant difference in overall survival between WPRT and PORT (84.7% vs. 84.3%, p = 0.94). Patients treated with NCHT had a 4-year disease-free survival of 52% vs. 49% for AHT (p = 0.56). When comparing all four arms, there was a clear benefit for patients who had undergone WPRT + NCHT (4-year disease-free survival of 60%) vs. all three other arms (44% vs. 49% vs. 50% respectively; p = 0.008).

These primary results were recently updated [121]. After a med-
ian follow-up of 6.6 years, there was a statistically significant differ-
ence in overall survival between the four arms (p = 0.027), mainly because of the substantial lower survival in the WPRT + AHT arm. However, the study was not powered to compare the four treat-
ment arms one against the other. When the two WPRT arms are considered together, as planned, no benefit was observed compared to the PORT cohort. The authors hypothesize that there might be a specific, sequence dependent interaction between hormonal ther-
apy and radiation in the lymph nodes (perhaps T-cell mediated), which could explain the lower survival in the WPRT + AHT arm [22,121]. From other randomized trials, it is clear that a short course of NCHT improves survival in intermediate- to high-risk patients, irrespective of the volume treated [14–16]. The necessary duration of adjuvant ADT in high-risk patients is still unclear, but most stud-
ies using long-term adjuvant hormonal therapy prescribed a con-
ventional dose to a large volume, often encompassing the whole pelvis [17–20]. It is intuitively appealing to assume that radiother-
apy is more successful in eradicating microscopic disease when combined with systemic therapy, as it is the case in most other cancer sites [122,123]. Still, the updated results from RTOG 94-13 re-
main difficult to interpret in the light of all the other data regarding the timing of hormonal therapy.

The most recent study was performed by the French Genitouri-
nary Study Group (GETUG) and included all localized, node-nega-
tive prostate cancer patients, irrespective of their prognostic group or indeed their LNI risk [124]. With a median follow-up time of 3.5 years, the 5-year disease-free survival and overall survival rates were similar in the two arms. Furthermore, in the subgroups of patients with an estimated LNI risk >15% (45% of total) or with a “high-risk” profile (79% of total), no benefit with pelvic radiother-
apy was observed, although the trial was statistically underpow-
ered for such subset analysis. Based on these data, elective radiotherapy of pelvic nodal regions is not advocated by the Euro-
pean Association of Urology [9].

The RTOG is currently conducting another randomized, phase III trial (RTOG 09-24, NCT01368588), in which patients with high-risk or locally advanced prostate cancer receive ADT in conjunction with either prostate-only or whole-pelvis RT. This trial started recruiting in June 2011, and results can be expected within 10–15 years.

In conclusion, there is currently insufficient evidence to advocate elective pelvic radiotherapy in intermediate- to high-risk patients. All three randomized-controlled trials were negative with respect to (biochemical) disease-free survival as well as overall survival. Regarding the retrospective analyses, some recent high-quality studies did show a benefit with WPRT, especially in (very) high-risk patients [108,110]. For future trials, it seems important to (1) only include patients with a sufficiently high risk of LNI (at least >20%, the cut-off for elective treatment in most other cancers), preferably estimated by the validated Briganti nomograms (including percentage of positives cores) or confirmed by positive SN, (2) treat the en-
tire pelvis up to the L5–S1 interface (and not lower), (3) deliver a sufficiently high dose to the prostate itself, and (4) prescribe neo-
adjuvant, concomitant and long-term adjuvant ADT in both arms.

**Volume definition**

It is to be expected that highly conformal techniques, such as intensity-modulated radiotherapy (IMRT), will improve the therapeu-
tic ratio of pelvic radiotherapy through more consistent cover-
age of the target volumes with increased sparing of the organs at
risk (OAR), such as bladder, rectum and small bowel [125]. How-
ever, accurate target volume delineation is obviously of crucial
importance in such a setting. In the oldest trials on WPRT, conven-
tional two-dimensional radiotherapy (2D-RT) was used, with large treatment portals based on radiographic simulation films [95–
103]. It is quite possible that some of the benefit ascribed to WPRT in these older studies resulted from more complete prostate coverage with the larger fields compared to inadequate prostate coverage due to prostate motion out of the smaller prostate-only fields. On the other hand, Foreman et al. found that conventional pelvic plans often had inadequate coverage of the pelvic lymph nodes, with up to 30% of the target nodal volumes treated to less than 60% of the prescribed dose [126].

In most RTOG trials, including RTOG 94-13, a four-field box tech-
ique was used to address the pelvic lymph nodes [118–
122]. The upper border was placed at the L4/L5 or L5/S1 interspace and the lower border at the bottom of the ischial tuberosities. Lat-
erally, 2 cm lateral to the true pelvis was recommended. In the lat-
eral fields, the anterior border was the anterior pubic symphysis to include the anterior aspect of the external iliac lymph nodes and the posterior border was to be posterior to the anterior bony sa-
crum (S3) so as to address the presacral lymph nodes superiorly
and then to spare the rectum inferiorly. A similar technique was
used in most retrospective analyses showing a benefit with elec-
tive pelvic radiotherapy [104–106,108–110]. Interestingly, the
two negative retrospective analyses placed the superior border at the lower sacroiliac joints, excluding the common iliac and (proxi-
mal) presacral lymph nodes [107,116]. The French GETUG trial de-
finned the upper limit as the level of the anterior portion of the junction between the first and second sacral vertebra [124].

A subset analysis of RTOG 94-13 was performed on patients who were treated with neo-adjuvant and concomitant ADT [127]. The PORT cohort of this group was dichotomized into “prostate-
only” (PO) with a radiation field size less than the median (10 cm x 11 cm) and “mini-pelvis” (MP) with a field size greater than or equal to the median. The 4-year disease-free survival was 60% for the WP, 48% for the MP and 40% for the PO groups respec-
tively (p = 0.0023). There was a measurable difference in the inci-
dence of late grade 3 toxicity between WPRT (4.5%) and MPRT (1.5%), and both were higher than PORT (0%, p = 0.023).
When CT-based treatment planning is available, it becomes possible to separately select distinct pelvic lymph node regions for elective treatment. Evidently, this can result in significant variation between institutions, or even between patients within a single institution [128]. The recent RTOG consensus guidelines specify that the pelvic clinical target volume (CTV) should include the distal common iliac, presacral (S1–S3), external iliac, internal iliac, and obturator lymph nodes [129]. Just as in gynecological malignancies, the nodal CTV should encompass the vessels (artery and vein) with a 7–mm radial margin, excluding bowel, bladder, bone, and muscle [26,129]. According to the RTOG consensus guidelines, the CTV should begin at the L5/S1 interspace and end at the superior aspect of the pubic bone [129].

Recently, two publications from the same group suggested that more than half of the suspected lymph nodes, based on MRL and/or $^{11}$C-choline PET-CT, mapped outside the RTOG CTV [130,131]. However, both studies lacked pathological validation, which remains the gold standard for lymph node staging. Based on the surgical data from extended lymphadenectomies, the RTOG proposition remains valid (Table 1).

**Toxicity**

With modern techniques, radiotherapy to the prostate and seminal vesicles is extremely well tolerated and results in little late toxicity [132,133]. Inevitably, prophylactic coverage of large portions of potentially normal pelvic tissue in an effort to avoid undesirable marginal failure will negate some of the possible organ-sparing advantages of highly conformal techniques [134]. As far as toxicity is reported, most retrospective analyses describe some increased acute side-effects, principally gastrointestinal rather than genitourinary, with pelvic radiotherapy [96,102,108]. Aizer et al., for instance, observed increased acute gastrointestinal toxicity (84.1% vs. 59.4%, $p = 0.048$), but no significant difference in acute genitourinary toxicity (88.2% vs. 73.7%, $p = 0.09$). No difference in late toxicity was found [108]. The two most recent studies, using 3D-CRT, observed no statistically significant differences in acute or late toxicity, although absolute numbers of acute toxicity were somewhat higher for the pelvic RT arms in both [109,110]. In RTOG 94–13, there was a trend for higher acute and late grade 3 gastrointestinal complications in the WPRT + NHT arm, but this did not reach statistical significance ($p = 0.06$ and 0.09, respectively). The reported 2-year rates of late grade 3 or higher genitourinary and gastrointestinal toxicity were low in both the WPRT and PORT arms, i.e. 1.7% and 0.6% respectively [120]. In the updated analysis, the incidence of late grade 3 or worse gastrointestinal toxicity was significantly different ($p = 0.002$), with 5% of patients in the WPRT + NHT arm experiencing grade 3 late toxicity vs. 1% of those in the PORT + NHT, 2% in the WPRT + AHT, and 2% in the PORT + AHT arms [121]. In the GETUG-01 trial, there were no significant differences in acute and late digestive toxicities and in QOL outcomes [124].

**Conclusion**

Currently, there is insufficient evidence to advocate WPRT in intermediate- or even high-risk localized PCa patients. All three randomized-controlled trials were negative with respect to (biochemical) disease-free survival as well as overall survival. Still, recent surgical series with eLND show a considerable incidence of microscopic disease in the pelvic lymph nodes of these patients, with the potential to affect survival. In many other cancers, radiotherapy can successfully eradicate such disease, but this has not yet been shown for prostate cancer. However, there are arguments to assume that the available studies could have underestimated the benefit from elective pelvic radiotherapy for some, albeit highly selected, patients. First, the equation most often used to estimate the risk of LNI in retrospective and prospective analyses was based on data from limited lymphadenectomies performed in the pre-PSA era, and does not include information from the percentage of positive cores. This has led to the inclusion of many patients with low-risk disease and might explain the failure in demonstrating a benefit with WPRT. It is possible that more complex nomograms, based on modern eLND series, will improve patient selection. Also, SN procedure should be considered to include patients in future trials, since patients with positive SN have a very high risk of harboring further pelvic disease. Secondly, the pelvic treatment volume was not consistent in all studies. Results from extended lymphadenectomies clearly indicate that the common iliac and (proximal) presacral lymph node should always be included. Third, the timing and duration of ADT differed between (and even within) trials, potentially masking (or delaying) the benefit from WPRT. Based on current evidence, WPRT should always be combined with at least neo-adjuvant and concomitant ADT. In conclusion, elective pelvic radiotherapy is certainly not standard of care for intermediate- or high-risk prostate cancer, but could be considered in patients at very high risk of LNI either based on validated and contemporary nomograms or on positive SN.

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**Conflict of interest**

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