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Local failure is a dominant mode of recurrence in locally advanced and clinical node positive prostate cancer patients treated with combined pelvic IMRT and androgen deprivation therapy

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Abstract

Background: The recurrence patterns of high-risk, N1 prostate cancer after radiation therapy (RT) including the pelvic lymph nodes have not been fully investigated.

Material and methods: We have a prospective clinical study since 2004 that has followed 138 men with locally advanced prostate cancer (T1-T4N0-N1M0) treated with definitive RT encompassing the prostate and pelvic lymph nodes and long-term androgen deprivation therapy (ADT). Forty nine of the 52 patients that developed recurrence were imaged at biochemical failure to detect the site of recurrence.

Results: Imaging identified the site of recurrence in 46 patients. Twenty five patients had prostatic recurrence only, none had local lymph node recurrence only, 11 had distant metastases only, 7 had prostatic recurrence and distant metastases, 2 had prostatic recurrence, local nodal recurrence and distant metastases, and 1 had local nodal recurrence with distant metastases. The mean time to recurrence was 62 months for prostate only, 40 months for distant only and 50 months for prostate and distant recurrence. There was a 69% recurrence rate for patients with magnetic resonance imaging -detected N1 disease. There was significantly longer survival for patients with prostate recurrence only compared to patients with distant recurrence ($P < 0.018$). Five-year prostate cancer-specific survival were 85% for prostate only, 44% for distant only and 48% for prostate and distant recurrence (prostate only vs. distant only; $P = 0.008$, prostate only vs. prostate and distant; $P = 0.018$, distant vs. prostate and distant; $P = 0.836$).

Conclusions: The predominant recurrence pattern for high-risk, N1 prostate cancer was prostatic recurrence and distant spread after pelvic RT and androgen deprivation therapy. Our data argue for further local dose escalation and pelvic nodal radiation to prevent recurrence in these sites. Lymph node metastasis at initial staging with an magnetic resonance imaging was a strong predictor of recurrence and poor survival and may identify patients in need of more aggressive treatment.

Keywords: Prostate cancer; External beam radiation; Relapse; MRI; Patterns of recurrence

Abbreviations: ADT, androgen deprivation therapy; BF, biochemical failure; CTV, clinical target volume; EBRT, external beam radiation therapy; HDR, high dose rate; IMRT, intensity-modulated radiation therapy; ITV, internal target volume; MRI, magnetic resonance imaging; OARs, organs at risk; OS, overall survival; PCSS, prostate cancer-specific survival; PI-RADS, prostate image reporting and data system; PSA, prostate specific antigen; PTV, planning target volume; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group

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1. Introduction

Optimal treatment of locally advanced, N1 prostate cancer has not been determined. The experience from extended lymphadenectomy suggests that for a subgroup of patients with limited positive pelvic lymph nodes (< 3), irradiation of the pelvic lymphatic structures could translate into long-lasting disease control [1,2]. Similarly, there are data that definitive radiation therapy (RT) and androgen deprivation therapy (ADT) in cN1 may be more beneficial than ADT alone [3−8]. Previously, we reported favorable outcomes, particularly in N1 disease, in patients with locally advanced and/or N1 prostate cancer undergoing intensity-modulated RT (IMRT) combined with long-term ADT [9]. In this study, we present the pattern of recurrence as visualized by magnetic resonance imaging (MRI) at biochemical failure (BF) and survival of this cohort.

2. Materials and methods

2.1. Study overview

Our IMRT-study [9] was a prospective, single-arm study initiated to determine patient-scored toxicity and survival for men with locoregional disease (cN1) that received pelvic nodal radiation and long-term ADT (≥ 6 months). In addition to International Union Against Cancer, (TNM/UICC) staging [10], the inclusion criteria were age < 75 years, no previous invasive cancer, diagnosis no older than 6 months, pN1M0 or a calculated N+ risk ≥ 15% using the Memorial Sloan Kettering Cancer Center nomogram [11], and prognostic high-risk disease defined by the D'Amico risk classification [12]. It had been standard in Norway to perform a pelvic lymph node dissection (surgical staging) in high-risk patients prior to primary RT. Low yield from lymph node dissections prior to definitive RT led to increased use of MRI for nodal-assessment (mrN) during the study [13]. All patients were treated with IMRT to the prostate, seminal vesicles, and pelvic nodal basins and/or positive nodal disease.

Patients were seen in the outpatient clinic at 3 to 4-month intervals the first 2 years, and then every 6 months for the next 5 years. Routine history and physical exam were performed and prostate-specific antigen (PSA) levels were checked for BF. Imaging at BF was reviewed to establish the recurrence pattern. Recurrences were treated with salvage therapy per their local oncologist's preference after being confirmed with biopsy. The protocol was approved by the Ethics Committee of the Health Region South/East of Norway. All patients gave written informed consent.

2.2. Study cohort

Patient and tumor characteristics of the IMRT-cohort are detailed in Table 1. The number of high-risk (T3a, PSA > 20 ng/ml, or Gleason 8-10) and very high-risk (T3b-T4, Gleason 5, or 2 or more high-risk factors) patients were 25% and 75%, respectively. Median follow-up of this entire cohort was 7.9 years (range 1.1−14.6 years). Of the 138 IMRT-patients, 52 had PSA recurrence as defined by the Phoenix definition [14]. Overall, 93 patients received lymph node dissection, and 43 (46%) of these patients were pN0, while 50 (54%) were pN1. The median number of nodes removed was 7 (range 2−27). In 121 patients a diagnostic MRI staging was done (Fig. 1). Median follow-up of the recurrence cohort was 8.1 years (range 1.1−14.1 years).

2.3. Initial staging and imaging at biochemical failure

The magnetic resonance (MR)-protocols evolved during the study period, but all were performed on 1.5 T scanners. In 2006, only morphological sequences were used; 3 plane high-resolution 2D T2W for T-staging, 2D T2W for size-based lymph node assessment and T1W for skeletal metastases detection. In 2008, diffusion weighting was added for prostate tumor detection. Furthermore, 3D T2W and diffusion weighting were added for morphological lymph node assessment, and interpreted as described in detail by [15]. In 2011, dynamic contrast-enhanced imaging was added. Since 2011 the MR protocols have been in accordance with the internationally recommended technical requirements published in 2012 [16].

Of the 138 IMRT-patients, 94 had surgical staging and 121 had MRI-staging, of whom 80 had prior surgical staging. Fig. 1 shows the overview of the N-staging including the degree of concordance between pN and mrN (2×2 table). Three patients had no lymph node staging. The radiological assessment of lymph nodes was based on shape, border, signal, and size [15]. Patients with equivocal mrN-status were re-examined after 6 months of ADT whereby unequivocal shrinkage of a lymph node was interpreted as metastasis (mrN1).

For the 52 patients with BF, all available images were retrospectively reviewed by an experienced MR-radiologist (K.H.H.) to establish the site of recurrence. The sites of recurrence were classified according to the TNM classification as prostatic recurrence (T2-4), local nodal recurrence (N1), and distant metastases (M1). From autopsy studies there is evidence for early spread to lumbar spine, pelvic, and paraaortic lymph nodes as first sites of metastasis [17]. Hence, MRI at BF consisted of a pelvic MRI with extension to the lumbar spine and paraaortic lymph nodes. The site(s) of recurrence were detected in 46 patients; 44 at MRI, 1 at CT, and 1 at Positron Emission Tomography/Computer Tomography (PET/CT) (Fig. 2). The MR sequences performed were not appropriate (no functional sequences or insufficient anatomical coverage) to detect prostatic recurrence in 5 patients (Tx) or local nodal recurrence in 3 patients (Nx). These 5 patients had M1 disease and were categorized as distant metastases only.

Table 1
Patient, tumor, and treatment characteristics

	Overall cohort ($N = 138$) Mean or N (%)	Median (IQR)	PSA recurrence ($n = 52$) Mean or N (%)	Median (IQR)
Age (y)	64.7	65.8 (60.4–69.3)	61.9	62.0 (57.3–66.0)
PSA (ng/ml)	30.8	24.6 (14.3–41.0)	31.3	23.5 (12.8–41.0)
PSA at BF	n/a	n/a	6.2	2.4 (2.1–3.4)
Duration of ADT (mo)	26.4	23.0 (11.0–35.0)	31.6	24.5 (21.0–33.0)
Gleason score				
6-7a	22 (15.9)		3 (5.8)	
7b-8	89 (64.5)		33 (63.4)	
9-10	27 (19.6)		16 (30.8)	
Clinial T-stage	8 (5.8)		2 (3.9)	
T1	18 (13)		4 (7.7)	
T2	56 (40.6)		19 (36.5)	
T3a	53 (38.4)		25 (48.1)	
T3b	3 (2.2)		2 (3.85)	
T4				
MRI T-stage	6 (4.3)		1 (1.92)	
T2	46 (33.3)		10 (19.2)	
T3a	60 (43.5)		33 (63.5)	
T3b	8 (5.8)		6 (11.5)	
T4	18 (13.1)		2 (3.9)	
Tx				

ADT = androgen deprivation therapy; BF = biochemical failure;IQR = interquartile range; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.

2.4. Treatment

The clinical target volume and organs at risk have been described in detail previously [18]. Briefly, the clinical target volume for the pelvic nodes was delineated by contouring a 0.7 cm radial area around the pelvic iliac vessels and adding a 2 mm margin to obtain a planning target volume. The medial portion of the presacral nodal area was left out in the delineation of lymph nodes, aiming to spare the recto-sigmoid, otherwise the contouring was per the Radiation Therapy Oncology Group recommendations. Predefined protocol-stated dose constraints to the organs at risk were used.

Treatment plans were generated by 7 coplanar fields to the delineated pelvic structures up to a total dose of 46 to 50 Gy encompassing the prostate, seminal vesicles, and nodal basins by use of 15-MV photon beams. Radiation to the boost volume (24 Gy to the seminal vesicles and the prostate for T3b; 24 Gy to the prostate alone for $\leq$T3a) was done by a 4-field box technique. All patients started neoadjuvant ADT 6 months prior to IMRT. The mean duration of ADT treatment was 26 months.

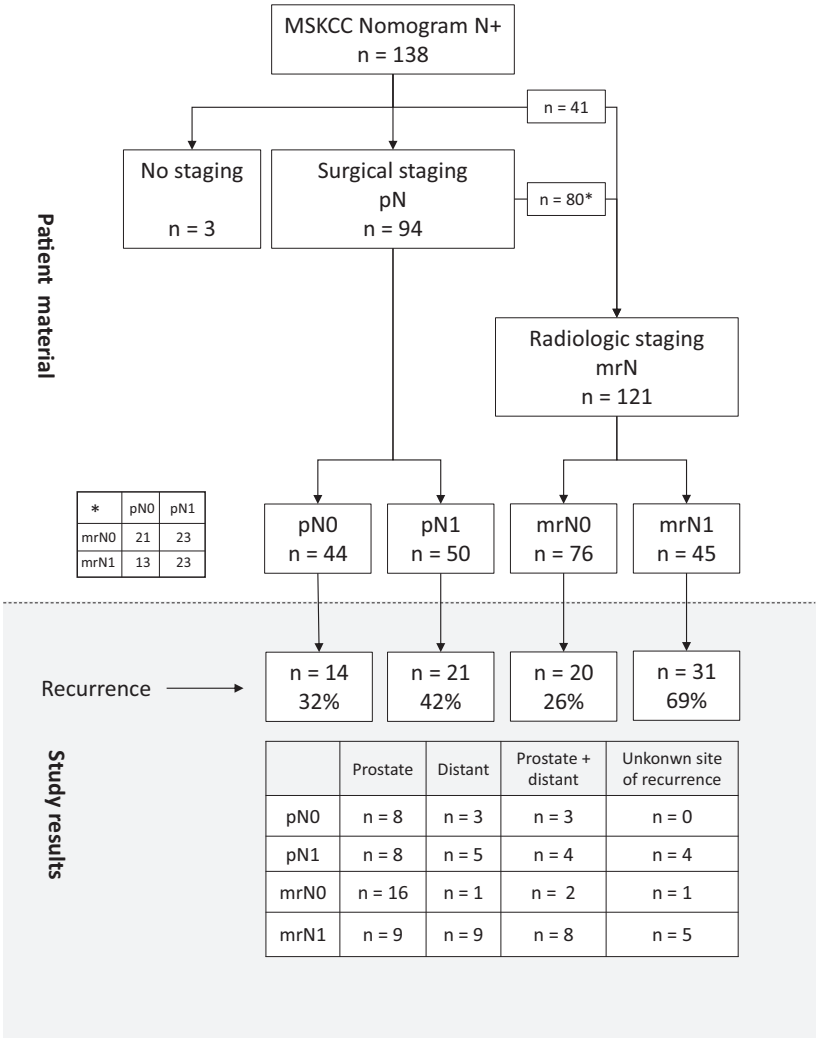
2.5. Survival and data analysis

Death due to prostate cancer was defined as death in a patient with a documented history of hormone-refractory metastatic prostate cancer, evidence of a rising PSA at last follow-up visit, and no other obvious cause of death. Additionally, death certificates were cross-referenced to confirm cause of death. Patients who were alive were censored at last follow-up. Survival endpoints were measured from the first day of initiation of ADT. Chi-square was used to compare recurrence rates between N0 and N1. Kaplan-Meier plots for survival endpoints were constructed using the log-rank test. All statistical analyses were performed in IBM SPSS Statistics version 23.

3. Results

3.1. Site of recurrence

Fig. 1 stratifies number and site of recurrence to N-staging from pathology and MRI. There is no difference in recurrence rate between patients with pN0 and pN1 ($P = 0.34$). However, there is a significantly higher recurrence rate for patients with mrN1 compared to mrN0 ($P < 0.001$). N1 does not predict site of recurrence. Three of the 52 patients had no imaging at BF and for 3 other patients the site of recurrence was undetected. Thus, the site of recurrence was detected in 46 patients (Fig. 2). Twenty-five patients had prostatic recurrence only, none had local lymph node recurrence only, 11 had distant metastases only, 7 had both prostatic recurrence and distant metastases, 2 had prostatic recurrence, local nodal recurrence and distant metastases, and 1 had local nodal recurrence and distant metastases. The mean time from initiation of ADT to BF was 62 months for prostate only, 40 months for distant only, and 50 months for prostate and distant recurrence. There was no significant differences between the groups ($P = 0.126$) (Fig. 3). The TNM-classifications for each



*	pN0	pN1
mrN0	21	23
mrN1	13	23

Fig. 1. Overview of the lymph node-specific analyses: The upper white section details the staging and status. The lower gray section presents the number and site of recurrence.

patient, at the time of diagnosis and at the time of BF, are provided in Supplementary Table 1.

3.2. Prostate cancer-specific survival

Prostate cancer-specific survival (PCSS) stratified by recurrence pattern is shown in Fig. 4A. Mean PCSS was 161 months for prostate only, 93 months for distant only and 90 months for prostate and distant recurrence. There was significantly longer PCSS for patients with prostate recurrence only compared to patients with distant recurrence (prostate only vs. distant only; $P = 0.008$, prostate only 'vs. prostate and distant; $P = 0.018$, distant vs. prostate and distant; $P = 0.836$). Five-year PCSS were 85% for prostate only, 44% for distant only and 48% for prostate and distant recurrence. PCSS stratified according to N-staging from surgical staging and MR N-staging is shown in Fig. 5. For surgical N-staging there was no difference in PCSS ($P = 0.96$) whereas there was a significantly longer PCSS for mrN0 patients compared to mrN1 patients ($P < 0.01$).

3.3. Overall survival

Overall survival (OS) stratified by recurrence pattern is shown in Fig. 4B. Mean OS was 161 months for prostate only, 90 months for distant only and 90 months for prostate and distant recurrence. There was significant longer survival for patients with prostate recurrence only compared to patients with distant recurrence ($P < 0.018$). Five-year OS were 85% for prostate only, 33% for distant only, and 48% for prostate and distant recurrence.

4. Discussion

This study reports the recurrence pattern for high-risk, locally advanced prostate cancer patients treated with definitive RT encompassing the prostate and pelvic lymph nodes

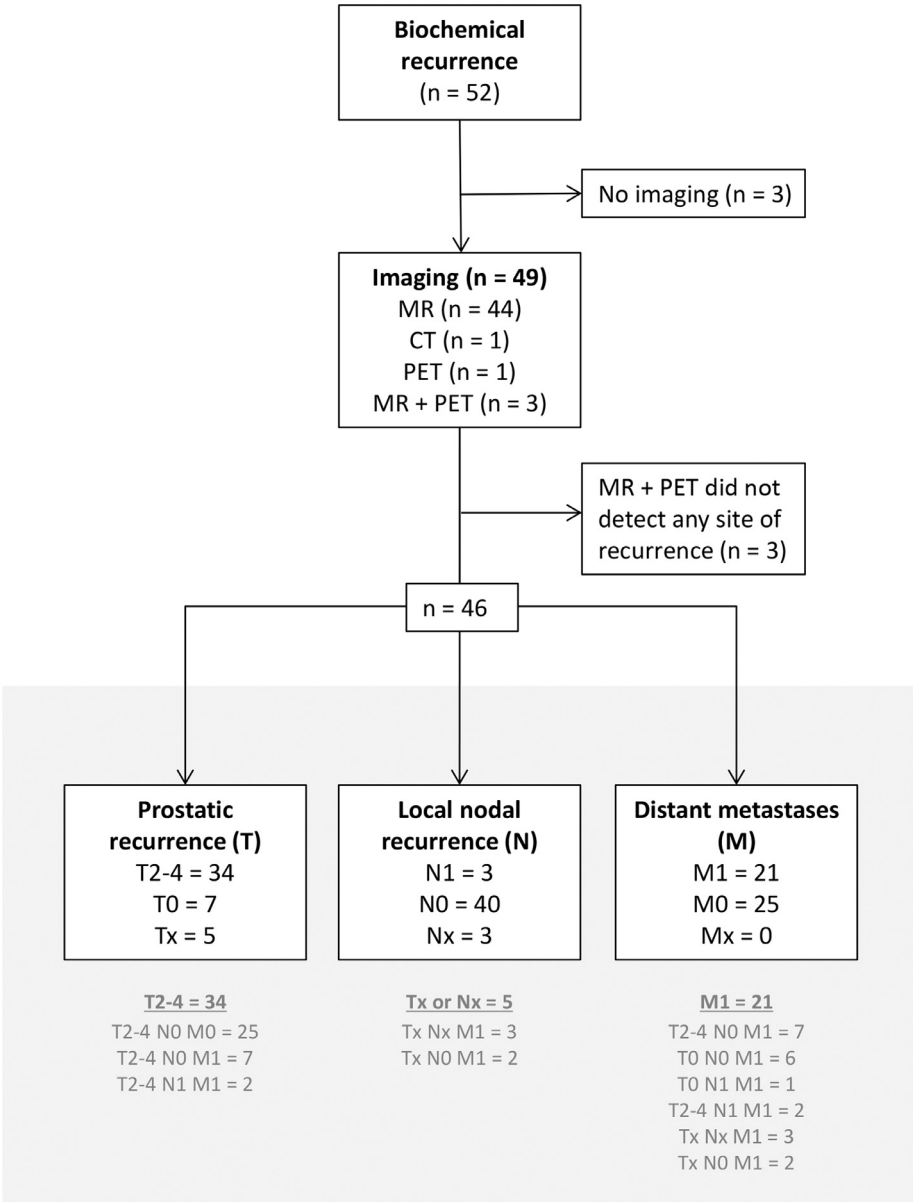


Fig. 2. Detected site of recurrence.

and long-term ADT. To our knowledge, this is the first data on patterns of recurrence after definitive RT with a standardized treatment of pelvic lymph nodes and long-term ADT. From this study, we believe a few clinically relevant conclusions can be drawn.

Two recurrence sites predominated; prostatic recurrence and distant spread. The predominance of prostatic recurrences suggests that local dose escalation may prevent many recurrences in high-risk prostate cancer. It is not possible to directly compare our data to other published results given their variable use of ADT and lack of nodal radiation, but Zumsteg et al. found a 32.7% risk of recurrence in high-risk prostate cancers [19] and at least 48.2% of recurrences in high-risk patients had a pelvic component (44.9% with prostate involvement, 37.5% isolated to the prostate, and 3.3% isolated to pelvic lymph nodes). Combined with our finding that 34 of the 46 (74%) recurrences had a prostatic component, one might speculate that local dose escalation could have prevented recurrences by eliminating radioresistant clones [20]. Given that some distant metastases were synchronous with local recurrence, some could have arisen due to insufficient sterilization of the primary as well (Fig. 3). There is significant literature that supports dose escalation with both external beam radiation therapy (EBRT) and combined modalities, with high-dose EBRT producing 78% 5-year freedom from BF and combined modality producing up to 78% 9-year freedom from BF [21,22]. At a median follow up of 6.5 years, Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) demonstrated a

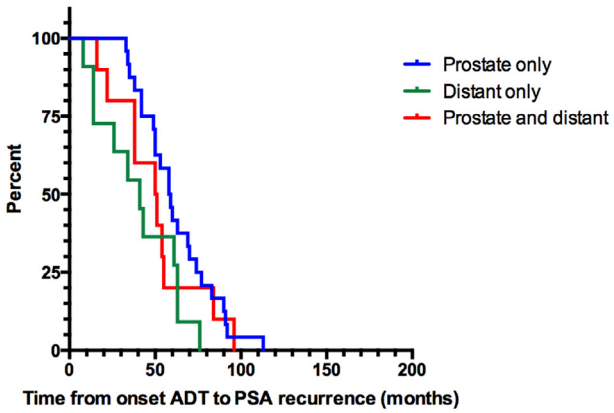


Fig. 3. Time from onset androgen deprivation therapy (ADT) to PSA recurrence stratified according to site of recurrence (prostate only; $n = 24$, distant only; $n = 11$, prostate and distant; $n = 10$).

significant increase in biochemical recurrence free survival among men who received brachytherapy and ADT with elective nodal radiation as compared to men who received only dose-escalated EBRT, and BF was predictive of worse OS [23]. The findings of ASCENDE-RT combined with our data indicate that it may be possible to reduce local (and potentially distant) recurrences through local dose escalation, concurrent-adjuvant ADT use and pelvic radiation.

Second, the risk of recurrence in the pelvic lymph nodes is similar for N1 and N0 patients. However, mrN1 patients had a high rate of prostatic and distant recurrence (69%), potentially identifying a high-risk phenotype among this cohort. Given that mechanism of metastasis is affected by and that therapy itself can induce oncogenic changes in phenotype [24], further genomic research could help determine which patients need aggressive treatment with local dose escalation. Interestingly, whereas there was a large difference in recurrence rate and survival between N0 and N1 as determined by MRI, no difference was found with surgical staging (Fig. 5). These results must however be interpreted with caution: the study design was not designed for comparison, and lymph node removal may have been therapeutic. Nevertheless, MRI nodal staging in our cohort was able to predict recurrence, potentially identifying a

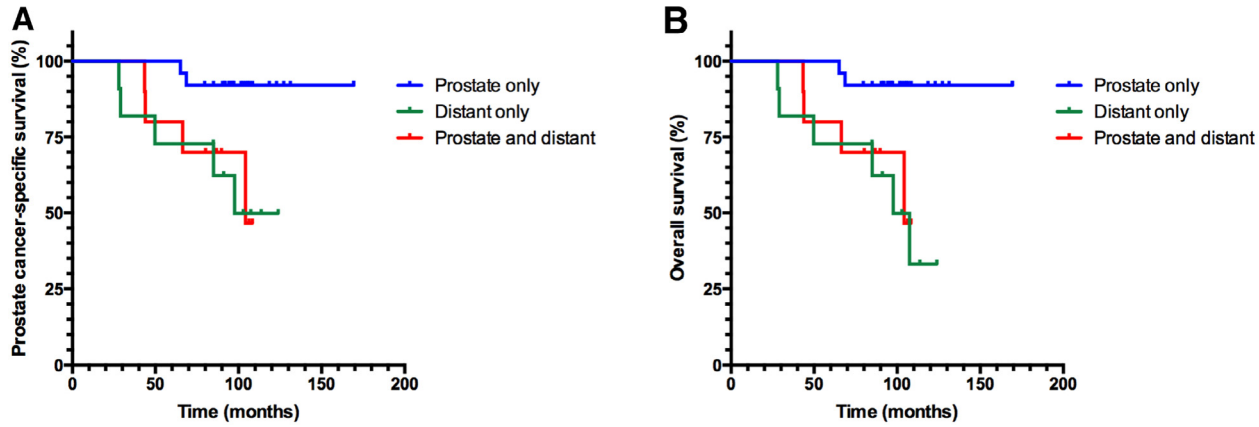


Fig. 4. Prostate cancer-specific survival (A) and overall survival (B) stratified according to site of recurrence ($n = 46$).

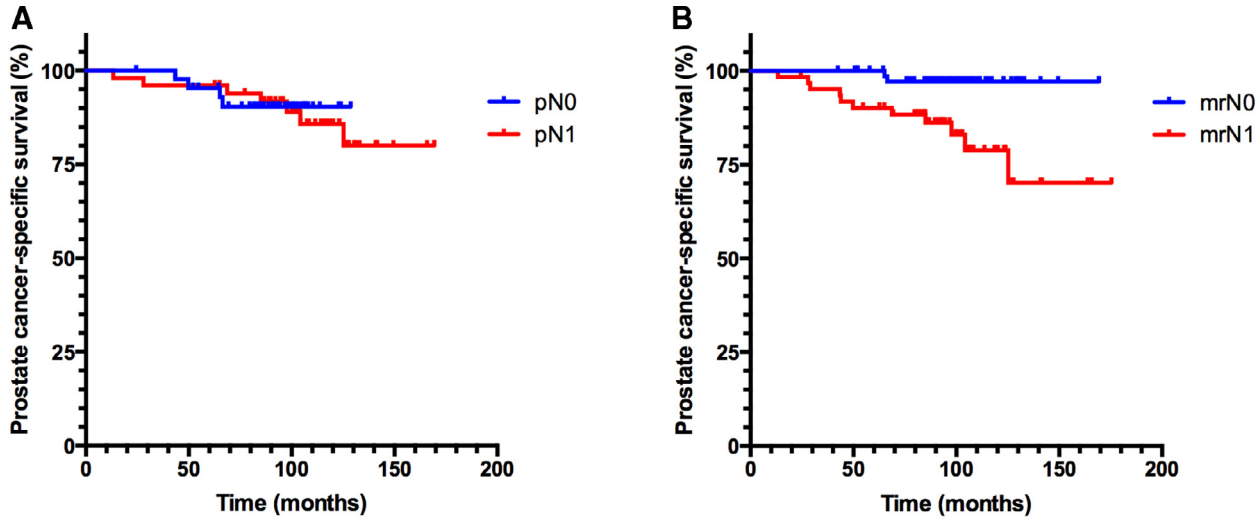


Fig. 5. Prostate cancer-specific survival according to surgical N-staging (A) og MR N-staging (B).

subset of patients that could benefit from more aggressive treatment.

Finally, pelvic lymph node dissection may not be necessary in high-risk patients as moderate dose radiation appears to consolidate this region. Forty-six patients had lymph nodes on MRI, but only 3 patients overall developed lymph node recurrence (all with distant metastasis). Recent studies have suggested that the addition of local therapy in N1 disease can have profound effects on survival [25]. Specifically, there may be long-term disease control for N1 patients treated locally [26] as patients with 2 or fewer positive lymph node metastases have experienced long survival in pN1 prostate cancer [27]. A recently published meta-analysis including over 270,000 patients echoes this sentiment, concluding that lymph node dissection had no direct benefit and potentially worse outcomes [28]. Taken with the above, our study suggests lymph node dissection may not be beneficial in patients with limited disease if they have nodal radiation with long-term ADT.

The main limitations of this study are related to study design and study cohort. The design was not appropriate for a diagnostic accuracy study for comparison of surgical vs. radiological staging. The aim was to discriminate between loco-regional and systemic recurrence, not to detect the number and localization of metastases that would require whole-body coverage. Even though it is likely that emerging technologies, such as whole-body MRI and Prostate Specific Membrane Antigen (PSMA) PET/CT would have detected more recurrences, the distinct pattern that appears in our data might not have been very different: Prostate cancer mainly spreads slowly upward [17] and higher sensitivity would probably affect all locations to the same extent. Limitations stemming from the small single institution cohort include: (1) There are no randomized controls and thus subject to many different types of potential bias. (2) The study size was small and may not reflect the population at large. (3) The population under study is ethnically homogeneous, which also may limit applicability to heterogeneous populations. (4) Social factors and other comorbidities are not accounted for, potentially introducing confounding factors. (5) Not all patients with purely local recurrence received confirmatory imaging. (6) A single radiologist reviewed all the imaging, potentially introducing bias.

5. Conclusion

In conclusion, this cohort of high-risk locally advanced prostate cancer patients had minimal lymph node recurrences, presumably due to nodal radiation, with prostatic recurrence and distant spread predominating. Our data argue for further dose escalation given the predominance of local recurrences. Unfortunately, metastatic disease still has high mortality, and alternative therapies should be explored for these patients.

Conflict of interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urolonc.2018.09.016.

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