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Overview

Prostate Radiotherapy in India: Evolution, Practice and Challenges in the 21st Century

V. Murthy *, I. Mallick †, M. Arunsingh †, P. Gupta *

* Department of Radiation Oncology, Tata Memorial Hospital and Advanced Centre for Treatment Research and Education in Cancer (ACTREC), Homi Bhabha National Institute, Mumbai, India
† Department of Radiation Oncology, Tata Medical Center, Kolkata, India

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Abstract

The practice of prostate radiotherapy is evolving rapidly while there is an increase in the incidence of prostate cancer in India. Here, the diverse socioeconomic milieu and varied healthcare delivery models interact to exert a significant influence on the adoption of new technologies and evidence emerging from the Western world. Using a targeted cross-country survey of radiation oncologists, this article captures the changing trends in prostate imaging, conformal techniques, dose escalation, hypofractionation, stereotactic ablation and prostate brachytherapy in the context of practice patterns in the West. New directions in research on prostate cancer are highlighted, reflecting the unique challenges of the disease profile and treatment resources in India.

Key words: India; patterns of practice; prostate cancer; prostate radiotherapy

Statement of Search Strategies Used and Sources of Information

This article refers to the key international randomized controlled trials that are pertinent to the topics covered in the article. These have been curated by the authors based on consensus. For each of the topics, the authors searched for English language articles published or presented from Indian institutions through a search that included the keyword 'India' in PubMed and Google Scholar. Curated results were incorporated in the context of the results of the nationwide survey.

Introduction

The incidence of prostate cancer has been steadily increasing in many Asian countries, including India. Curative treatments for prostate cancer, including radiotherapy, are simultaneously evolving due to better awareness, improved diagnosis, expansion of radiotherapy services and availability of modern treatment techniques. With a backdrop of prostate radiotherapy evolution in the West, this article focuses on the changing treatment patterns of prostate radiotherapy in India. We trace the adoption (or the lack thereof) of conformal techniques, image guidance and brachytherapy, and assess the evolution of hypofractionation and stereotactic techniques in the context of rapidly emerging evidence from the West.

For the purpose of this review, a targeted email-based survey was undertaken among radiation oncologists in India to understand the patterns of practice of prostate radiotherapy (Table 1). The survey was specifically sent to a cohort of oncologists who, in the opinion of the authors, would be representative of the geographical diversity, varying experience and the different healthcare delivery models in the country (Figure 1). They were asked a range of questions aimed at identifying patterns of patient presentation, current practices in workup and curative-intent radiotherapy treatment practices in the radical, postoperative and oligometastatic settings. It also asked about

Author for correspondence: V. Murthy, Department of Radiation Oncology, Tata Memorial Hospital, Dr Ernest Borges Road, Parel, Mumbai 400 012, India. Tel: +91-22-24177029.
E-mail address: vmurthy@actrec.gov.in (V. Murthy).

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Table 1
Survey questionnaire

1. Name
2. Email address
3. About your institution
- Governmental
- Non-governmental/Non-profit
- For profit hospital
4. Among the prostate cancer patients treated with curative-intent radiotherapy at your centre, specify the distribution of the following groups in percentage:
- Radical external beam radiotherapy
- Post-prostatectomy radiotherapy
- Brachytherapy
- Prostate-directed radiotherapy for oligometastatic disease
- Metastasis-directed radiotherapy for oligometastatic disease
5. Does a multidisciplinary team (MDT) decide the treatment strategy for prostate cancers?
- Most patients with prostate cancer are discussed in the MDT
- Some patients with prostate cancer are discussed in the MDT
- We don't have an MDT for discussing prostate cancer cases
6. Do you routinely use MRI pelvis for radiotherapy planning?
- Yes
- No
7. Do you routinely use PSMA PET CT for staging?
- Yes
- No
8. What is the most common risk group that patients present with?
- Low risk
- Intermediate risk
- High risk
- Node positive
9. When using EBRT for radical-intent radiotherapy, do you perform
- Conventionally fractionated radiotherapy
- Moderate hypofractionated radiotherapy
- Ultra-fractionated radiotherapy/stereotactic radiotherapy
10. What proportion of radical EBRT are treated with moderate hypofractionation?
11. What proportion of radical EBRT are treated with ultra-fractionation?
12. Most common dose fractionation (Answer in this format: xxxx cGy in yy fractions over zz weeks)
- You use currently
- You used 5 years ago
13. Most common EBRT technique used
- 3D conformal radiotherapy
- IMRT with or without IGRT
14. Use of image guidance
- None
- 2D kV orthogonal imaging
- CBCT
15. Frequency of use of image guidance
- Once daily
- Less than daily
16. If you don't routinely treat using hypofractionation, choose from the options below why you don't use hypofractionation?
- I don't believe it to be superior to conventional fractionation
- It causes more toxicity
- I don't have the technology needed to confidently practice hypofractionation
17. If you don't routinely treat with brachytherapy, choose from the options below why you don't use brachytherapy?
- I am not trained in prostate brachytherapy
- I don't believe it to be superior to EBRT
- There are not enough patients suitable for prostate brachytherapy to run a cost-effective brachytherapy service at my institute
- It causes more urinary toxicity
18. In post-prostatectomy with high-risk features (pT3/4, margin positive, seminal vesicle involvement, high Gleason), what is your usual institutional practice?
- Adjuvant radiation therapy
- Monitor and treat with early salvage treatment if required

(*continued on next page*)

Table 1 (*continued*)

19. What is your common fractionation schedule in the postoperative setting?
• Conventional fractionation
• Hypofractionated radiotherapy
20. In patients with oligo-metastatic prostate cancer, do you perform
a. Prostate-directed radiotherapy
• Yes
• *No*
21. In the last 5 years of your clinical/institutional practice, have you noted any changes in the following (answer as increased/unchanged/decreased)
• No. of patients treated with radical-intent radiotherapy
• No. of patients treated with post-prostatectomy radiotherapy
• Patients treated with IMRT
• Patients treated with image guidance
• Patients treated with hypofractionated schedules
• Postprostatectomy patients treated with early salvage instead of adjuvant therapy
• Radiation for oligometastatic disease

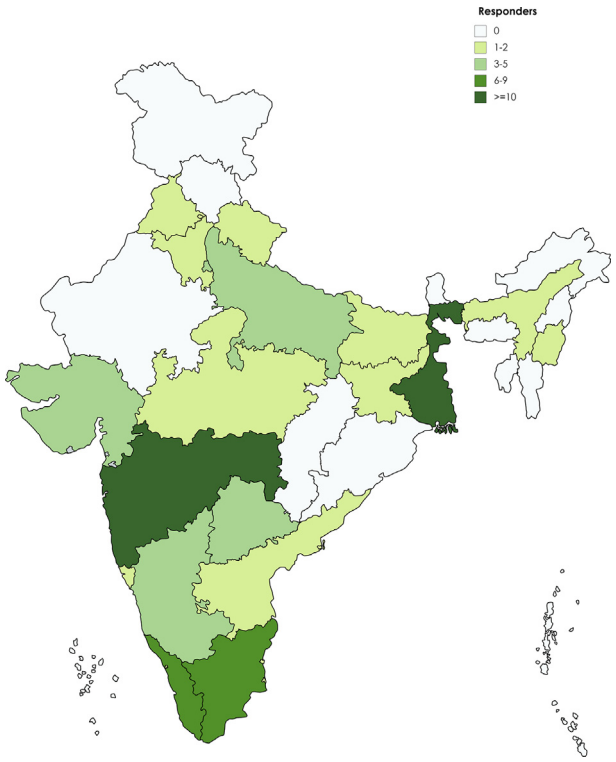

Fig 1. Geographical distribution of the radiation oncologists responding to the survey.

the changes in individual clinical practice in the last 5 years. The survey was emailed to 126 candidates; 88 complete responses (70%) were received over a period of 4 weeks (Appendix 1). The results from the survey are incorporated in each section of the article.

Epidemiology

Incidence and mortality trends of prostate cancer across continents reflect a stark healthcare divide. The age-standardised rate of incidence for prostate cancer per 100 000 in 2018 was 62.1 in Europe but was only 11.5 in Asia. For India, a high number of prostate cancer deaths in relation to its low overall incidence is reflected in the incidence and mortality age-standardised rates of 4.4 and 2.9, respectively, in contrast to the UK, where these rates are 80.7 and 12.7, respectively [1]. Large swathes of the Asian population have restricted access to systematic cancer screening and guideline-based cancer care, whereas low-risk prostate cancer is being over-detected in the West. GLOBOCAN 2018 projects a 100% increase in prostate cancer incidence in Asia by 2040 [2]. India is projected to have 61 222 prostate cancer cases by 2020 [3], similar to many European nations. Population-based cancer registries of Delhi, Mumbai and Bangalore metropolitan cities already have prostate cancer as the third most common male cancer [3].

Global prostate cancer guidelines emerge from multi-institutional trials with very low representation of the Asian–Indian ethnicity. Population-specific traits of prostate cancer in India may be overlooked [4]. Higher cut-offs for prostate-specific antigen (PSA) and PSA density may be required in Indian men for transrectal biopsies to improve yield [5,6]. National guidelines to standardise patient care are therefore needed, recognising the challenges and solutions for prostate cancer management in India in the context of large socioeconomic diversity and swift urbanisation.

Clinical Presentation

Screening for prostate cancer is absent in India as it is considered to be a low priority in public healthcare. In the West, PSA-based screening programmes have led to the diagnosis and treatment of a large proportion of low-risk cancers without very clear evidence of benefit, leading to recent modifications in practice recommendations [7]. By contrast, in India, the diagnosis of prostate cancer is most often prompted by clinical symptoms rather than routine PSA screening and >80% of new patients present with advanced disease [8]. Almost 60% of new prostate cancer patients at Tata Memorial Hospital in Mumbai had metastatic disease [9]. In one study examining four different

populations, a smaller proportion of patients from India had a Gleason 6 score at diagnosis [10]. Mortality is therefore disproportionately high, despite the lower relative incidence; annual prostate cancer deaths are estimated to be 17 184 in India against 13 145 in the UK [11]. Respondents to our survey uniformly indicated that about 81% of the patients presenting with non-metastatic disease were in the high-risk group. Less than 5% of patients had low-risk disease. This proportion was similar in governmental/non-profit centres and for-profit hospitals. Low awareness and restricted healthcare access are major obstacles in India, especially for the elderly and advanced-stage patients. Considering the healthcare budget constraints, targeted improvement in primary clinician awareness and symptom-based screening seem to be more practical than population-based screening to reduce mortality.

Appropriate use of available diagnostic and staging tools is also a challenge, such as a simple PSA assay for early detection. Enzyme-linked immunosorbent assay (ELISA)-based manual PSA assays are still common in smaller Indian cities, but they are prone to high inter-assay variability and discordance from automated assays with possible management-altering consequences [12]. Most of the advanced imaging facilities such as magnetic resonance imaging [MRI] and positron emission tomography-computed tomography [PET-CT] are privately owned, leading to high out-of-pocket expenditure. Ironically, this largely non-insurance healthcare spending pattern is stimulating the enthusiastic embracement of newer technologies by a burgeoning, upwardly mobile middle-income group. For instance, prostate-specific membrane antigen (PSMA)-based PET-CT is increasingly available, even in smaller metropolitan areas of India, despite being more costly and scarce than FDG PET-CT, based on its promise of being 'prostate specific'. Of the survey respondents, 51% reported the use of PSMA PET-CT for some or all of their patients for staging prostate cancer. Expectedly, a higher proportion of respondents from for-profit centres used PSMA PET-CT compared with government/non-profit centres (58% versus 42%). Its rising use in both diagnosis and response assessment is pushing down costs further due to economics of scale. This process is often lengthier in the West owing to tighter regulations for justifying governmental or insurer expense.

The role of multidisciplinary assessment is well appreciated in our survey results. Only 19% of the survey respondents did not have any multidisciplinary team meetings for prostate cancer in their institution and as many as 37% discussed most of their patients in multidisciplinary teams. Although this is encouraging, there is clearly much scope for closer multidisciplinary co-operation to optimise patient outcomes in prostate cancer.

Prostate Radiotherapy

Access to radiotherapy has grown rapidly over the last two decades. From 35 linear accelerators and 290 telecobalt units in 2001 [13], India now has >450 linear accelerators, with over 95% capable of delivering intensity-modulated radiotherapy (IMRT). Most survey respondents (73%) felt that the number of patients they were treating with radical-intent radiotherapy had increased in the last 5 years.

Dose Escalation in Prostate Radiotherapy

In the last two decades, technological advances in conformal radiotherapy have successfully allowed dose escalation in prostate cancer. High-dose radiotherapy up to 74 Gy equivalent in 2 Gy fractions (EQD2) is the new standard for radical radiotherapy in prostate cancer, achieving better biochemical control [14,15] and also possibly overall survival [16]. The UK guidelines by the National Institute for Health and Care Excellence recommend 74 Gy in 2 Gy fractions for localised prostate cancer [17] and a UK survey in 2014 showed that only 6% of centres escalated the dose beyond an EQD2 of 74 Gy [18]. However, the latest European guidelines now recommend a definitive radiotherapy dose of 76–78 Gy EQD2 for localised disease in the prostate [19]. Our survey results indicate that dose-escalated radiotherapy is also widely practised in India. About 20% of respondents reported using an equivalent dose <74 Gy 5 years ago, whereas 86% reported routine use of an EQD2 dose of 74 Gy or higher in current practice. Interestingly, 64% of respondents were routinely using dose escalation up to 77–82 Gy EQD2.

Use of Intensity-modulated Radiotherapy

The benefit of IMRT over three-dimensional conformal radiotherapy (3DCRT) for reducing both acute and late genitourinary and gastrointestinal toxicities has been shown in a randomised setting [20] as well as in numerous large prospective series [21,22]. IMRT is recommended as the technique of choice for a definitive prostate radiotherapy dose >70 Gy [17,23,24]. A recent UK study showed high usage of various IMRT techniques but 55% of centres still used 3DCRT [18]. In the present survey, as many as 93% of centres reported using IMRT as their standard technique. Only four centres reported using 3DCRT as the standard technique by virtue of not having IMRT-capable teletherapy units. Most (69%) felt that the use of IMRT had increased in the last 5 years.

Use of Image Guidance in Prostate Radiotherapy

Advancements in image guidance have been crucial to the successful adoption of high-dose IMRT in prostate cancer. Daily fiducial-based image-guided radiotherapy (IGRT) to deliver high-dose radiotherapy to the prostate has been shown to reduce urinary toxicity and improve biochemical control, especially in high-risk disease [25]. Given the cost and invasiveness of inserting prostate fiducials, the use of on-board cone beam computed tomography

(CBCT) is more popular than fiducial-based imaging in the UK [18] as well as in India. Among the survey respondents, 78% used CBCT, whereas two-dimensional orthogonal imaging was only used by 17%. A lack of any image guidance facility was reported by only 5% of respondents. An increased use of image guidance in the last 5 years was reported by 78% of respondents.

The frequency of imaging is a concern for most radiotherapy centres with high patient numbers. In this context, a study from India showed that daily online imaging was superior to weekly offline no-action-level imaging protocol by correcting random errors due to variable bladder and rectal filling in prostate cancer IMRT [26]. Another study from India showed that less-than-daily imaging mandated larger planning target volume margins in IMRT and the risk of geographical miss increased by 5% for every 15% decrease in imaging [27]. About 60% of centres in the UK carry out daily imaging for prostate radiotherapy [18]. In the USA, 89–96% of centres also reported a high use of daily CBCT for prostate radiotherapy [28]. Daily image guidance was reported by 71% of respondents in our survey, which is quite encouraging.

Hypofractionated Radiotherapy for Prostate Cancer

After recognising the low α/β ratio of prostate cancer ranging 1.5–2 Gy in the last few decades, [29,30], hypofractionated radiotherapy for 4–5 weeks is emerging as the new standard of care for localised prostate cancer, based on the equivalent tumour control, survival and toxicity outcomes achieved in the HYPRO, CHHiP and PROFIT trials [14,29–31]. Global practice, however, will take some time to change [32]. Until 2017, conventionally fractionated 74 Gy was the most common schedule in 92% of centres in the UK; only 21% of centres reported the use of hypofractionation [18]. However, updated global guidelines now recommend hypofractionated radiotherapy for localised prostate cancer [19,33,34]. Given the large volume of high-risk prostate cancer in India, many leading cancer centres have been early adopters of hypofractionated radiotherapy based on the much smaller trial by Arcangeli *et al.* [35]. In fact, a randomised controlled trial of moderately hypofractionated prostate-only versus whole pelvic radiotherapy in high-risk node-negative patients is underway at Tata Memorial Hospital [35]. Although global evidence is more sparse for node-positive disease, a hypofractionated schedule of 60 Gy in 20 fractions has shown excellent 4-year biochemical control with acceptable late toxicity in a node-positive cohort of Indian patients [36].

Of the survey respondents, 61% reported the use of moderate hypofractionation in some or all of their patients and 69% felt that the use of hypofractionation had increased in the last 5 years. Moderate hypofractionation was used in >50% of patients by 49% of responders and in >90% of patients by 25% of responders. Common hypofractionation schedules were 60 Gy in 20 fractions, 65–68 Gy in 25 fractions and 70 Gy in 28 fractions. Of the 37 respondents who did not use hypofractionated radiotherapy, 46% felt that they were technically not equipped for it, 30% felt that they were not convinced that it was a better approach compared with conventional fractionation, whereas 24% felt that it would cause more toxicity.

Extreme hypofractionation, with stereotactic ablative radiotherapy (SBRT), delivers five or fewer fractions of 5–10 Gy each to achieve an extremely high biologically equivalent dose within the prostate. Recent evidence for SBRT in early prostate cancer has shown high rates of biochemical control and low toxicity rates [37,38], as well as the practical advantage of 1–2 weeks of SBRT compared with a tedious conventional schedule of 7–9 weeks [39,40]. Although global SBRT trials have concentrated on low- risk and intermediate-risk groups, recent Indian studies in higher risk groups are emerging. A phase I/II prospective study of prostate SBRT delivering 35 Gy in five once-weekly fractions in a predominantly high-risk cohort from Tata Medical Center in India showed favourable toxicity and biochemical control [41]. Early experience in very high-risk or node-positive Indian patients has shown SBRT to be effective for biochemical control and is well tolerated [42].

An inadvertent diagnosis of prostate cancer after transurethral resection of the prostate (TURP) is relatively common in India, and about 27% of prostate cancer patients presenting for curative radiotherapy have had prior TURP to relieve symptoms of bladder outlet obstruction [63], in contrast to about a 10% incidence in large trials from the West [29]. This poses a particular challenge in delivering high-dose, hypofractionated radiotherapy due to toxicity concerns. A recent matched-pair analysis from India showed promising results for the safety of SBRT in patients with previous TURP, with the time interval from TURP to radiotherapy and good pre-radiotherapy urinary function as important considerations to minimise post-treatment toxicities [43].

SBRT also seems to have made inroads into the routine clinical care of prostate cancer in India. As many as 15% of respondents reported that SBRT was one of their clinically used schedules for radical treatment. Five centres reported using SBRT for more than half of their patients. A randomised trial is in progress in India comparing moderate hypofractionation to SBRT in high-risk and node-positive prostate cancer patients (ClinicalTrials.gov NCT03561961).

Prostate Brachytherapy

The role of low dose rate (LDR) and high dose rate (HDR) brachytherapy is being expanded from low-risk disease to higher risk groups by recent randomised controlled trials showing improved biochemical control than external beam radiotherapy (EBRT) alone, albeit with higher acute toxicity [44–46]. With most low-risk patients now candidates for active surveillance, prostate brachytherapy rates, especially for LDR monotherapy, are falling across the USA and the UK [47,48].

Prostate brachytherapy has not been used routinely in India. A predominance of locally advanced disease, the lack of a prostate-specific brachytherapy infrastructure and the absence of a prostate brachytherapy training programme have been responsible for this gap. LDR brachytherapy seeds for prostate cancer have not been indigenously available in India. Recently, however, the Department of Atomic Energy under the Government of India has planned a plant for the manufacture of I-125 seeds [49]. India has had a long history of HDR brachytherapy in many cancer sites. As of 2014, 232 HDR and 91 LDR brachytherapy units were functioning in the different hospitals across the country [50]. However, the key issue remains the cost and logistics of acquiring prostate-specific brachytherapy equipment for a 'non-essential' treatment in a small patient population.

Only three of the 88 respondents reported using brachytherapy in up to 5% of their patients. Of the different reasons cited for not using brachytherapy, the two most common were lack of training in brachytherapy (55%) and the lack of enough patients to maintain a viable service (68%).

Postoperative Radiotherapy

Randomised trials from the pre-PSA era showed a substantial benefit in biochemical control with postoperative radiotherapy to the prostate bed for pT3 disease and positive surgical margins [51–53]. Over last few decades, however, the availability of highly sensitive PSA tests has enabled early detection of progression. The practice patterns have accordingly migrated towards early salvage radiotherapy, supported by encouraging results of early salvage radiotherapy with PSA between 0.2 and 0.5 ng/ml [54,55]. Guidelines by the American Society for Radiation Oncology and the American Urological Association also recommend early multidisciplinary consultation and discussion with patients regarding the benefits of postoperative treatment and the importance of early salvage. A large majority of respondents in the survey (86%) reported using adjuvant radiotherapy for high-risk pathological features after radical prostatectomy as their standard practice. Early salvage radiotherapy was practised as standard by the remaining 14% of respondents. However, 43% of respondents felt an increasing trend of patients being offered early salvage treatment in the last 5 years.

Hypofractionated radiotherapy has not been widely used in the post-prostatectomy setting, although phase I/II studies in Canada and Italy have shown acceptable toxicity rates [56,57]. Conventional fractionation was the predominantly used fractionation in the postoperative setting by 89% of the respondents.

In urban centres in India, radical prostatectomy is becoming increasingly common, with the rapid uptake of robotic-assisted surgery. There are currently about 65 centres in India with a robotic surgery infrastructure. Early data suggest increasing use of robotic prostatectomy in patients with a higher Gleason score and other high-risk features [57], although its effect on the rates of margin positivity and subsequent adjuvant treatment remains to be seen. Just over 40% of the survey respondents felt that the number of patients being treated with post-prostatectomy radiotherapy had increased in the last 5 years of their practice.

Radiotherapy for Oligometastatic Disease

There is currently no accepted definition for oligometastatic disease, with 14, 66 and 20% of the experts voting for two, three and five metastases, respectively, as the cut-off at the second Advanced Prostate Cancer Conference in 2017 [58].

Radiation in the setting of metastatic prostate cancer can either be prostate-directed radiotherapy (PDT) or metastasis-directed radiotherapy (MDT). MDT has been shown to improve the androgen deprivation therapy (ADT)-free interval in a multicentre phase II randomised trial [59]. In another phase II randomised trial of oligometastatic cancers, including prostate cancer, MDT was shown to improve the median progression-free survival [60]. At the same time, PDT has also gained ground in the metastatic setting. In a prespecified subset analysis of the STAMPEDE trial (Arm H), PDT has been shown to improve overall survival in patients with low metastatic burden as defined by the CHAARTED trial [61,62]. This emerging evidence has provided an impetus for the use of prostate radiotherapy in metastatic cancer. Unlike brachytherapy, this clinical setting is not only more common but also does not need the significant addition of infrastructure or specialised equipment.

Surprisingly, most survey respondents (76%) reported practising PDT in oligometastatic disease. Increasing use of radical-intent radiotherapy for oligometastases in the last 5 years was reported by 80% of respondents. The proportion of patients who received this treatment was not captured in the survey.

Challenges to Practice in India

A rising age-adjusted incidence and common use of PSA within the context of increasing corporate health check-ups along with lack of awareness, advanced stage at presentation and absence of population-based screening presents unique challenges for prostate cancer practice in India. Prostate cancer awareness is low among patients as well as the community doctors or general urologists who are generally the first port of call. This gap needs to be closed with innovative approaches in education and targeted screening of patients with lower urinary tract symptoms. Procedures such as orchiectomy or TURP are commonly performed by community urologists in India even before a complete diagnostic evaluation. Data from an ongoing randomised trial in India [63] shows that about 20% of patients presenting to a tertiary cancer centre for curative radiotherapy had already undergone surgical castration. Early referral to a specialist centre for appropriate curative treatment without resorting to such avoidable surgical interventions will be the key to reducing treatment-induced morbidity for prostate cancer in India.

Health expenditure in India is largely out-of-pocket, unlike the public healthcare service in the UK and the insurance-driven system in the USA. This leads to a significant influence of commercial and market forces to adopt cutting edge technology, often without establishing robust evidence or cost-effectiveness. This considerably drives up the direct healthcare cost for the patient. Establishing the cost-effectiveness of newer technology within the context of the Indian healthcare system should be seriously considered. As an example, the PRIME trial (ClinicalTrials.gov NCT03561961) is comparing, as an *a priori* secondary end point, the out-of-pocket expenditure in patients undergoing 25 fraction hypofractionated radiotherapy versus five fraction SBRT in high-risk prostate cancer.

Although most of the centres in the survey have forayed into hypofractionated radiotherapy, there still seems to be a section of radiation oncologists unconvinced about the risks and benefits of shorter schedules. A greater awareness and handholding may be necessary for a more uniform application of practical and safe hypofractionated schedules in Indian centres.

As shown in the survey, the integration of brachytherapy into prostate cancer management in India remains woefully inadequate due to the reasons mentioned above. Although mounting evidence is establishing brachytherapy as a core component of prostate radiotherapy, especially for high-risk localised disease, it is unlikely that it will be able to overcome the stiff challenge from the more 'acceptable' SBRT in India anytime soon.

The spectrum of prostate cancer in India is still dominated by advanced stage at presentation, although the proportion of patients with high-risk localised stage cancer is increasing. The trend towards early adoption of technological developments such as IGRT and hypofractionation should be encouraged further to meet the growing challenge of prostate cancer care in India.

Conflicts of interest

The authors state no conflict of interest.

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Appendix 1. Radiation oncologists responding to the survey (alphabetically listed)

Abdul Malik, Adnan Calcuttawala, Amitabh Ray, Anish Banerjee, Ankita Parikh, Arunlal M, Bhargavi Ilangovan, Bhavin Visariya, Bhooshan Zade, Chandani Hotwani, Debnarayan Dutta, Deepa Joseph, Devleena Mukherjee, Francis James, Gautam K Sharan, Giri G V, Gunaseelan, Gunjan Baijal, Hemendra Mod, Jatin Bhatia, Jose Paul, Jyotirup Goswami, Kanishka Sarkar, Karan Chanchlani, Kaustav Talapatra, Kiran Phere, Kirti Ranjan Mohanty, L Jaichand Singh, Madhu Sairam R, Madhup Rastogi, Mangesh Patil, Manish Chandra, Manish Mathankar, Vikram Maiya, Moses Arunsingh, Moujhuri Nandi, Nagraj Huilgol, Neeraj Rastogi, Nikhil Kalyani, Nilesh Deshmane, Phulkumari Talukdar, Piyush Joshi, Prahlad Yathiraj, Prakash Pandit, Pramod Tike, Prasad Dandekar, Prasad Tanawade, Pritanjali Singh, Raghavender Reddy, Rahul Patil, Rajesh Pasricha, Rakesh Kapoor, Ramesh Bilimagga, Ramya Rangarajan, Renuka Masodkar, Resham Srivastava, Sajeev George, Sandeep De, Sapna Nangia, Satish Srinivas, Shailesh Shende, Sharmila Agarwal, Shirley Lewis, Shyama Satpathy, Siddhesh Tryambake, Simon Pavamani, Shyam Kishore Shrivastava, Sneha Jha, Sonali Pingley, Sourav Guha, Srinivas Chilukuri, Sumit Basu, Suparna Ghosh(Ray), Suruchi Singh, Swarupa Mitra, Tanweer Shahid, Tapas Kumar Dora, Tejinder Kataria, Trinanjan Basu, Uday Krishna, Vedang Murthy, Venkata Krishna Reddy, Vijay Palwe, Vijay Anand Reddy, Vikas Jagtap, Vineeta Goel, Yogesh Anap.

References

[1] Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, *et al.* Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* 2018;144:31937. https://doi.org/10.1002/ijc.31937. ijc.

[2] Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, *et al. Global cancer observatory: cancer tomorrow*. Lyon: International Agency for Research on Cancer; 2018. Available at: https://gco.iarc.fr/tomorrow.

[3] Three Year Report of PBCR 2012–2014. *National Cancer Registry Programme (ICMR)* 2016. Available at: http://www.ncdirindia.org/ncrp/ALL_NCRP_REPORTS/PBCR_REPORT_2012_2014/index.htm; 2016.

[4] Hariharan K, Padmanabha V. Demography and disease characteristics of prostate cancer in India. *Indian J Urol* 2016;32:103. https://doi.org/10.4103/0970-1591.174774.

[5] Agnihotri S, Mittal RD, Kapoor R, Mandhani A. Raising cut-off value of prostate specific antigen (PSA) for biopsy in symptomatic men in India to reduce unnecessary biopsy. *Indian J Med Res* 2014;139:851–856.

[6] Patil SR, Pawar PW, Sawant AS, Patil AV, Narwade SS, Mundhe ST, *et al.* TRUS biopsy yield in Indian population: a retrospective analysis. *J Clin Diagn Res* 2017;11:PC01–PC5.

[7] Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2012;157:120. https://doi.org/10.7326/0003-4819-157-2-201207170-00459.

[8] Hebert JR, Ghumare SS, Gupta PC. Stage at diagnosis and relative differences in breast and prostate cancer incidence in India: comparison with the United States. *Asian Pac J Cancer Prev* 2006;7:547–555.

[9] Prakash G, Bakshi G, Shinde R, Bhamre R, Murthy V, Rent E, *et al.* Stage distribution of prostate cancer at a tertiary care oncology centre in India - reflections of an unscreened population. *Eur Urol Suppl* 2017;16:e426.

[10] Zeigler-Johnson CM, Rennert H, Mittal RD, Jalloh M, Sachdeva R, Malkowicz SB, *et al.* Evaluation of prostate cancer

characteristics in four populations worldwide. *Can J Urol* 2008;15:4056–4064.
[11] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424. https://doi.org/10.3322/caac.21492.
[12] Murthy V, Rishi A, Gupta S, Kannan S, Mahantshetty U, Tongaonkar H, *et al*. Clinical impact of prostate specific antigen (PSA) inter-assay variability on management of prostate cancer. *Clin Biochem* 2016;49:79–84. https://doi.org/10.1016/j.clinbiochem.2015.10.013.
[13] Lakshmanan AV. Evolution of radiotherapy machines and changing scenario in India. Available at: https://mohfw.gov.in/sites/default/files/Evolution Of Radiotherapy Machines And Changing Scenario In India.pdf; 2016.
[14] Incrocci L, Wortel RC, Alemayehu WG, Aluwini S, Schimmel E, Krol S, *et al*. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol* 2016;17:1061–1069. https://doi.org/10.1016/S1470-2045(16)30070-5.
[15] Hou Z, Li G, Bai S. High dose versus conventional dose in external beam radiotherapy of prostate cancer: a meta-analysis of long-term follow-up. *J Cancer Res Clin Oncol* 2015;141:1063–1071. https://doi.org/10.1007/s00432-014-1813-1.
[16] Kalbasi A, Li J, Berman AT, Swisher-McClure S, Smaldone M, Uzzo RG, *et al*. Dose-escalated irradiation and overall survival in men with nonmetastatic prostate cancer. *JAMA Oncol* 2015;1:897–906. https://doi.org/10.1001/jamaoncol.2015.2316.
[17] NICE. Prostate cancer. Available at: https://www.nice.org.uk/guidance/conditions-and-diseases/cancer/prostate-cancer. [Accessed 12 April 2019].
[18] Ariyaratne H, Chesham H, Alonzi R. Image-guided radiotherapy for prostate cancer in the United Kingdom: a national survey. *Br J Radiol* 2017;90:20160059. https://doi.org/10.1259/bjr.20160059.
[19] Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, *et al*. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2017;71:618–629. https://doi.org/10.1016/j.eururo.2016.08.003.
[20] Viani GA, Viana BS, Martin JEC, Rossi BT, Zuliani G, Stefano EJ. Intensity-modulated radiotherapy reduces toxicity with similar biochemical control compared with 3-dimensional conformal radiotherapy for prostate cancer: a randomized clinical trial. *Cancer* 2016;122:2004–2011. https://doi.org/10.1002/cncr.29983.
[21] Budäus L, Bolla M, Bossi A, Cozzarini C, Crook J, Widmark A, *et al*. Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. *Eur Urol* 2012;61:112–127. https://doi.org/10.1016/j.eururo.2011.09.027.
[22] Zelefsky MJ, Levin EJ, Hunt M, Yamada Y, Shippy AM, Jackson A, *et al*. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:1124–1129. https://doi.org/10.1016/j.ijrobp.2007.11.044.
[23] Bauman G, Rumble RB, Chen J, Loblaw A, Warde P. Intensity-modulated radiotherapy in the treatment of prostate cancer. *Clin Oncol* 2012;24:461–473. https://doi.org/10.1016/j.clon.2012.05.002.
[24] Expert Panel on Radiation Oncology-Prostate:Zaorsky NG, Showalter TN, Ezzell GA, Nguyen PL, Assimos DG, *et al*. ACR Appropriateness Criteria® external beam radiation therapy treatment planning for clinically localized prostate cancer, part I of II. *Adv Radiat Oncol* 2017;2:62–84. https://doi.org/10.1016/j.adro.2016.10.002.
[25] Zelefsky MJ, Kollmeier M, Cox B, Fidaleo A, Sperling D, Pei X, *et al*. Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;84:125–129. https://doi.org/10.1016/j.ijrobp.2011.11.047.
[26] Mallick I, Prasad D, Das P, Saha N, Chatterjee S, Achari R. Image guidance in prostate cancer - can offline corrections be an effective substitute for daily online imaging? *J Cancer Res Ther* 2014;10:21. https://doi.org/10.4103/0973-1482.131342.
[27] Gupta M, Gamre P, Kannan S, Rokde G, Krishnatry R, Murthy V. Effect of imaging frequency on PTV margins and geographical miss during image guided radiation therapy for prostate cancer. *Pract Radiat Oncol* 2018;8:e41–e47. https://doi.org/10.1016/j.prro.2017.09.010.
[28] Nabavizadeh N, Elliott DA, Chen Y, Kusano AS, Mitin T, Thomas CR, *et al*. Physics contribution image guided radiation therapy (IGRT) practice patterns and IGRT's impact on workflow and treatment planning: results from a national survey of American Society for Radiation Oncology members. *Int J Radiat Oncol Biol Phys* 2016;94:850–857. https://doi.org/10.1016/j.ijrobp.2015.09.035.
[29] Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, *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;17:1047–1060. https://doi.org/10.1016/S1470-2045(16)30102-4.
[30] Catton CN, Lukka H, Gu CS, Martin JM, Supiot S, Chung PWM, *et al*. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. *J Clin Oncol* 2017;35:1884–1890. https://doi.org/10.1200/JCO.2016.71.7397.
[31] Aluwini S, Pos F, Schimmel E, Krol S, van der Toorn PP, de Jager H, *et al*. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): late toxicity results from a randomised, non-inferiority, phase 3 trial. *Lancet Oncol* 2016;17:464–474. https://doi.org/10.1016/S1470-2045(15)00567-7.
[32] Lee WR. Hypofractionation for prostate cancer: tested and proven. *Lancet Oncol* 2016;17:1020–1022. https://doi.org/10.1016/S1470-2045(16)30150-4.
[33] National Institute For Health and Care Excellence Guideline. Prostate cancer: diagnosis and management (update). Available at: https://www.nice.org.uk/guidance/gid-ng10057/documents/draft-guideline; 2016.
[34] American Urological Association. Prostate Cancer: hypofractionated radiotherapy guideline, https://www.auanet.org/guidelines/prostate-cancer-hypofractionated-radiotherapy-guideline. [Accessed 14 April 2019].
[35] Arcangeli G, Saracino B, Gomellini S, Petrongari MG, Arcangeli S, Sentinelli S, *et al*. A prospective phase III randomized trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2010;78:11–18. https://doi.org/10.1016/j.ijrobp.2009.07.1691.
[36] Mallick I, Das A, Arunsingh M. Moderately hypofractionated radiotherapy in node-positive prostate cancer. *Clin Oncol* 2019;31:260–264. https://doi.org/10.1016/j.clon.2019.01.004.

[37] King CR, Freeman D, Kaplan I, Fuller D, Bolzicco G, Collins S, *et al*. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiother Oncol* 2013;109: 217–221. https://doi.org/10.1016/j.radonc.2013.08.030.

[38] Kishan AU, King CR. Stereotactic body radiotherapy for low- and intermediate-risk prostate cancer. *Semin Radiat Oncol* 2017;27:268–278. https://doi.org/10.1016/j.semradonc.2017.02.006.

[39] King CR, Collins S, Fuller D, Wang PC, Kupelian P, Steinberg M, *et al*. Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: results from a multi-institutional consortium of prospective trials. *Int J Radiat Oncol Biol Phys* 2013;87:939–945. https://doi.org/10.1016/j.ijrobp.2013.08.019.

[40] Beckta JM, Nosrati JD, Yu JB. Moderate hypofractionation and stereotactic body radiation therapy in the treatment of prostate cancer. *Urol Oncol* 2019. https://doi.org/10.1016/j.urolonc.2019.01.015.

[41] Mallick I, Arunsingh M, Prasath S, Arun B, Nallathambi C, Gupta S. Phase 1/2 study on stereotactic hypofractionated once-weekly radiation therapy for nonmetastatic prostate cancer. *Int J Radiat Oncol Biol Phys* 2017;99:S156. https://doi.org/10.1016/j.ijrobp.2017.06.360.

[42] Murthy V, Gupta M, Mulye G, Maulik S, Munshi M, Krishnatry R, *et al*. Early results of extreme hypofractionation using stereotactic body radiation therapy for high-risk, very high-risk and node-positive prostate cancer. *Clin Oncol* 2018;30:442–447. https://doi.org/10.1016/j.clon.2018.03.004.

[43] Murthy V, Sinha S, Kannan S, Datta D, Das R, Bakshi G, *et al*. Safety of SBRT in post TURP prostate cancer patients: a propensity score matched pair analysis. *Pract Radiat Oncol* 2019. https://doi.org/10.1016/j.prro.2019.04.003.

[44] Hoskin PJ, Rojas AM, Bownes PJ, Lowe GJ, Ostler PJ, Bryant L. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother Oncol* 2012;103:217–222. https://doi.org/10.1016/j.radonc.2012.01.007.

[45] Morris WJ, Tyldesley S, Rodda S, Halperin R, Pai H, McKenzie M, *et al*. Androgen suppression combined with elective nodal and dose escalated radiation therapy (the ASCENDE-RT trial): an analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost. *Int J Radiat Oncol Biol Phys* 2017;98:275–285. https://doi.org/10.1016/j.ijrobp.2016.11.026.

[46] Rodda S, Tyldesley S, Morris WJ, Keyes M, Halperin R, Pai H, *et al*. ASCENDE-RT: an analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017;98:286–295. https://doi.org/10.1016/j.ijrobp.2017.01.008.

[47] Corey G, Yoosuf ABM, Workman G, Byrne M, Mitchell DM, Jain S. UK & Ireland prostate brachytherapy practice survey 2014–2016. *J Contemp Brachyther* 2018;10:238–245. https://doi.org/10.5114/jcb.2018.76839.

[48] Orio PF, Nguyen PL, Buzurovic I, Cail DW, Chen Y-W. Prostate brachytherapy case volumes by academic and nonacademic practices: implications for future residency training radiation oncology. *Int J Radiat Oncol Biol Phys* 2016;96:624–628. https://doi.org/10.1016/j.ijrobp.2016.07.013.

[49] DAE-BRIT Annual Report 2017–2018. Available at: http://www.britatom.gov.in/docs/pdf/ar_2017_18desc.pdf; 2016.

[50] Banerjee S, Mahantshetty U, Shrivastava S. Brachytherapy in India – a long road ahead. *J Contemp Brachyther* 2014;3: 331–335. https://doi.org/10.5114/jcb.2014.45761.

[51] Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, *et al*. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet* 2012;380:2018–2027. https://doi.org/10.1016/S0140-6736(12)61253-7.

[52] Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, *et al*. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol* 2009;181:956–962. https://doi.org/10.1016/j.juro.2008.11.032.

[53] Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Störkel S, *et al*. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol* 2009;27:2924–2930. https://doi.org/10.1200/JCO.2008.18.9563.

[54] Briganti A, Karnes RJ, Joniau S, Boorjian SA, Cozzarini C, Gandaglia G, *et al*. Prediction of outcome following early salvage radiotherapy among patients with biochemical recurrence after radical prostatectomy. *Eur Urol* 2014;66: 479–486. https://doi.org/10.1016/j.eururo.2013.11.045.

[55] Tendulkar RD, Agrawal S, Gao T, Efstathiou JA, Pisansky TM, Michalski JM, *et al*. Contemporary update of a multi-institutional predictive nomogram for salvage radiotherapy after radical prostatectomy. *J Clin Oncol* 2016;34:3648–3654. https://doi.org/10.1200/JCO.2016.67.9647.

[56] Massaccesi M, Cilla S, Deodato F, Digesù C, Macchia G, Caravatta L, *et al*. Hypofractionated intensity-modulated radiotherapy with simultaneous integrated boost after radical prostatectomy: preliminary results of a phase II trial. *Anticancer Res* 2013;33:2785–2789.

[57] Gladwish A, Loblaw A, Cheung P, Morton G, Chung H, Deabreu A, *et al*. Accelerated hypofractioned postoperative radiotherapy for prostate cancer: a prospective phase I/II study. *Clin Oncol* 2015;27:145–152. https://doi.org/10.1016/j.clon.2014.12.003.

[58] Gillessen S, Attard G, Beer TM, Beltran H, Bossi A, Bristow R, *et al*. Management of patients with advanced prostate cancer: the report of the Advanced Prostate Cancer Consensus Conference APCCC 2017. *Eur Urol* 2018;73:178–211. https://doi.org/10.1016/j.eururo.2017.06.002.

[59] Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, De Bruycker A, *et al*. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. *J Clin Oncol* 2018;36: 446–453. https://doi.org/10.1200/JCO.2017.75.4853.

[60] Palma DA, Olson RA, Harrow S, Gaede S, Louie AV, Haasbeek C, *et al*. Stereotactic Ablative Radiation Therapy for the Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET): results of a randomized trial. *Int J Radiat Oncol Biol Phys* 2018;102. https://doi.org/10.1016/j.ijrobp.2018.06.105. S3–4.

[61] Parker CC, James ND, Brawley CD, Clarke NW, Hoyle AP, Ali A, *et al*. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised

controlled phase 3 trial. *Lancet* 2018;392:2353–2366. https://doi.org/10.1016/S0140-6736(18)32486-3.

[62] Sweeney CJ, Chen Y-H, Carducci M, Liu G, Jarrard DF, Eisenberger M, *et al*. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 2015;373:737–746. https://doi.org/10.1056/NEJMoa1503747.

[63] Murthy V, Bhatia J, Kannan S, Gurav P, Krishnatry R, Chourasiya D, *et al*. PV-0629 Late toxicity and PROMs in pelvic or prostate RT in high risk prostate cancer: A randomized trial. *Radiother Oncol* 2019 Apr 1;133:S335.