Advanced Radiotherapy Techniques in Prostate Cancer

16

Cem Onal and Ozan Cem Guler

Abstract

Prostate cancer (PC) is the most common tumor in males. Treatment options for localized prostate cancer include radical prostatectomy and radiation therapy (RT), which is delivered either as external beam radiation therapy (EBRT) or brachytherapy (BRT). According to "European Association of Urology" guidelines, although radical prostatectomy is the gold standard treatment option in localized PC, definitive RT could be an alternative treatment option in medically inoperable patients or who refused surgery. Treatment of PC has been evolving since the last decades with the innovation in technology. More precise radiotherapy (RT) techniques provides sharper isodoses while sparing organs at risk (OAR). It is also important that setup margins could be reduced with image guidance. Hence, precisely defining targets and considering organ movement are gaining much more importance. As a consequence of sharper isodoses and image guidance, dose escalation comes into question. It is well known that there is a positive correlation between RT dose and biochemical progression-free survival (BPFS) but not overall survival (OS) rates, with dose escalated conventionally fractionated up to 76–80 Gy in 2 Gy fractions, which is a biologically equivalent dose ($BED_{1.5}$) of 180–200 Gy, assuming an α/β of 1.5. A recent meta-analysis clearly demonstrated an increased disease

C. Onal, M.D. (✉)
Department of Radiation Oncology, Adana Dr Turgut Noyan Research and Treatment Center, Başkent University, Adana, Turkey
e-mail: hcemonal@hotmail.com

O.C. Guler, M.D.
Department of Radiation Oncology, Karadeniz Technical University, Trabzon, Turkey

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control with a $BED_{1.5}$ to 200 Gy, with no additional clinical benefit with doses above 200 Gy. In order to deliver higher doses to the prostate without increasing surrounding organs at risk, it is essential to delineate target volumes properly, deliver RT with high-technology devices, immobilize patient, and track prostate during RT. The aim of this chapter is to review recent advances in prostate RT.

16.1 Advances in Imaging and Tumor Delineation

Major advances in diagnostic imaging dramatically improved the ability to accurately target the prostate with smaller treatment volumes. This, in turn, led to better toxicity profiles, safe dose escalation, and improved disease control [2, 3, 4–6]. More recently, onboard imaging devices (cone beam computed tomography [CBCT]) used to image the prostate during treatment have led to further increase in dose delivered per treatment and an associated decrease in total treatment duration. Trends toward earlier diagnosis during the PSA screening era have led to detection of more focal and smaller volume disease within the prostate. In an effort to intensify treatment and avoid adverse effects in these patients, focal ablative techniques have been used to target only intraprostatic lesions (IPL) as opposed to traditional treatment of the whole gland or dose escalation to IPL lesion with simultaneous integrated boost (SIB) technique.

With increasing technology in radiological imaging, functional and metabolic imaging is taking the place of conventional modalities in oncology. Additionally, functional imaging modalities, such as positron emission tomography (PET-CT), diffusion-weighted magnetic resonance imaging (DW-MRI), or MR spectroscopy, may be potentially used to define the tumor biology. It is important to clearly define the tumor biology during RT because there may be discordance between clinical and pathological staging and Gleason scores of biopsy and prostatectomy specimens. For this reason, a thorough evaluation of the entire prostate is essential before performing definitive RT, in which histopathological evaluation is based on prostate biopsy only, and staging is performed with clinical and radiological findings. Noninvasive methods to evaluate the entire prostate and the tumor biology before performing RT may be a promising alternative. Moreover, this approach would allow optimized treatment delivery to adequately stratified patient risk groups.

The best method of imaging prostate cancer is endorectal T2-weighted MRI, which has 60–82% sensitivity and 55–70% specificity for detecting cancer [7, 8]. Additionally, recent studies have aimed to determine the value of MR correlates of cellular density, metabolite concentration, and tumor vascularization for predicting tumor

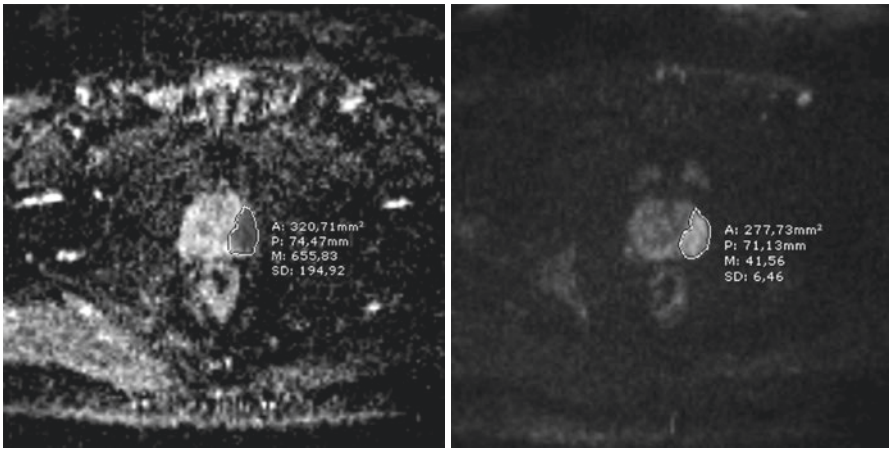

Fig. 16.1 Axial apparent diffusion coefficient map of a corresponding patient demonstrating prostate tumor at left peripheral zone

aggressiveness [9, 10]. The DW-MRI is advantageous in tumor localization [11, 12], and it may also provide qualitative information regarding the pathophysiological character of prostate cancer [13, 14] (Fig. 16.1).The DW-MRI is sensitive to the microscopic motion of water molecules and allows biological characterization of tissues based on their water-diffusion properties. The degree of diffusion is quantified as the apparent diffusion coefficient (ADC).

Conventional 18-fluorodeoxyglucose (FDG) PET-CT has been widely used for various tumors [15–19]; however, its role in prostate cancer is limited. Choline PET and 18F-fluciclovine PET are other nuclear imaging modalities for prostate cancer [20]. The use of choline PET remains unclear for its value in initial staging. In the restaging phase, the detection rate of choline PET varies between 21% and 82%, which is dependent on site of recurrence and PSA levels [21]. A systematic review showed that the sensitivity and specificity of 18F-fluciclovine PET for prostate cancer was 87% and 66% [20]. There is an increasing investigation about specific markers related to prostate cancer. Prostate-specific membrane antigen (PSMA) is overexpressed in prostate cancer cell membranes [22]. The PSMA-PET is a highly selective imaging tool for detecting the primary, involved lymph nodes and distant metastasis in prostate cancer patients (Fig. 16.2). Also the importance of PSMA PET in identification of both local and distant recurrences was shown in many trials with a detection rate for recurrent disease of approximately 85–90% [23, 24]. The detection rate is correlated with PSA value and decreasing to 58% between PSA values of 0.2–0.5 ng/ml [24]. Furthermore, PSMA-PET is useful in demonstrating IPL, for further dose escalation during prostate RT (Fig. 16.3).

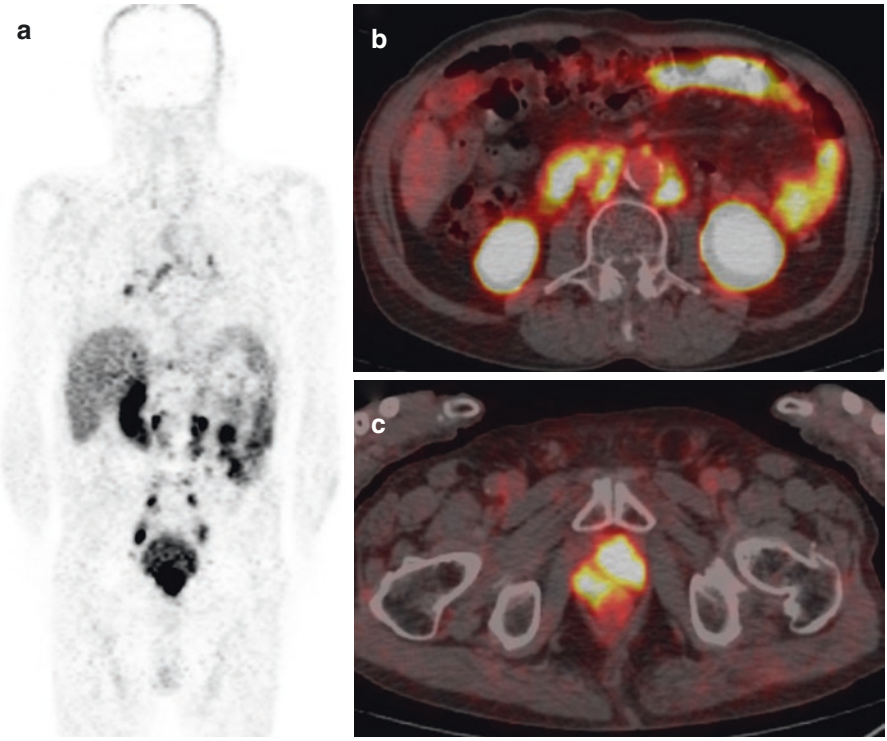

Fig. 16.2 68 Ga-PSMA ligand positron emission tomography/computed tomography images of a representative prostate cancer patient. (**a**) PSMA-PET-CT image, demonstrating increased uptake in the pelvic and para-aortic lymphatics (arrows). (**b**) The co-registered images of PET and CT, demonstrating increased Ga-PSMA uptake in the para-aortic lymphatics and (**c**) in the prostate

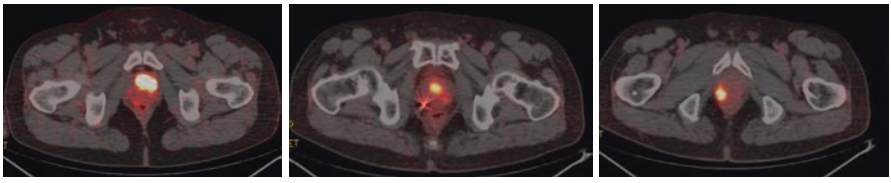

Fig. 16.3 68 Ga-PSMA ligand positron emission tomography/computed tomography images demonstrating intraprostatic lesion (*light yellow area*) in three different representative prostate cancer patients

16.2 New Radiotherapy Delivery Approaches

Historically, the prostate was treated with four static radiation fields designed based on anatomic landmarks. However, with this technique, it is difficult to get idea about the target volume doses and also surrounding organs. As a consequence, geographic misses may be seen more than expected, and it is difficult to know

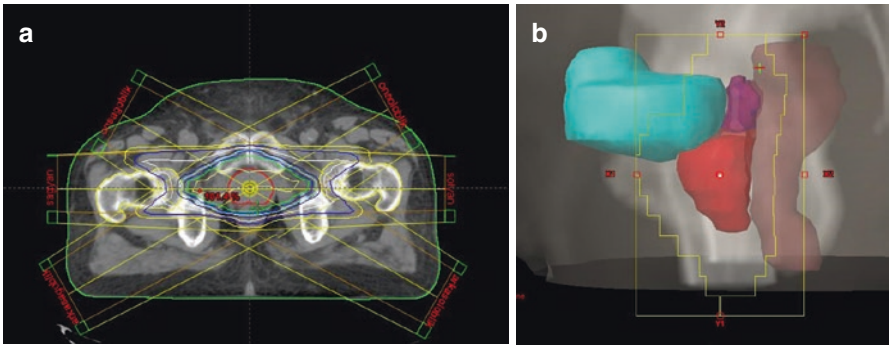

Fig. 16.4 (**a**) Dose distributions of a seven-field coplanar three-dimensional conformal radiotherapy plan. (**b**) Beam's eye view of lateral irradiation field demonstrating prostate and seminal vesicles (*red*), rectum (*brown*), and bladder (*magenta*)

about the toxicities. With the use of a 3D conformal RT (3DCRT) technique, the dose escalation above 70 Gy resulted in a modest increase in rectal and bladder toxicity. With advancements in imaging, more focal three-dimensional treatment plans were developed to target the prostate and seminal vesicles only (Fig. 16.4). Further advances in radiation delivery techniques such as IMRT and volumetric modulated arc therapy (VMAT) led to greater sparing of adjacent normal tissue to reduce toxicity. Techniques such as VMAT and IMRT are able to generate conformal isodoses, which significantly reduce the OAR doses and normal tissue toxicity [25]. Although IMRT is a commonly used method to treat prostate cancer, the potential downsides of IMRT include increased RT delivery time, resulting in a greater integral body dose, which might increase the risk of secondary cancer development [26].

VMAT is an innovative form of IMRT optimization that allows the radiation dose to be efficiently delivered using a dynamic modulated arc. The VMAT simultaneously coordinates gantry rotation, multi-leaf collimator (MLC) motion, and dose-rate modulation, facilitating highly conformal treatment with better normal tissue sparing [27]. Compared with IMRT, the potential advantages of VMAT include a large reduction in monitor units (MU) required to deliver a given fraction size and a concomitant reduction in treatment time (Figs. 16.5 and 16.6). Helical tomotherapy (HT) is an arc-based application of IMRT that uses a fan beam of radiation in conjunction with binary MLC. The gantry rotates at a constant speed, while the binary MLC leaves open 51 times per rotation and close entirely between projections. This rotational treatment modality can establish target dose conformity and OAR dose reduction (Fig. 16.7). Several recent studies have evaluated the use of VMAT delivery methods in prostate cancer (Table 16.1) [28–38].

Image guidance is essential for delivering the high radiation doses to the prostate accurately. The prostate is a mobile organ influenced by bladder and rectal filling. The position of these structures as defined on the planning CT can vary during and between fractions. Delivery of highly conformal treatments

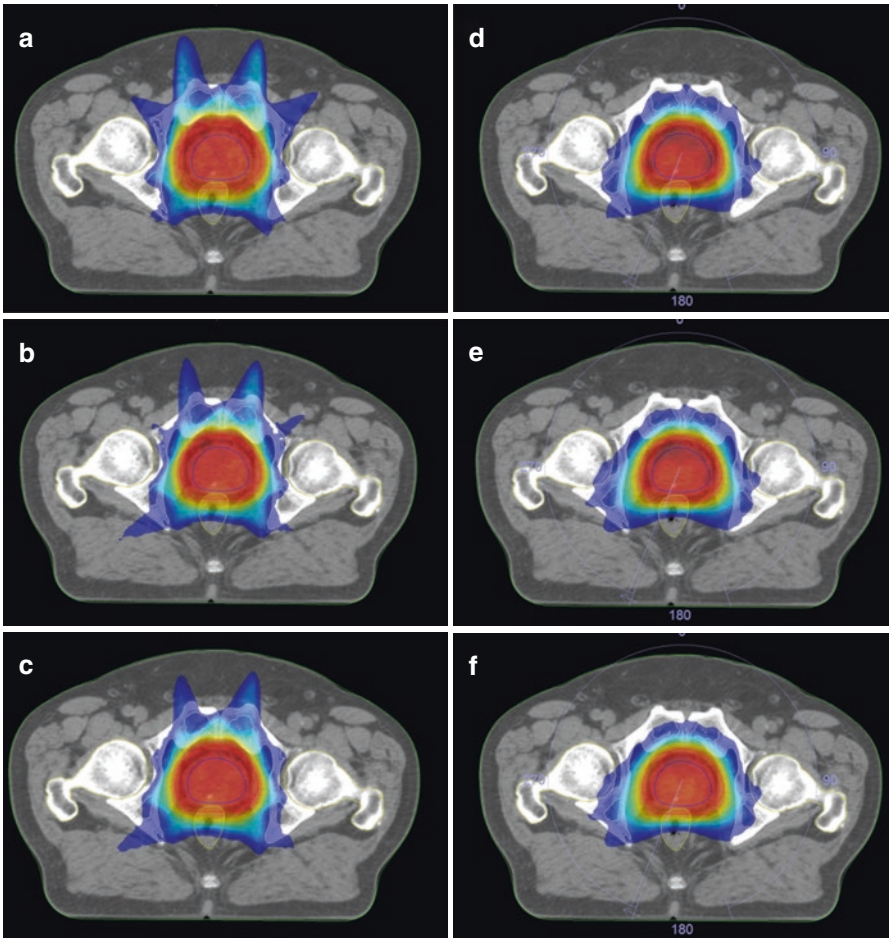

Fig. 16.5 Representative axial computed tomography slices showing 50% of prescribed dose distributions for (**a**) 6 MV, (**b**) 10 MV, and (**c**) 15 MV energy IMRT plans and (**d**) 6 MV, (**e**) 10 MV, and (**f**) 15 MV energy VMAT plans. *Blue* area represents 50%, *red* area represents 95%, and *yellow-orange* area represents 50–95% of prescribed dose

with steep dose gradients demands confidence in localization of the target because motion can lead to geographic miss, underdosing of the tumor, and/or unwanted overdosing of organs at risk. Dedicated CBCT equipment can acquire a 3D CT image in real time in the treatment position just before treatment (Fig. 16.8). Resolution is not of diagnostic quality but enables visualization of soft tissues (prostate, bladder, and rectum) so that table shifts can be made if needed. CBCT can be used in conjunction with fiducial seeds. However, the implantation of fiducial markers is an invasive procedure with the potential for

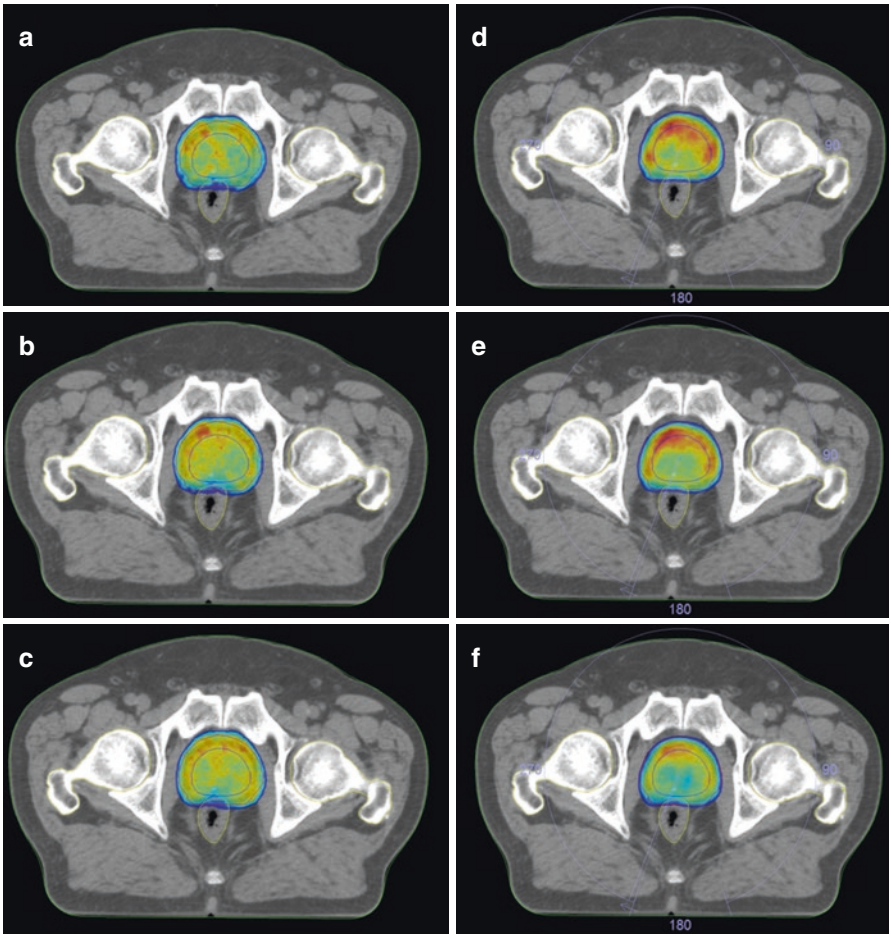

Fig. 16.6 Representative axial computed tomography slices showing 90% of prescribed dose distributions for (**a**) 6 MV, (**b**) 10 MV, and (**c**) 15 MV energy IMRT plans and (**d**) 6 MV, (**e**) 10 MV, and (**f**) 15 MV energy VMAT plans. *Yellow* area represents 95%, and *red* area represents hot spots within the target volume

discomfort, bleeding, and infection. Furthermore, fiducial markers provide little information on deformation of the target, localization of the seminal vesicles, or alteration in the neighboring normal tissue and may cause deformation of the prostate gland after implantation. Although fiducial marker implantation for image-guided RT in prostate cancer allows the localization of the prostate during treatment, this application may cause some complications and dosimetric uncertainties. Therefore, alternative noninvasive methods of CBCT should be considered for IGRT of prostate cancer patients [39].

Fig. 16.7 Helical tomotherapy version HDA used for external beam radiotherapy

Table 16.1 Published studies comparing VMAT and IMRT plans for prostate ± seminal vesicle irradiation

Author (year)	Patient no	TPS	RT dose (Gy)	IMRT beam no	VMAT arc no	IMRT MU/VMAT MU
Palma et al. (2008)	10	Eclipse/Eclipse	2/74	5	1/358°	1.73
Wolff et al. (2009)	9	Hyperion/ERGO++	2/76	7	1/360° 1/360° + 2/100°	1.41 1.47
Zhang et al. (2010)	11	MSKCC/MSKCC	1.8/86.4	5	1/360°	2.22
Rao et al. (2010)	6	Pinnacle/Pinnacle SmartArc	2/78	7	1/356°	1.16
Sale et al. (2011)	8	Eclipse/Eclipse	1.8/75.6	5	1/360° 2/360°	
Tsai et al. (2011)	12	Pinnacle/ERGO++	2/78	5	1/360°	1.08
Hardcastle et al. (2011)	10	Pinnacle/Pinnacle SmartArc	2/78	7	1/360°	1.23
Sze et al. (2012)	14	Eclipse/Eclipse	2/76	7	1/360° 2/360°	1.48 1.23
Fontenot et al. (2012)	5	Pinnacle/Pinnacle SmartArc		7	1/350°	1.25
Onal et al. (2014)	12	Monaco/Monaco	2/78	7	1/360°	1.10

Abbreviations: *TPS* treatment planning system, *IMRT* intensity-modulated radiotherapy, *VMAT* volumetric modulated arc therapy, *MU* monitor units, *MSKCC* Memorial Sloan Kettering Cancer Center

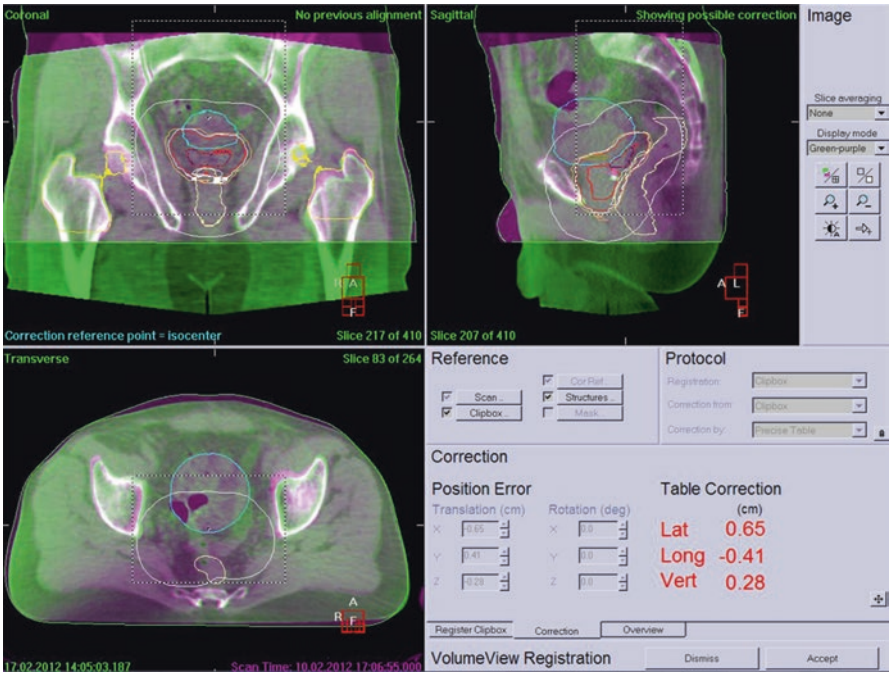

Fig. 16.8 Registration of cone beam CT images and reference CT images. After corrections according to prostate at lateral, superoinferior, and anteroposterior directions, the treatment was delivered with less setup errors

16.3 Radiotherapy Dose Escalation

External beam radiotherapy (EBRT) focusing on intensity-modulated RT (IMRT) and image-guided RT (IMRT), hypofractionation and stereotactic body RT (SBRT), high-dose rate (HDR) brachytherapy, proton beam RT (PBRT), and ablative therapies such as cryoablation, high-intensity focused ultrasound (HIFU), and radiofrequency ablation (RFA) are therapeutic modalities that have been investigated in patients with PC in an attempt to reduce toxicity while improving cancer control. These treatment modalities could be used as monotherapy, whole prostate, or IPL boost.

A 3 mm thickness planning CT should cover the whole pelvis for RT planning. Patients need to be asked to have a comfortably full bladder and an empty rectum [40]. If MRI or PET fusion is planned to fuse with planning CT, these imaging modalities should be obtained in closest possible condition. In addition to that, in patients planning to receive androgen blockade, imaging should be preferred before the initiation of hormonal therapy [31]. Gross tumor volume (GTV), clinical tumor volume (CTV), and planning tumor volume (PTV) are basically defined in the

International Commission of Radiation Units and Measurements (ICRU) [41]. CTV is based on clinical or pathological staging, while appropriate PTV margin is based on the RT technique and image guidance in the oncological center. The rectum, sigmoid colon, small bowels, bladder, and femoral heads are recommended to delineate as OAR. The rectum needs to be delineated from the anal verge to the rectosigmoidal junction. Femoral heads need to be delineated to the level of ischial tuberosities.

Dose escalation for prostate cancer causes improved biochemical control and reduced distant metastasis [2]. However, local failure still occurs in one-third of patients after 78 Gy ERT, and the original IPL is the most frequent location of relapse [42]. Therefore, selectively boosting radiation to these lesions to a very high dose has been hypothesized to be a more effective method to improve the therapeutic ratio than a homogeneous, but more modest, dose escalation to the entire prostate [43]. Randomized trials have shown a gain in BPFS using dose escalation for PC [1, 2]. However, isolated local failure is still reported in nearly one-third of patients, even with higher RT doses [2]. Local recurrence is of clinical importance because a relationship has been suggested between local control, distant metastasis, and survival [44]. Also, it has been demonstrated that local failure mainly originates at IPL. This could be a result of intrinsic resistance of radioresistant tumor clones [42]. So, delivering higher doses to IPL using SIB technique may potentially increase local control and treatment outcomes. The SIB technique can be safely performed by static IMRT, VMAT, or HT (Fig. 16.9). With VMAT plan (Fig. 16.10) and HT plan (Fig. 16.11), a homogeneous dose distribution was observed in target volumes with better sparing of the surrounding organs.

There are several studies investigating SIB boost to IPL/whole gland in treatment of PC [12, 32, 45–47] (Table 16.2). A boost to the IPL has been found to be effective and safe [48]. The reported BRFS and DFS rates were 78–92% and 90–100%, respectively [48]. Although SIB to IPL is not a standard approach, several ongoing studies will evaluate whether this approach is effective in local tumor control or not.

The investigate the benefit of a focal lesion ablative microboost in prostate cancer (FLAME) trial (ClinicalTrials.gov identifier NCT01168479) is a phase III study evaluating an EBRT boost to the DIL [49]. The tumor TARGET PC trial is a nonrandomized phase II study (ClinicalTrials.gov identifier, NCT01802242) comparing a combination of a boost to the DIL with high-dose-rate brachytherapy and a moderate dose of volumetric modulated arc therapy (VMAT) for the rest of the prostate, with VMAT as monotherapy for the whole prostate.

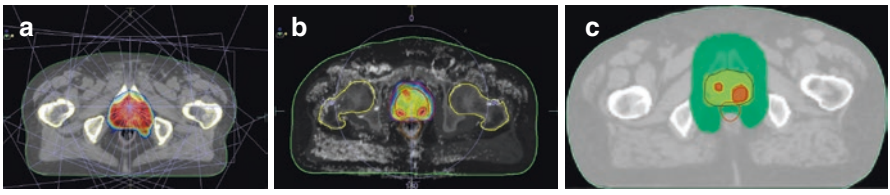

Fig. 16.9 The dose distributions of prostate irradiation and simultaneous integrated boost to intraprostatic lesion in (**a**) static IMRT plan, (**b**) VMAT plan, and (**c**) helical tomotherapy plan

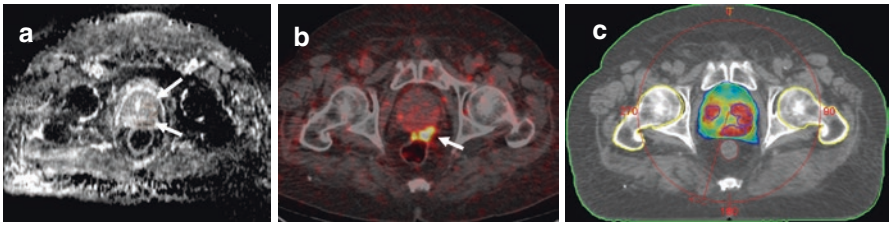

Fig. 16.10 The intraprostatic lesion demonstrated in (**a**) diffusion-weighted MRI and (**b**) 68 Ga-PSMA-PET/CT. (**c**) The dose distribution of prostate (*green-yellow area*) and intraprostatic lesions (*red area*) obtained from VMAT plan

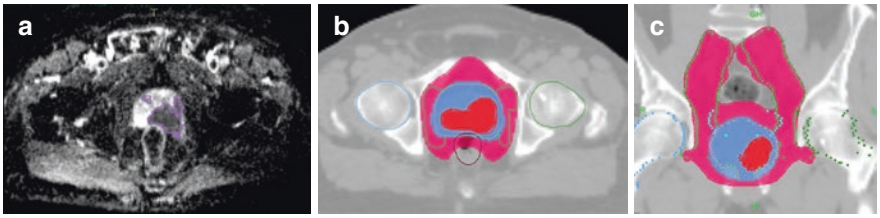

Fig. 16.11 The intraprostatic lesion demonstrated in (**a**) diffusion-weighted MRI. (**b–c**) The dose distribution of prostate (*blue area*) and intraprostatic lesions (*red area*) together with pelvic lymphatics (*pink area*) obtained from helical tomotherapy plan

Table 16.2 Published studies demonstrating the feasibility of simultaneous integrated boost intraprostatic lesion during prostate radiotherapy

Author (year)	Patient no	Imaging	RT technique/dose	Toxicity
De Meerleer et al. (2005)	15	MRI	Step-shoot IMRT Prostate + 7–10 mm 74 Gy IPL + 0 mm 80 Gy	Acute GI Gr II 3/15 Acute GU Gr III 1/15 Acute GU Gr II 6/15
Singh et al. (2007)	3	MRI + fiducial	Step-shoot IMRT Prostate + 7–10 mm 75.6 Gy IPL + 3 mm 94.5 Gy	Acute Gr I 1/3 Acute GU 2/3
Fonteyne et al. (2008)	118 (boost) 112 (no boost)	MRI	Step-shoot IMRT Prostate + 8 mm 78 Gy IPL + 4 mm 80 Gy	No increase in toxicity with SIB plan
Miralbell et al. (2010)	50	MRI	Prostate 64–64.4 Gy Hypofractionated boost 5–8 Gy	Late GI Gr II 10% Late GI Gr III 10% Late GU Gr II 12%
Ippolito et al. (2012)	40	MRI	Step-shoot IMRT Prostate + 10 mm 72 Gy IPL + 5 mm 80 Gy	Late GI Gr II 5% Late GI Gr III 2.5% Late GU Gr II 5%

(continued)

Table 16.2 (continued)

Author (year)	Patient no	Imaging	RT technique/dose	Toxicity
Wong et al. (2011)	Total 71 SIB 14	Indium-111-capromad	Step-shoot IMRT Prostate + 4–8 mm 76 Gy IPL + 4 mm 80 Gy	Late GI Gr II 21% Late GU Gr II 39% Late GU Gr III 4%
Pinkawa et al. (2012)	Total 67 SIB 46	18F-choline PET	Step-shoot IMRT Prostate + 6 mm 75.6 Gy IPL + 0 mm 80 Gy	No increase in toxicity with SIB plan
Aluwini et al. (2013)	50 14 IPL (+)	MRI + fiducial	Prostate + 3 mm 38Gy/4 fx (daily) IPL 44Gy/4fx	Late GI Gr II 3% Late GU Gr II 10% Late GU Gr III 6%
Onal et al. (2016)	173	MRI	Dynamic IMRT/VMAT Prostate + 5–8 mm 78 Gy IPL + 4 mm 86 Gy	Late GI Gr II 4% Late GU Gr II 3%

16.4 Hypofractionation/Stereotactic Body Radiotherapy

Larger fraction per treatment is hypothesized with better radiobiological effect in the treatment of PC [50]. In addition to that, the potentially low alpha/beta ratio of PC is hypothesized as the rationale of hypofractionation and SBRT [51–53]. In moderate hypofractionation, 2.2–4 Gy per fraction is generally delivered with linear accelerators, while doses above 5 Gy are used in SBRT. SBRT uses more intensive immobilization and tracking systems to safely deliver high doses of radiation compared to IMRT.

SBRT and hypofractionation studies generally investigated low-risk and intermediate-risk patients. Because high-risk disease requires more comprehensive approach due to risk of regional spread, SBRT is generally used as boost in such patients. Also, greater likelihood of local recurrence and resistance of conventional RT dose makes high-risk patients a candidate for dose escalation with larger RT fraction [54].

Summaries of hypofractionation and SBRT studies are depicted in Table 16.3. Briefly, SBRT and hypofractionated RT could be used as monotherapy, whole-gland boost therapy, or focal boost of IPL. There are various RT schemes for monotherapy of PC, but the optimal fractionation has not been determined. Most of the studies investigated the BPFS, quality of life (QoL), and toxicity. In general, hypofractionation or SBRT is well tolerated with acceptable results without any serious increase in toxicity.

Radiofrequency tracking or implanted markers such as fiducial can be used for delivering SBRT. Prostate movement can be minimized with careful bladder and rectal/small bowel preparation [55]. If standard cone beam computerized tomography (CBCT) is used instead of tracking systems, it is recommended to perform before and after treatment. Rectal protection is the one of the major issues in PC SBRT. Care should be taken to ensure the rectum receives less than the prescribed radiation dose. The use of an inflatable rectal balloon for rectal distension or

Table 16.3 Published studies of stereotactic radiotherapy and hypofractionation in prostate cancer treatment

Author	Year	n	Design	Risk group	Fractionation	Therapy	Follow-up	Outcome	Toxicity
Arcangeli et al.	2011	168	Randomized	HR	Conv. vs 3.1 Gy × 20 fr	Monotherapy	70 months	5y BPFS 79–85% No difference	Late Grd 2 ≥ 11–17% No difference
Pollack et al.	2013	303	Randomized	HR	Conv. vs 2.7 Gy × 26 fr	Monotherapy	68 months	5y BPFS 81–85% No difference	Late Grd 2 ≥ 13–23% No difference
Hoffman et al.	–	204	Randomized Phase III	LR, IR, HR	Conv. vs 2.4 Gy × 30 fr	Monotherapy	57 months	–	Late Grd 2 ≥ 5.1–16.5%
Norkus et al.	2013	124	Randomized	HR	Conv. vs 3.15 Gy × 20 fr	Monotherapy		–	Acute tx No difference
Wilkins et al. (CHHiP trial)	2015	2054	Randomized Phase III	LR, IR, HR	Conv. vs 3 Gy × 19–20 fr	Monotherapy	50 months	No difference	No difference
Aluvini et al. (HYPRO trial)	2016		Randomized Phase III	IR, HR	Conv. vs 3.4 Gy × 19 fr	Monotherapy			Hypofractionation is more toxic
King et al.	2013	1100	Prospective Phase II	LR, IR, HR	7 Gy × 5 fr 8 Gy × 5 fr	Monotherapy		5y BPFS 81%	
Kang et al.	2011	44	Retrospective	LR, IR, HR	8 Gy × 4 fr 9 Gy × 4 fr	Monotherapy	40 months	5y BPFS 90.8%	Late Grd 2 ≥ 6.8–11.4%
Anwar et al.	2016	48	Prospective	IR, HR	9.5–10.5 Gy × 2 fr	Prostate boost	43 months	5y BPFS 90%	Late Grd 3 ≥ 2.1%
Kim et al.	2016			IR, HR		Prostate boost			
Oermann et al.	2010	45		IR, HR		Prostate boost		5y BPFS 83%	Late Grd 3 ≥ 2.2%
Aluwini et al.	2013	50	Prospective	LR, IR	9.5 Gy × 4 fr SIB: 11 Gy × 4 fr	IPL boost	23 months		Late Grd 3 ≥ 8%
Kotecha et al.	2016	24		IR, HR	7.25 Gy × 5 fr SIB: 10 Gy × 5 fr	IPL boost	25 months	2y BPFS 95.8%	Late Grd 2 ≥ 8%

rectoprostatic injectable hydrogel can be used for organ motion. Another issue about PC SBRT is homogeneity. Ideally care should be taken with maximal dose inhomogeneity of less than 107% of the prescription dose within the prostate to prevent ureteral complications. Caution and care must be taken for appropriate education, immobilization, and RT delivery.

16.5 Brachytherapy

High-dose rate (HDR) BRT delivers radiation at a dose rate of >12 Gy/h. Iridium-192 is the most commonly used isotope in BRT. The use of BRT allows for a degree of conformality and dose distribution that is difficult to achieve with EBRT.

BRT is recommended in patients with cT1-2a, PSA $\leq$ 10, GS $\leq$ 7, and prostate volume $\leq$ 50 cc [56].

16.6 Proton Beam Radiation Therapy

PBRT aims to deliver radiation to the prostate while taking advantage of the physical property of protons to minimize dose to surrounding tissue and OAR [57]. Researchers mainly focus on low-risk PC [58, 59], but it is possible to use PBRT in combination with photon energies as a boost treatment [60, 61].

Mendenhall et al. conducted a prospective study investigating the role of PBRT in 40 high-risk PC patients. Patients were given weekly concomitant docetaxel chemotherapy followed by hormonotherapy for 6 months. Five-year BPFS was 76% and grade III toxicities for GIS and GUS were 0.5% and 1%, respectively [57]. Bryant et al. retrospectively analyzed 229 high-risk PC patients treated with PBRT. They reported 5 year BPFS of 76, and grade III or higher toxicities for GIS and GUS were 0.6% and 2.9%, respectively [62]. Unlike these authors, Slater et al. reported a relatively poor 5 year BPFS of 48–50% in the 133 high-risk patients in retrospective analysis [59]. Caution should be taken when interpreting these findings because of small sample sizes and lack of the number of studies.

16.7 Ablative Focal Therapies

Alternative focal treatment methods to RT and RP continue to be investigated for the treatment of PC. There are various focal treatments but cryoablation, high-intensity focused ultrasound (HIFU), and radiofrequency ablation (RFA) are the most studied approaches. These technologies aim to deliver focal ablation with minimally or noninvasive methods. Although most investigations are about low-risk PC, it is unclear for high-risk patients [63].

16.7.1 Cryoablation

Cryoablation is based on focal areas of freezing (minus 30 °C) and cell death. Because it is not possible for this technique to use it for the whole gland, studies focused on partial or targeted treatments. Bahn et al. investigated hemiablation in 73 low- and intermediate-risk patients. The authors reported that potency sparing is about 86–100% [64]. Also, cryoablation is investigated as salvage therapy after recurrence of postradiation treatment [65].

16.7.2 High-Intensity Focused Ultrasound (HIFU)

HIFU is based on coagulation necrosis by thermal energy and cell death. It has been investigated for mostly low-risk PC. Generally the treatment is considered as more toxic and potentially less efficacious than modern RT treatments [66, 67]. Also, rectourethral fistula after HIFU had been reported [68]. Therefore, the role of HIFU against RT is limited by only experimental studies.

16.7.3 Radiofrequency Ablation (RFA)

RFA uses thermal damage to cause death. RFA has two major differences from HIFU. Firstly, RFA is an invasive technique with interstitial electrodes. Secondly, RFA uses electric energy instead of ultrasonography. Nevertheless, the lack of data concerning RFA and its role in PC still remain controversial.

Conclusion

The evidence in PC treatment continues to increase. Sharper dose gradients can be obtained, and OAR doses can be reduced with new technologies, but care must be taken to organ motion and targeting. The use of SBRT, BRT, and PBRT is promising. Clinical data supports the use of SBRT in selected patients with low-risk and intermediate-risk, while it is still controversial in high-risk PC. Focal ablation therapies are not recommended in routine clinical practice unless in clinical trial.

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