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Pelvic lymph node recurrence in high-risk prostate cancer following prostate-only radiotherapy

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Original Article

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Abstract

Introduction: High-risk prostate cancer is the most common presentation at our institute among patients with non-metastatic prostate cancer. Traditionally, pelvic lymph nodes were given a prophylactic dose of radiotherapy while the prostate was given a curative dose of radiation. This study aims to evaluate patterns of failure in patients who had prostate-only radiation at our centre.

Materials and Methods: All high-risk prostate cancer patients who underwent radical radiotherapy to prostate only since 2014 were retrospectively analysed. Local T stage, baseline prostate-specific antigen (PSA) and Gleason score were recorded. Bone scan and staging CT scan data were collected. Various dose levels prescribed to prostate were analysed. The follow-up records of these patients were assessed. Patients who failed in pelvic lymph nodes were recorded separately. Overall survival and failure-free survival were calculated using Kaplan–Meier curve.

Results: One-hundred five patients fulfilling the inclusion criteria were analysed. Only three patients developed recurrence in pelvic lymph node following prostate-only radiotherapy (PORT). Five year overall survival was 77% while failure-free survival was 64%. Forty patients had a PSA failure after a median follow-up of 62 months.

Conclusions: Most high-risk prostate cancer patients who progress following hormone therapy and PORT have metastases outside pelvis. Till further conclusive evidence is available PORT can be considered as a safe option.

Introduction

Prostate cancer is the most common malignancy among male patients presenting to Oncology Department at this hospital which is in line with international statistics.[1] Being an underdeveloped nation combined with a lack of primary care, most patients with prostate cancer present late in our set-up. Hence among non-metastatic disease, high-risk prostate cancer is the most common presentation as opposed to western population where low-risk disease is more common.[2] Risk grouping in non-metastatic prostate cancer was initially coined by D'Amico et al. which has been adopted ever since globally and with some modifications in most recent National Comprehensive Cancer Network prostate cancer management guidelines.[3,4] Higher the risk group, more are the chances of distant metastases as well as pelvic lymph node failure. Ever since the publication of RTOG 9413 results, elective treatment of pelvic lymph nodes with radiation therapy has been practised with some scepticism as there was no overall survival (OS) benefit seen with this approach despite having disease-free survival advantage.[5] Initial and long-term results of GETUG-01 have showed no survival benefit in a cohort of patients who received a prophylactic dose of radiotherapy to pelvic lymph nodes, that is, whole-pelvis radiotherapy (WPRT).[6,7] Because of lack of standardisation regarding treatment of radiotherapy, STAMPEDE trial protocol did not mandate WPRT or prostate-only radiotherapy (PORT) and left it to organisational or individual decision.[8]

Primary lymph node drainage area for prostate includes proximal external iliac, obturator, internal iliac, peri-rectal and pre-sacral lymphatic regions.[9] The aim of treating these lymph nodes electively is to eliminate the micrometastases harbouring in them.[6] WPRT was performed routinely at our hospital since long until results from RTOG 9413 and GETUG-01 were available. Since then, there is a trend to omit pelvic lymph nodes from the radiotherapy treatment volume to avoid unnecessary side effects and a gradual move towards PORT. With the availability of 3D techniques and the use of the latest radiotherapy techniques like intensity-modulated radiotherapy (IMRT), dose escalation for better disease control was the preferred approach. While IMRT helped in dose escalation, it also helped in decreasing doses to organ-at-risk (OAR) which resulted in lesser toxicity from WPRT. The dose escalation for prostate stems from the concept of lower α/β ratio for prostate cancer, which has been proposed

at 1·5–3 Gy range.[10–12] With this low α/β ratio, hypofractionation is hypothesised to enhance the therapeutic ratio by increasing local control without increasing the side effects. With better techniques of targeting the prostate, interest in PORT with escalated doses increased significantly. At our institute, since the availability of 3D simulation techniques in 2013, an overwhelming majority of high-risk non-metastatic prostate cancer patients were treated with PORT with neoadjuvant and adjuvant hormone therapy for a total of 2–3 years.

The aim of this study is to analyse the data of patients treated with PORT at this institute and see patterns of recurrence, especially those who had recurrence in pelvic lymph nodes.

Materials and Methods

A retrospective analysis of prostate cancer patients treated with PORT from 2014 to 2017, at Radiation Oncology Department of this hospital was carried out. All patients with prostate cancer who received PORT were initially shortlisted. Patients having histopathological diagnosis of prostate adenocarcinoma with Gleason score (GS) 8–10, or prostate-specific antigen (PSA) more than 20 ng/mL or AJCC stage T2c or above were included in the study.[13] Patients having any one of the above factors were classified as high-risk group as per NCCN guidelines version 2021·1.[4] A small cohort of patients with low burden metastatic disease (as per STAMPEDE trial criteria) who also received radical dose PORT were included in the study. Shortlisted patients had Hb > 10 g/dL, normal serum urea and creatinine, normal liver function tests and were Eastern Cooperative Oncology Group (ECOG) performance status 0–1. Any patients with prior history of another malignancy, prior radiotherapy or prior chemotherapy for another malignancy were excluded from the cohort. Patients having metastatic disease detected on CT scan or a bone scan combined with a PSA > 100 but were treated as metastatic prostate cancer without a biopsy, were excluded from the study.

All eligible patients underwent histopathological diagnosis either through Transrectal Ultrasound biopsy or were incidentally diagnosed following Trans Urethral Resection of Prostate for treatment of their lower urinary tract symptoms. Patients having GS of 8–10, who did not undergo prior staging investigations had their staging investigations done with a bone scan and CT scan of chest, abdomen and pelvis. MRI pelvis was also carried out if not done prior to biopsy. Pre-biopsy PSA was recorded and in patients where pre-biopsy PSA was not recorded, PSA was measured 4 weeks after biopsy. All patients were treated with gonadotrophin-releasing hormone (Gnrh) agonist leuprolide or goserelin. Bicalutamide 50 mg per day was advised at commencement of hormone therapy and was offered for at least 14 days prior to first dose of Gnrh agonists. Patients with metastatic disease went on to receive chemotherapy or abiraterone in first 12 weeks at the start of hormone therapy. Androgen deprivation therapy (ADT) was continued for 2–3 years for non-metastatic cohort and indefinitely for the patients with metastatic disease.

Radiotherapy was planned at an interval of 4–6 months after the start of hormone therapy to have maximal downstaging before local definitive treatment. Different radical dose schedules of radiotherapy were permitted. Contouring guidelines of CHIPP trial protocol were widely followed for radiotherapy planning purpose.[14] Radiotherapy planning was done using IMRT or volumated arc therapy using ECLIPSE treatment planning software by VARIAN Inc. Daily cone beam CT scan (CBCT) was used for positional verification during treatment delivery.

At the end of radiotherapy, all patients were monitored with serial PSA reading done every 3–4 months for 5 years according to American Society of Therapeutic Radiation Oncology guidelines for localised prostate cancer.[15] After 5 years, patients were advised to have PSA repeated every 6 months for another 5 years. These readings were recorded and all those patients who had a PSA failure based on Phoenix definition of a rise of PSA of more than 2 ng/mL above the nadir value were further investigated with bone scan and CT scan only as choline or PSMA PET scans were not available back then.[16]

Patients with rising PSA despite castrate levels of testosterone who were receiving ADT were reclassified as either metastatic castrate resistant prostate cancer (mCRPC) or non-metastatic castrate-resistant prostate cancer (nmCRPC) depending on whether metastases were detected or not, respectively. Patients who had completed ADT were restaged and classified as metastatic hormone-sensitive prostate cancer (mHSPC) if metastasis was detected. Primary endpoint was pelvic lymph node failure rate. OS and failure-free survival (FFS) was also calculated using the Kaplan–Meier survival analysis using SPSS version 20.

Results

Two-hundred thirty-six prostate cancer patients were treated during the specified time period at this institute. A total of 105 prostate cancer patients fulfilling the inclusion criteria were retrospectively analysed. Mean age was 68·8 years (SD: 6·18). Median follow-up time was 62 months (Range: 18–94). Approximately 9 out of 105 patients had metastatic disease while only one patient had positive lymph node at diagnosis. Basic features are detailed in Table 1.

There were 40 patients in the cohort who had a PSA failure as per Phoenix definition. Only 3 out of these 40 had a metastatic disease in their pelvic lymph nodes either alone or in combination with metastasis at other sites as well. First patient had a GS of 5 and a T4 disease due to invasion of pelvic side wall at diagnosis. This patient was found to have a normal bone scan but a 2·2 cm lymph node in right internal iliac region without any other suspicious site on the scan for metastasis after being reinvestigated secondary to PSA failure. He was treated with stereotactic radiotherapy to the lymph node and responded well to that since he was alive at follow-up of 86 months without any on going hormone therapy.

Second patient who relapsed in pelvic lymph nodes had a GS of 10 and involvement of bilateral seminal vesicles at diagnosis and a PSA of 66·8 ng/mL. He had a PSA relapse at 13 months. His restaging scans showed multiple vertebral metastases along with left external and internal iliac lymph nodes. He progressed quite rapidly to subsequent lines of treatment and died of prostate cancer at 36 months post-diagnosis.

Third patient had a GS of 9 and pelvic floor muscle abutment at diagnosis. He also had low volume metastatic disease as per CHAARTED definition.[17] Thus, he was offered PORT. He had a PSA relapse at 29 months. There was no progression in bones but a solitary lymph node of 1·5 cm in short axis diameter was seen adjacent to bladder on the right side. Stereotactic radiotherapy was not suitable due to high bladder dose during prior PORT. Subsequent therapy with abiraterone showed good PSA response and patient is continuing on that till last follow-up at 46 months.

Sixty-five patients had adequately controlled PSA while 40 had a PSA failure at some point during their follow-up. Out of these 40 who had PSA failure, 4 were diagnosed as nmCRPC and were treated with ADT and enzalutamide. Twenty-two patients were

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Table 1. Patient characteristics

Sample characteristics	Statistics
Age	Mean : 68·8 years (SD: 6·18)
PSA	Mean: 49·4 ng/mL (SD: 31·7)
	Median: 42·3 ng/mL (range: 3·6–164)
GS	Frequency (%)
6	10 (9·5)
7	16 (15·2)
8	31 (29·5)
9	31 (29·5)
10	17 (16·2)
T stage	Frequency (%)
T1–T2a	13 (12·4)
T2b	5 (4·8)
T2c	27 (25·7)
T3	54 (51·4)
T4	6 (5·7)
PSA failure	Frequency (%)
No	65 (61·9)
Yes	40 (38·1)
Dose	
55 Gy in 20 fraction	42 (40·0)
74 Gy in 37 fractions	17 (16·1)
60 Gy in 20 fractions	42 (40·0)
57 Gy in 19 fractions	3 (2·8)

reclassified as mCRPC. Ten patients had mHSPC while no metastases were detected in five patients but they remained sensitive to hormone therapy. Only one patient had isolated progression in pelvic lymph node without having any metastatic disease and was treated with stereotactic radiotherapy as mentioned above. FFS was 64% at 5 years. Median time to PSA failure in the 40 patients was 35·5 months (Range: 8–94). Kaplan–Meier curve for FFS is shown in Figure 1.

Seventeen patients had died during follow-up; out of which, 11 were due to prostate cancer and 6 patients succumbed to other causes. Seventeen patients in total were lost to follow-up. Reasons are not available for this high number of patients being lost to follow-up. Five year OS was 77%. Kaplan–Meier survival curve is shown in Figure 2.

Discussion

Radiotherapy to the prostate is crucial part of treatment for high-risk non-metastatic prostate cancer since long. Recently STAMPEDE trial has shown benefit of PORT in low-risk metastatic prostate cancer as defined by CHAARTED trial protocol.[17,18] However, whether to include pelvic lymph nodes in high-risk non-metastatic prostate cancer inside the treatment field or not has long been studied with variable answers. Occult pelvic lymph node metastases, despite negative radiological imaging studies are common in high-risk prostate cancer. We retrospectively analysed our practise and found very few pelvic lymph node failures as mentioned above. Whether these results are in line with prior randomised trials or not will be discussed here.

RTOG 9413 was among the first of these trials to explore the issue in question.[5] With more than 600 patients in each RT arm with or without pelvic RT, the nodal failure rates were exceptionally low at 1·3 and 2·5%, respectively. Eight percentage of patient population in GETUG-01 had local, nodal or distant failure in whole study population without any significant differences in arms with or without radiotherapy.[7] Although not separately mentioned, it amounts to approximately 17 cases of PORT arm which had 222 patients. Pelvic lymph node failures were not separately reported by GETUG-01. In our study, 2·8% patients, that is, 3 out of 105 cases developed failure in their regional lymph nodes. This bodes well with prior studies mentioned above. A very recently published POP-RT trial showed 15 regional recurrences in 114 patients (13·1%) in PORT arm as compared to 1 out of 110 patients treated with WPRT (0·9%).[19] This is the only known prospective randomised trial to have shown a significant difference in this regard.

Not all studies published on this subject had reported pelvic lymph node failure rates separately but have mentioned the lack of definitive benefit of WPRT in terms of OS, event-free survival or progression-free survival (PFS). A retrospective comparative study of 596 patients by Vargas et al showed no benefit of WPRT in terms of OS, rates of clinical failure or cause-specific survival.[20] While RTOG 9413 did show a significant 4-year PFS advantage without translating into OS advantage even with longer follow-up; there was no PFS advantage seen in GETUG-01 trial in favour of WPRT.[5,7] POP-RT did show significant biochemical failure-free survival, distant metastases free survival and disease-specific survival in favour of WPRT.[19] While RTOG 9413 and GETUG-01 do not recommend WPRT, POP-RT did conclude in favour of WPRT based on significant differences in above-mentioned endpoints.[5,7,19]

No OS benefit was seen in POP-RT, RTOG 9413 or GETUG-01 trials.[5,7,19] Five year OS from our analysis has been compared with PORT arms of these trials in Table 2 and it shows that OS in our study is somewhat less than these studies. This may be explained by the fact that the population in our study had 10% patients with metastatic disease. Also that median PSA in our study was markedly higher than all three randomised trials in discussion as shown in Table 2. Eight out of 17 patients were lost before reaching median follow-up time. Variations in OS are also expected due to different inclusion criteria among these trials, for example, intermediate-risk disease patients being included in GETUG-01.[7] Forty-two patients in our study received 55 Gy in 20 fractions which was the dose in arm H of STAMPEDE.[18] However, this has since been replaced with 60 Gy in 20 fractions after publication of CHIPP trial results.[14] Fifty-five Gy in 20 fractions is no more practised at our centre as a radical dose to prostate.

Since the publication of STAMPEDE arm H, it is well accepted that radiotherapy to the primary disease site is the corner stone of treatment.[18] Based on prior results from RTOG 9413 and GETUG-01, WPRT was not tested in arm H of STAMPEDE while the patients included in this trial were at the highest risk of lymph node metastases in the pelvis.[18] It would be interesting to know how the patients in arm H faired in terms of relapse in the regional lymph nodes. The final answer to the question of treating pelvic lymph nodes or otherwise is awaited from RTOG 0924; results of which are expected in late 2021 since the accrual has long been closed. It is testing the same question in unfavourable and

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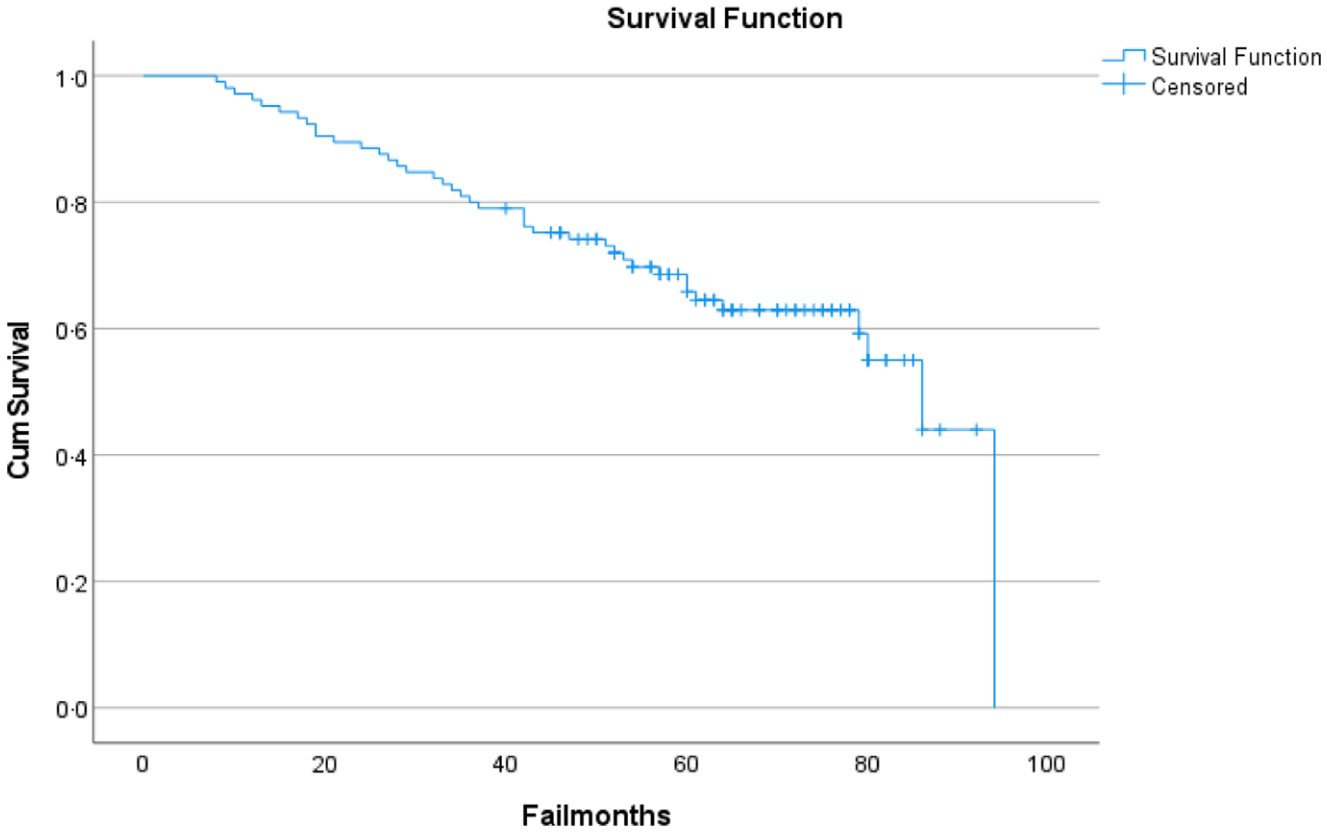

Figure 1. Kaplan–Meier curve for failure-free survival.

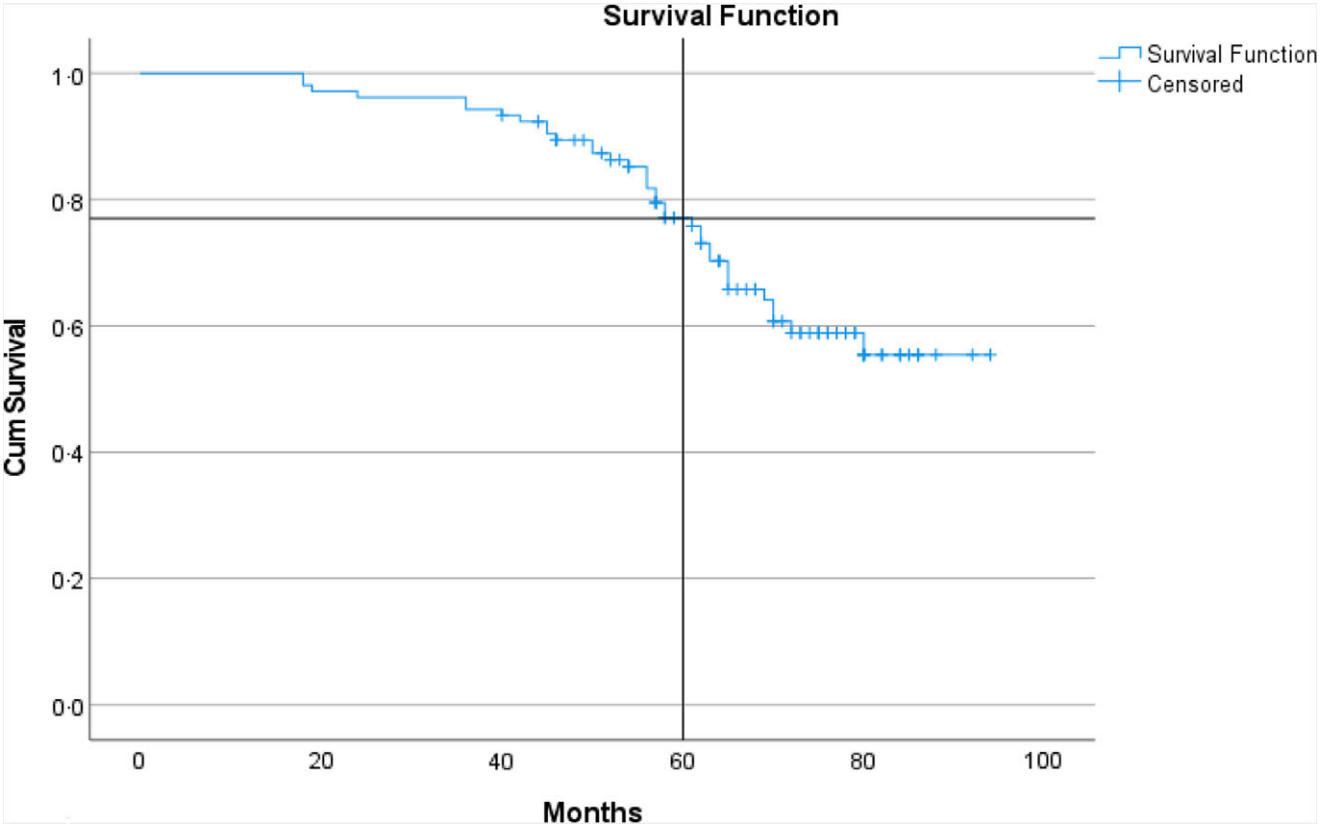

Figure 2. Kaplan–Meier curve for overall survival.

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Table 2. Comparison of Inclusion criteria, 5-year overall survival, prostate-specific antigen (PSA) levels pelvic LN failure rates

Clinical trial	Inclusion criteria	5 year OS (%)	Median PSA (ng/mL)	Pelvic LN failure rates in PORT (%)
RTOG 94,13[5]	Non-metastatic prostate cancer with estimated LN involvement of >15% based on Roach formula who were cN0	84·3	22·6	2·5
GETUG-01	Non-metastatic prostate cancer who were cN0	88·3	11	Not reported
POP-RT	Non-metastatic prostate cancer with estimated LN involvement of >20% based on Roach formula	90·8	28·2	13·1
Current study	High-risk non-metastatic prostate cancer and low burden metastatic prostate cancer	77	42·3	2·8

Abbreviation: LN, lymph node.

high-risk non-metastatic prostate cancer. Some might argue in favour of WPRT since we have some positive results from POP-RT, but the number of patients in the trial were quite less for a phase –III trial ($n = 224$).

In this study, we tried to analyse outcome in our patient population treated with PORT and compare it with available data. The obvious weakness of the study is that it is a retrospective analysis and that too single arm. We wanted to compare it with data from patients treated at our centre who had received WPRT prior to the current trend but data were insufficient to make a comparison. Based on available results, prophylactic pelvic lymph node radiation may not be necessary due to very low rates of disease failure in pelvic lymph nodes, in patients with high-risk non-metastatic prostate cancer and metastatic prostate cancer who do not harbour lymph node disease at presentation till further Phase 3 data is available. Till then, prostate-only radiation can be practised as a safe option after thorough discussion with the patient.

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Conflicts of Interest. The authors declare none.

References

1. Stavrinides V, Parker CC, Moore CM. When no treatment is the best treatment: active surveillance strategies for low risk prostate cancer. Cancer Treat Rev 2017; 58: 14–21 doi: 10.1016/j.ctrv.2017.05.004
2. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow up. Lancet 2014; 384 (9959): 2027–2035. doi: https://doi.org/10.1016/S0140-6736(14)60525-0
3. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. J Am Med Assoc 1998; 280: 969–974.
4. National Comprehensive Cancer Network Guidelines for Prostate Cancer. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1459. Assessed on 30th April 2021.
5. Roach M, DeSilvio M, Lawton C, et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. J Clin Oncol 2003; 21 (10): 1904–1911. doi: 10.1200/JCO.2003.05.004
6. Pommier P, Chabaud S, Lagrange JL, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Update of the long-term survival results of the GETUG-01 randomized study. Int J Radiat Oncol Biol Phys 2016; 96 (4): 759–769. doi: 10.1016/j.ijrobp.2016.06.2455
7. Pommier P, Chabaud S, Lagrange JL, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. J Clin Oncol 2007; 25 (34): 5366–5373. doi: 10.1200/JCO.2006.10.5171
8. STAMPEDE Trial Protocol. http://www.stampedetrial.org/media/2530/stampede-protocol_v210_20-oct-20_clean.pdf. Assessed 30 April 2021.
9. Breyer BN, Greene KL, Dall'Era MA, Davies BJ, Kane CJ. Pelvic lymphadenectomy in prostate cancer. Prostate Cancer Prostatic Dis 2008; 11 (4): 230–324.
10. Onjuka E, Uzan J, Baker C, Howard L, Nahum A, Syndikus I. Twenty fraction prostate radiotherapy with intra-prostatic boost: results of a pilot study. Clin Oncol 2017; 29: 6–14.
11. Hegeman SN, Guckenberger M, Belka C, Ganswindt Ute, Manapov F, Li M. Hypofractionated radiotherapy fpr prostate cancer. Radiat Oncol 2014; 9 (275). https://doi.org/10.1186/s13014-014-0275-6
12. Tree AC, Alexander EJ, Van As NJ, Dearnaley D, Khoo V. Biological dose escalation and hypofractionation: what is there to be gained and how will it best be done? Clin Oncol (R Coll Radiol) 2013; 25: 483–498.
13. Amin HB, et al. AJCC Cancer Staging Manual, 8th Edition. Switzerland: Springer International Publishing, 2017.
14. Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high dose intensity-modulated radiotherapy for prostate cancer: 5 year outcomes of the randomised, non-inferiority, phase 3 CHHIP trial. Lancet Oncol 2016; 17 (8): 1047–1060. doi: 10.1016/S1470-2045(16)30102-4
15. Clinically Localised Prostate Cancer. https://www.astro.org/uploadedFiles/_MAIN_SITE/Patient_Care/Clinical_Practice_Statements/Content_Pieces/ClinicallyLocalizedProstateCancer.pdf. Assessed on 4th April 2021.
16. Matthew C, Abramowitz MC, Tiaynu Li T, et al. The Phoenix definition of biochemical failure predicts for overall survival in patients with prostate cancer. Cancer 2008; 112 (1): 55–60. https://doi.org/10.1002/cncr.23139
17. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015; 373: 737–746. doi: 10.1056/NEJMoa1503747
18. Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet 2018; 392 (10162): 2353–2366. doi: https://doi.org/10.1016/S0140-6736(18)32486-3
19. Murhy V, Maitre P, Kannan S, et al. Prostate-only versus whole-pelvic radiation therapy in high-risk and very high-risk prostate cancer (POP-RT): outcomes from phase III randomized controlled trial. JCO 2021; 39 (11): 1234–1242. doi: 10.1200/JCO.20.03282
20. Vargas CE, Galalae R, Demanes J, et al. Lack of benefit of pelvic radiation in prostate cancer patients with a high risk of positive pelvic lymph nodes treated with high-dose radiation. Int J Radiat Oncol Biol Phys 2005; 63 (5): 1474–1482. doi: 10.1016/j.ijrobp.2005.04.026. Epub 2005 Jun 20.

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