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Original Article

ESTRO ACROP consensus guideline on the use of image guided radiation therapy for localized prostate cancer

Pirus Ghadjar [a], Claudio Fiorino [b], Per Munck af Rosenschöld [c], Michael Pinkawa [d], Thomas Zilli [e], Uulke A. van der Heide [f,g,*]

[a] Department of Radiation Oncology, Charité Universitätsmedizin Berlin, Germany; [b] Department of Medical Physics, San Raffaele Scientific Institute, Milano, Italy; [c] Radiation Physics, Department of Hematology, Oncology and Radiation Physics, Skåne University Hospital, Lund, Sweden; [d] Department of Radiation Oncology, MediClin Robert Janker Klinik, Bonn, Germany; [e] Department of Radiation Oncology, Geneva University Hospital, Switzerland; [f] Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam; and [g] Department of Radiation Oncology, Leiden University Medical Center, The Netherlands

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ABSTRACT

Use of image-guided radiation therapy (IGRT) helps to account for daily prostate position changes during radiation therapy for prostate cancer. However, guidelines for the use of IGRT are scarce.

An ESTRO panel consisting of leading radiation oncologists and medical physicists was assembled to review the literature and formulate a consensus guideline of methods and procedure for IGRT in prostate cases. Advanced methods and procedures are also described which the committee judged relevant to further improve clinical practice. Moreover, ranges for margins for the three most popular IGRT scenarios have been suggested as examples.

INTRODUCTION

In the treatment of prostate cancer using external beam radiotherapy (EBRT), the motion of the prostate gland affects an accurate delivery of the treatment dose. Image-guided radiotherapy (IGRT) is understood as the use of imaging technology to secure localization of the target position during treatment. IGRT is essential for compensating the motion of the prostate gland in the patient during radiotherapy, ensuring that dose distributions are deposited correctly. The use of IGRT is especially important when modern techniques utilizing highly conformal dose distributions such as intensity-modulated radiation therapy (IMRT) or stereotactic body radiation therapy (SBRT) are used. The clinical target volume (CTV) needs to be surrounded with a safety margin to account for set-up errors and target motion, thus establishing the planning target volume (PTV) to prevent a geographical miss. IGRT is used to reduce systematic (e.g. a treatment preparation, positioning or target delineation error) and possibly random positioning errors (e.g. treatment execution error, varying every fraction). Systematic errors shift the whole dose distribution away from the CTV while random errors lead to a dose spread around the CTV. When IGRT is applied, safety margins should account only for residual uncertainty.

A large body of literature exists on image guidance for position verification in prostate cancer. Nevertheless, clear guidelines on the use of image guidance techniques in prostate cancer are lacking. Therefore, we assembled a panel of experts to formulate an ESTRO ACROP consensus and derive specific guidelines.

The purpose of the paper is to aid radiotherapy professionals in the design of IGRT protocols, as well as in the selection of corresponding PTV margins.

The current guideline applies only to patients without prior radical prostatectomy, eligible for definitive EBRT. IGRT of the prostate bed in post-prostatectomy patients is a separate topic, not covered in this document.

MATERIALS AND METHODS

The authors conducted a non-systematic literature review regarding a) interfractional and intrafractional prostate motion, b) technical aspects of different IGRT approaches, c) clinical results of IGRT in terms of cancer control and toxicity, d) choice of margins. The search words “prostate cancer” “radiation therapy” “radiotherapy” “image guidance” “IGRT”, “positioning” were used. Based on the identified literature, discussions, emails and live meetings, consensus recommendations for target margins were made.

The resulting consensus identifies methods and procedures that are recommended for IGRT as well as more advanced recommendations that the committee encourages clinicians to adopt as further improvements of clinical practice.

* Corresponding author at: Department of Radiation Oncology, the Netherlands Cancer Institute Amsterdam, the Netherlands.
E-mail address: u.vd.heide@nki.nl (U.A. van der Heide).

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RESULTS

Prostate motion and deformation

Interfractional prostate motion

Interfractional motion describes translational and rotational movements of the prostate gland relative to the bony anatomy that can occur between EBRT fractions [1]. The largest translational variability is seen in the anterior-posterior (AP) direction and in the superior-inferior (SI) direction, with less motion in the left-right (LR) direction [2,3]. Rotations (mostly roll and pitch) are also frequently observed with the prostate base more mobile than the apex [4].

Interfractional motion has multiple causes. In addition to general patient setup, variations in rectum filling have the greatest impact on prostate translational shifts, with a modest impact on rotational movements in the sagittal plane (pitch) by tethering the apex [5]. Bladder filling has much less influence [6–12] and only weak correlations exist between leg rotation and pelvic and prostate motion [12].

Intrafractional prostate motion

During a treatment session, non-resolving slow drift, mainly in the AP direction due to rectal filling, and sudden transient motion, more common in the AP and SI directions due to bowel peristalsis, are the two main types of intrafractional prostate displacements [13]. Pelvic muscle clenching can also contribute to AP displacement. As observed for interfractional motion, systematic and random motion are large in the AP and SI axes, while less significant in the LR axis [2]. With longer treatment session times, such as with SBRT, the risk of intrafractional motion becomes more significant [14,15].

Treatment in prone position increases the risk of intrafractional prostate motion [16,17]. Patient's body-mass index [18–20], respiration [21], or use of abdominal compression [22] do not seem to impact prostate displacements.

Rectal volume variations [23,24] cause intrafractional prostate motion. Bowel regimens have not shown clear efficacy in reduction of intrafractional motion and are therefore not recommended as routine practice. However, for patients with a high degree of intrafractional motion, they may be indicated [13,25–27]. Immobilization approaches such as the use of endorectal balloons may limit intrafractional motion, especially for treatment sessions longer than 150 s [28]. On the other hand, recto-prostatic spacers do not significantly influence intrafraction prostate movements [29,30].

Prostate deformation and seminal vesicles motion

Prostate deformation can be observed during the whole treatment course at the level of the base, mostly due to the differences in rectal filling [31]. A distended rectum in the planning CT should be prevented as it may deform the prostate. The impact of the anterior shift of the prostate is however negligible when an adequate IGRT procedure is applied. A prostate shrinkage effect has also been described during EBRT with an estimated volume decrease in prostate gland of 0.5% per fraction, corresponding to a decrease up to 24% at the end of the whole treatment course [7]. Use of neoadjuvant androgen deprivation therapy [32,33] and previous transurethral resection [7] are other factors influencing prostate deformation.

The seminal vesicles (SV) move particularly in the AP and SI direction [34], strongly correlated to rectal volume and independent of prostate movements [2,9,35–37]. SV may have a significant deformation especially in the posterior direction [31,38]. Although direct tumor invasion may limit SV mobility [39], control of SV motion is challenging, with intrafractional displacements increasing with time [14]. Immobilization approaches such as the use of endorectal balloons may limit intrafractional SV motion [28].

The bladder volume in the planning CT correlates with interfraction position variation in the AP direction [40] but the effect is small. Arguably this means bladder filling protocols are not needed to improve positioning stability of the prostate. However, there is a dosimetric advantage to bladder filling protocols given that the bowel and parts of the bladder would move out of the high-dose volume.

Position verification and correction technology

We consider that IGRT for prostate cancer should be based on the position of the prostate itself. A multitude of technological solutions are available for this purpose (Table 1). Since the bony anatomy is not representative of the position of the prostate or organs at risk, IGRT based on bony anatomy alone is inadequate for prostate only treatments.

For a treatment of both the prostate and pelvic lymph nodes (PLN), IGRT is preferentially based the position of the prostate, given the more stable position of the PLN. IGRT based on the bony structures may be considered but margins for prostate should then be enlarged compared to the sizes suggested in Table 3, in order to accommodate prostate organ motion.

For set-up of the patient, traditional visual inspection of the patient position with a laser system can be complemented by surface scanning methods, using cameras of infrared or near visual light projections. However, surface scanning technology is not considered to be an adequate replacement to image guidance, but rather a complement to sophisticated IGRT.

Radio-opaque intraprostatic fiducial markers

Consecutive radiographs can be made either with stereoscopic imaging using two or three X-ray tubes and imagers mounted obliquely to avoid interference with the accelerator gantry [41], consecutive use of multiple images acquired with 1 X-ray tube mounted to the gantry, with a single electronic portal imaging device (EPID) mounted on the gantry [42], or a combination of the former two. These methods require the use of radio-opaque fiducial markers [43].

Typically, markers are implanted via a transperineal or transrectal approach, the latter being associated with a higher rate of complications. Markers are implanted about one week before simulation in order to reduce edema. Often, two markers are placed at the posterior base of the prostate and one at the apex, but alternative configurations are possible as long as the orientation of the prostate can be determined. A prerequisite for safe use of radio-opaque markers for positioning is that the slice thickness of the planning CT must be sufficiently small to allow an accurate fiducial marker reconstruction. A drawback of fiducial markers is the invasive implantation procedure. Furthermore, for patients who received a transurethral resection of the prostate, stable positioning of the fiducial markers can be a challenge. Nonetheless, clinical use of transperineally implanted fiducial gold markers for position verification in EBRT of prostate cancer is considered a feasible and safe procedure without negatively impacting a patients' quality of life [44].

A limitation of fiducial markers in combination with stereoscopic or single X-ray imaging is the lack of information about deformations of the prostate gland and surrounding organs at risk (OAR). In particular, the independent movement of prostate and SV cannot be detected. Moreover, it may be difficult to determine the rotational angle of the prostate with high accuracy, given the small distance between the fiducials.

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Table 1
Overview of recommended IGRT technology solutions.

Technology	Means	Field of view	Prostate Positioning information	Primary use for prostate IGRT	Approximate imaging dose***
Radio-opaque fiducial markers	X-rays of implanted markers	Markers	Translation Rotation (surrogate**)	Inter-fraction localization	0.1–2 mGy [49,73]
Electromagnetic transponders	Implanted transponders	Markers	Translation Rotation (surrogate**)	Inter/intra-localization	N/A
CT-based	CT imaging using conebeam/MVCT	Prostate/Markers/Seminal vesicles/ Pelvic lymphnodes	Translation Rotation Deformation	Inter-fraction localization	10–100 mGy* [74,75]
MRI	Magnetic resonance	Prostate/SV Pelvic lymphnodes	Translation Rotation Deformation	Inter/intrafraction localization	N/A

* more than 160 mGy with MVCT was reported [76] ** the system only present surrogate information of the prostate position (e.g. assumes constant fiducial marker position within the gland) *** imaging dose per image set: data from selected references (the actual value depends greatly on settings and may vary).

Stereoscopic or single X-ray imaging has the capacity to track the prostate position during irradiation by means of fluoroscopy. This makes gating of the treatment or real-time tracking of the prostate motion and corresponding adaption of the treatment fields of the multi-leaf collimator feasible [45,46].

CT-based image guidance

With on-board and in-room CT systems, which can be discriminated by beam quality (kV or MV) and beam collimation (fan-beam or cone-beam CT (CBCT)), the prostate gland, PLN and OAR can be visualized at the start of a treatment fraction. Visibility depends on image protocol, equipment and other factors. Indeed, kV-imaging is associated with better soft-tissue contrast compared to MV-imaging due to a higher contribution of the photoelectric effect. CT-based methods may allow for image matching on the alternative structures, such as the anterior rectal wall, in order to maintain control of the OAR dose. Also, the rotational angle of the prostate can be determined. However, to support localization of the prostate gland and image registration, implanted fiducial markers in combination with CBCT may help to reduce inter-observer variability compared to soft-tissue alignment [47]. Acquired CT-data information may also be used for adaptive radiation therapy (ART) strategies [48,49].

Electromagnetic transponder systems

Electromagnetic (EM) transponders, although not based on imaging and thus strictly not an IGRT method, have been utilized for gathering information of the prostate gland position. There are advantages and disadvantages of these transponders comparable to radio-opaque fiducial markers. Compared to X-ray based techniques, an advantage is that no additional radiation dose is given as part of the IGRT procedure (Table 1). A disadvantage is that the EM transponders may adversely influence magnetic resonance imaging (MRI) quality, reducing their applicability when MRI is part of the clinical workflow [50]. As with radio-opaque fiducial markers and X-ray imaging, the systems allow for frequent (real-time) readout of positioning information, thus allowing tracking of the prostate gland motion and potentially adapting the treatment fields of the multi-leaf collimator [51].

Ultrasound

Localization using ultrasound (US) is a non-invasive and non-radiation based approach by trans-abdominal or trans-perineal transducers in treatment position, that allows for continuous imaging. Camps et al. [52] reviewed the current status for prostate cancer US-guided EBRT treatments and presented an overview of studies comparing trans-abdominal and trans-perineal US with IGRT based on fiducial markers or cone-beam CT. Trans-perineal US appeared to correspond more closely to fiducial-markers or cone-beam CT than trans-abdominal US, but limits of agreement nonetheless varied between 3.2 and 9.4 mm. Li et al [53] showed that the pressure applied by a perineal US probe has a quantitatively similar impact on prostate displacement as transabdominal pressure. While US is a viable option for prostate IGRT, for now it must be considered less accurate compared to visualization of implanted fiducial markers or CT-based image guidance.

MRI-guidance

Currently, integrated linear accelerators with MRI scanners have been made commercially available, generating a lot of interest within the community [54]. MR-guided EBRT systems offer the opportunity for correcting translations, rotations and deformations of the prostate and SV in real time throughout the treatment. Through both inter- and intra-fraction corrections have become feasible through this method [2], its benefit for IGRT of prostate cancer still needs to be established.

Recommended technology

In general, systems using markers (single/stereoscopic X-ray imaging or CBCT) have been reported to be able to detect smaller shifts than CT-based IGRT using soft tissue matching [55–58]. Nonetheless, since the differences are small, we conclude that IGRT to account for interfractional prostate movement for conventionally fractionated and moderately hypofractionated EBRT as a minimum standard must be based on either fiducial markers or CT-based approaches with soft-tissue matching. Because CT-based IGRT offers the advantage of visualizing the rotations and deformations of the prostate and SV, a combination of fiducial markers with CT-based approaches is preferred. When the lymph nodes are part of the treatment, volumetric imaging (e.g. CBCT) is highly recommended.

Combining implanted fiducial markers with CBCT may help to reduce inter-observer variability compared to soft-tissue alignment and thus facilitate adaptive strategies.

As far as intra-fraction motion is concerned, only selected systems, such as EM transponders or single/stereoscopic X-ray imaging of implanted markers, may monitor the prostate position during treatment. To estimate the uncertainty in intra-fraction prostate motion, the limits of the system in detecting rapid shifts should be considered. Moreover, for on-line tumor tracking, which is still an uncommon treatment modality for prostate cancer, the uncertainty of the chain detection-delivery should be accounted for [59].

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Correction protocols

Different scenarios for correcting localization errors may be divided in terms of the frequency of imaging and correction, and the intent of the procedure. Off-line correction procedures have been used widely as an efficient method for IGRT. Here the aim is to correct systematic localization errors during a course of fractionated EBRT. Random errors that happen between fractions and intrafraction localization errors are not corrected for. For off-line correction protocols different schedules of IGRT can be applied [60,61]. These schedules typically involve a daily check during the first few fractions followed by a correction and then less frequent IGRT monitoring. On-line correction procedures aim primarily to reduce the systematic error, however they also reduce the random uncertainties by applying daily image guidance and correction prior to each treatment. Daily on-line correction procedures are recommended over off-line procedures because of the proven benefit in biochemical progression-free survival (bPFS) and rectal toxicity [62,63]. Monitoring and ideally tracking of intra-fraction motion may be considered for extreme hypofractionation, although its clinical relevance is not established.

Regardless if an on-line or an off-line correction protocol is used, often only translational corrections are performed. However, rotational corrections potentially could improve dose coverage, in particular when small PTV margins are applied [64]. While it can be difficult to determine rotational angles accurately based on fiducial markers alone, corrections of rotations are feasible in an on-line setting using 6 degree-of-freedom couches [65,66] or with robotic delivery systems, by properly rotating the robot [67]. Alternatively, adaptive strategies can be considered [68].

IGRT – clinical evidence

The clinical outcome of IGRT of prostate cancer radiotherapy depends not only on treatment techniques and PTV margins, but also on the definition of the CTV. Studies in the past usually defined gross tumor volume (GTV) and CTV as the prostate with or without a portion of SV. The recently published ESTRO ACROP guideline on CT- and MRI-based target volume delineation of localized prostate cancer gives recommendations for CTV delineation, including the expansion of the prostate contour to compensate for potential extracapsular extension that needs to be considered particularly for patients with intermediate- and high-risk cancer [69].

Several studies demonstrated that the introduction of IGRT techniques allows safe dose escalation. Dose escalation using three-dimensional conformal radiotherapy (3DCRT) without IGRT has been shown to improve bPFS, but to increase ≥grade 2 rectal toxicity [70]. Most studies used conventionally fractionated EBRT, with daily IGRT as a method to localize the prostate based on fiducial markers or soft tissue matching (CT-based or ultrasound). The majority of studies evaluating the clinical benefit of IGRT are retrospective. IGRT, IMRT and dose escalation have been introduced at the same time. As IGRT is associated with more accurate target detection, safety margins could be reduced and consequently the dose to the OAR allowing a safe prescription of higher doses. Hypofractionated or even extreme hypofractionated presciptions have been introduced recently with increasing data.

Several groups have reported that patients with a distended rectum during the planning CT yielded worse bPFS compared to those with an empty rectum [71–73] though posterior margins of 0.75–1 cm were applied to account for prostate position uncertainties. Patients were positioned based on skin-marks and bony land marks as seen on weekly portal film. The rectum volume is known to decrease during treatment, especially for patients with larger rectum volumes in the planning CT. As a consequence, the prostate moves posteriorly out of the predefined PTV and the cancer may not be treated adequately. This corroborates that IGRT based on bony land marks must be considered inadequate and more sophisticated IGRT techniques are warranted.

Likewise, after using a CT-based offline adaptive IGRT technique, that define an internal target volume generated by the union of CTVs created on five different days, Park et. al. analyzed 962 patients after a median follow-up of 5.5 years and did not find the rectal volume in the initial planning CT to be predictive of bPFS or toxicity [74]. This strategy was introduced in 1997 and appears to be a good solution, if other IGRT options are not available. With an analysis of 488 patients who were treated with daily US-based IGRT (4 mm posterior margins, hypofractionated treatment), Kupelian et al. [75] supported the elimination of initial rectal distension as predictive factor for outcome.

To explore whether the use of IGRT improves cancer control rates Zelefsky et al. [76] retrospectively compared two groups treated up to 86.4 Gy with IMRT, with or without IGRT, based on fiducial markers, and the same margins. IGRT was associated with lower 3-year ≥grade 2 late genitourinary toxicity (10% vs. 20%) and significantly improved 3-year bPFS for high-risk patients (97% vs. 78%). The incidence of ≥grade 2 late rectal toxicity was low (<2%) in both patient groups. A quality of life analysis has demonstrated that a dose escalation up to 76 Gy in 2 Gy fractions is not associated with increased toxicity in comparison to lower doses of 70.2–72 Gy in 1.8–2 Gy fractions, if combined with US-based IGRT and IMRT [77]. Chung et al. [78] evaluated the impact of fiducial marker-based IGRT on toxicity after IMRT in whole-pelvic treated high-risk prostate cancer patients. Lower grade 2 rectal (13% vs. 80%) and urinary (13% vs. 60%) toxicities were found in the IGRT group. However, this difference could also be attributed to considerably smaller safety margins in the IGRT group (2–3 mm vs. 5–10 mm).

Regarding the impact of IGRT on toxicity rates, several other retrospective studies reported decreased acute and late both genitourinary and rectal toxicity after introduction of IGRT. Valeriani et al. [79] found reduced late ≥grade 2 rectal toxicity (2% vs. 15%) as a result of daily kV CBCT-based soft tissue matching (and posterior margin reduction from 6 mm to 5 mm) in a hypofractionated concept after a median follow-up of 31 months, in comparison to EPID bone matching). After a median follow-up of 22 months, Kok et al. [80] reported reduced ≥grade 2 late rectal toxicity and reduced duration of genitourinary toxicity in the IGRT group (fiducial markers, 78 Gy in IGRT group vs. 74 Gy in non-IGRT group, same posterior margins, larger percentage of IMRT in IGRT group). In an analysis of 503 high-risk patients the dose in the IGRT group (fiducial markers) was escalated from 76 Gy to 78 Gy, additionally IMRT and reduced margins were introduced, with the consequence of reduced 2-year ≥ grade late 2 urinary (30% vs. 42%) and ≥grade late 2 rectal toxicity (6% vs. 57%) [41].

Moreover, comparing two prospective Dutch cohorts treated up to 78 Gy, reduced ≥grade 2 acute genitourinary and rectal toxicity was reported for patients treated with IMRT, IGRT (fiducial markers or CBCT) and reduced margins compared to 3DCRT without IGRT [81]. The analysis of late side effects has shown lower 5-year ≥grade 2 rectal toxicity (25% vs. 38%) [82]. Zapatero et al. [83] found reduced ≥grade 2 acute and late genitourinary toxicity after IMRT and IGRT (fiducial markers) in spite of higher total doses in comparison to a 3DCRT group without IGRT. Delobel et al. [84] generated a nomogram to predict rectal toxicity following prostate cancer EBRT. In a population of 972 patients with different fractionations and techniques, the combination of IMRT with IGRT (fiducial markers or CBCT) markedly decreased acute and late rectal toxicity. The 3-year ≥grade 2 rectal toxicity (mainly rectal bleeding) was 19%, 13% and 4% following 3DCRT, IMRT alone and IMRT combined with IGRT, respectively.

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However, Engels et al. [85] found IGRT (fiducial markers) to be a risk factor for biochemical failure after a median follow-up of 53 months. However, only 25 patients with fiducial markers were included and lateral margins were reduced to 3 mm. The authors concluded that extensive margin reduction might be detrimental and should be avoided. This study shows that margin around the prostate should not be reduced beyond what is considered a necessary CTV expansion. Explicit definition of the CTV as recommended in [69] is critical, particularly when PTV margins are small.

Two randomized studies that evaluated the impact of IGRT have been recently published. In the RIC-trial (257 patients), daily CBCT treatment with 7 mm uniform margins was compared to a treatment with weekly EPID verified irradiation with 15 mm uniform margins (78 Gy in 2 Gy fractions in both groups, margin reduction to 3 mm in both groups after 70 Gy) [63]. A 3D conformal technique with a rectal dose constraint of 60 Gy to no more than half of the circumference was defined in both groups, so that a posterior blocking had been used in the majority of patients with 15 mm margins, actually leading to reduced posterior margins. Currently, only patient outcomes at the end of treatment were reported and significant differences have not been found, so that final conclusions cannot be drawn from this study yet.

In a randomized study including 470 patients, de Crevoisier et al. [62] compared daily with weekly IGRT (fiducial markers or CBCT or ultrasound). After a median follow-up of 4.1 years, daily IGRT has been found to be associated with lower ≥grade 1 rectal toxicity, improved bPFS and improved clinical progression free-survival. However, an increased rate of second cancers was found in the daily IGRT group. An association with additional radiation delivered with daily IGRT is unlikely within the short follow-up period suggesting this finding is spurious.

Moderately hypofractionated concepts are increasingly used for prostate cancer treatment, based on results of several randomized studies showing outcomes equivalent to conventional fractionation, if the same techniques are used [86]. Limited experience exists with extreme hypofractionation, using single fraction doses of 7–8 Gy. These studies often use implanted fiducials for real-time monitoring and/or tracking with either a regular linac or a robotic gantry, as intrafraction prostate displacements are more relevant in these concepts. Extreme hypofractionation proved to be feasible and well tolerated within limited follow-up periods. As shown in a cohort study from 2142 men enrolled in 12 phase 2 trials of stereotactic body radiotherapy, most studies used 3 mm posterior margins. Only 2 of 12 studies did not use any form of intrafraction tracking, using 4–5 mm posterior margins. High rates of biochemical control and low rates of severe toxic events were reported after a median follow-up period of 7 years [87]. MRI-guided prostate adaptive IGRT is a method that needs to be evaluated in the future [2].

Margins

Historical PTV margin recommendations introduced in the '90s [12,88] were based on population-based data of systematic and random positioning uncertainties in order to keep the minimum dose to CTV within 95% of the prescribed dose. The most commonly used margin recipe by Van Herk et al. [12] aims to guarantee a minimum dose of 95% in 90% of all patients, in its simplified form: $M = 2.5\,\Sigma + 0.7\sigma$, where M is the margin, Σ and σ are respectively the systematic and random component of the uncertainty. Any IGRT system has its own accuracy and precision in determining the position of the CTV and provide different levels of information: fiducial marker-based methods only provide information about the rigid translation and rotation. Deformations may be detected with 3D imaging techniques such as CBCT. Some techniques only provide data prior to a treatment fraction, others can monitor intra-fraction motion. The impact of random components in inter-fraction motion and intra-fraction motion will depend on the fractionation schedule. And finally, the steepness of dose gradients needs to be considered in margin calculations. While the simplified Van Herk equation is widely utilized, its assumptions about conformal dose distributions may not be valid for IMRT and VMAT dose distributions. Despite its limitations, the simplified van Herk formula can be useful in some situations, as discussed in the next sections. Nonetheless, while the extended Van Herk equation [12] may be more appropriate, only with probabilistic planning, this can be rigorously addressed.

Defining different sources of residual uncertainties

In IGRT, many different uncertainties need to be considered:

(a) Intrinsic accuracy and precision of the IGRT system.
(b) Inter-fraction rigid error: in the case of application of off-line correction protocols, the estimate of the error is based on a limited sample of measurements. Consequently, for the remaining fractions, a residual (rigid) error is expected.
(c) Inter-fraction non-rigid error: dealing with both deformation of CTV with respect to the planning situation and residual shift/rotation of CTVs or their portion not properly accounted for by the rigid correction, as may typically happen for SV and PLN after prostate-based correction.
(d) Intra-fraction rigid error: dealing with changes during a single fraction that can be corrected by rigid translations/rotations.
(e) Residual intra-fraction error: dealing with intra-fraction shifts that cannot be corrected due to both local deformations occurring during a single fraction and due to the time left between two consecutive intra-fraction corrections.

The impact of the different residual errors is strongly dependent not only on the technology used and on the applied protocol (Off-line vs. On-line; CTV defined on prostate only, prostate + SV, prostate + SV + PLN) but also on several factors such as the number of fractions, the protocols for patient preparation (including patient positioning and bladder/rectum filling protocols or use of endorectal balloons) and the shape of the dose distribution. In most IGRT scenarios, prostate rotations cannot be easily corrected, contributing to the residual error after rigid translation corrections. Rotations can have a significant impact, in particular when small PTV margins are applied, and the magnitude of prostate rotations is an insufficient predictor of dose decrement to the target during radiotherapy. The consequence of rotations depends on the prostate shape and the location of the rotational centroid within the prostate [64].

For each component of residual error, it is necessary to estimate the extent of systematic error throughout the entire treatment, and the extent of random error. The size of safety margins in prostate cancer critically depends on the residual errors associated with a particular IGRT technique and there hardly is a one-fit all solution.

The accuracy of detecting the center of mass of the prostate with fiducial markers is high, with an estimated standard deviation of about 0.6 mm [89] and this influences both the systematic and random error. The intrinsic accuracy of the IGRT system needs to be investigated: if we focus on LINAC-based technology using volumetric imaging, values are typically in the range of 0.5–1.5 mm (1SD), with lower values using markers.

Yartsev et al. reviewed the margins reported in more than 100 publications according to the type of IGRT, showing large variations (range: 1.5–14 mm) [90]. On the other hand, a recent survey based on data coming from about 600 US-based institutes [91] reported a limited inter-institutional variation of the (most critical)

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posterior margins (median value: 5 mm, inter-quartile range: 5–6 mm), reflecting margin reduction to prevent rectal toxicity.

Margins for IGRT scenarios

Each IGRT scenario is associated with residual uncertainties. While the details will depend on the specific implementation in each clinic, some guiding principles can be articulated:

(1) Centers should make an effort to estimate their particular residual uncertainties and derive safe margins from these individual estimates; errors that have to be typically considered are summarized in Table 2 for the three main scenarios of off-line correction, on-line correction and on-line prostate tracking protocols.
(2) IGRT based on fiducial markers or CT-based approaches with soft tissue matching is recommended to account for inter-fractional prostate movement. Daily on-line IGRT is preferred for conventionally fractionated radiotherapy and recommended in case of hypofractionated radiotherapy.
(3) In case of inclusion of PLN different margins need to be applied. SV have a larger variability compared to the prostate. As the motion is not detected and corrected with fiducial markers, larger margins are needed to ensure that the prescribed dose is indeed delivered.
(4) The impact of intra-fraction error may be assessed by acquiring images before and after the delivery or by systems permitting continuous monitoring of the prostate position.

Based on literature, experience and expert opinions, a range of plausible margins for the most popular IGRT scenarios (Table 3) are discussed below. Any choice of margins out of these ranges should be justified.

Off-line correction of rigid prostate translations for conventional fractionation schedules

In this scenario, an off-line no-action-level (NAL) correction protocol [92] is followed where the average localization error after few fractions (systematic error) is applied as correction. Weekly verification measurements follow to correct for possible trends, but random errors are not corrected for. No correction for rotations or intra-fraction motion is performed.

With fiducial makers, no information is obtained about the shape of the prostate or relative motion of the SV and/or PLN. Intra-fraction motion is in this scenario not detected. With CT-based approaches, some information about shape and relative motion of SV is obtained, but not corrected for. After 3–5 fractions, the systematic localization error can be estimated with limited accuracy [61]. With this correction protocol, the dominant factors in the uncertainty are the systematic residual errors (rigid inter-fraction), a smaller contribution of the random inter-fraction error, and still minor contribution of the inter-fraction non-rigid and intra-fraction motion. While considering its limitations, the common margin recipe [12] can be used as a basis for estimating margins, with possible integration of the impact of not-rigid residual error on SV and/or PLN [39,93,94]. As a result (Table 3), margins in the AP and SI directions of 7–8 mm would be required. In the LR direction slightly smaller margins of 5–6 mm can be considered safe. If the PLN are part of the target volume for part of the treatment in cN0 high-risk cases (usually up to 50 Gy) or during the whole treatment (cN+) larger margins would be required.

Table 2
Residual errors in prostate margin definition for the three main IGRT scenarios.

Off-line	On-line	On-line + tracking
Intrinsic uncertainty of IGRT system	Intrinsic uncertainty of IGRT system	Intrinsic uncertainty of IGRT system
Inter-fraction non-rigid	Inter-fraction non-rigid	Residual Intra-fraction
Intra-fraction (rigid + residual)	Intra-fraction (rigid + residual)	
Residual inter-fraction systematic error rigid		
Interfraction random error rigid		

Table 3
Examples for target margins for prostate, seminal vesicles and pelvic node according to IGRT approaches (off-line, on-line, on-line with prostate tracking).

Correction protocol	Margins (mm)		
	Prostate	Seminal Vesicles*	Pelvic Nodes*
Off-line**	*LR:* 5–7 *AP:* 7–9 *CC:* 7–9	*LR:* 7–9 *AP:* 8–12 *CC:* 8–12	*LR:* 7–9 *AP:* 7–9 *CC:* 7–9
On-line	Iso: 4–6	*LR:* 5–6 *AP:* 7–9 *CC:* 7–9	*LR:* 7–8 *AP:* 7–8 *CC:* 7–8
On-line + tracking	Iso: 2–4	N/A	N/A

Iso = isotropic; N/A: not applicable; LR: left–right; AP: anterior-posterior; CC: cranial-caudal; *based on prostate matching; **without further corrections after the first correction of systematic error

On-line correction of rigid prostate translations

On-line correction of rigid prostate translations is nowadays the most popular approach for prostate IGRT [91,95]. Before delivering each fraction, the prostate is visualized and the set-up is corrected. In this case, rigid translations are generally applied to correct the set-up daily, without correcting any rotations. There is also a residual non-rigid error that needs to be accounted for as well as intra-fraction motion. The impact of rotations depends on patient-specific factors such as shape and location of the centroid within the prostate. Amro et al. [64] showed that adequate target coverage was met in 39%, 65%, and 84% of the patients for plans with 2, 3, and 5 mm PTV margins, respectively. Non-rigid changes typically result in a SD of 0.5–1.5 mm [38]. Intra-fraction motion may be estimated by comparing images before and immediately after the treatment or taken during the treatment: typically, the 95% percentile of intra-fraction rigid shifts were reported to be of the order of 3–5 mm for a typical 5–10 min period between set-up correction and end of delivery [23,96]. Overall, margins for prostate may be expected to stay in the range 4–6 mm. Regarding PLN again larger margins are necessary (Table 3).

Real-time prostate tracking

We consider the case of the treatment of prostate only CTV (i.e. no SV or PLN irradiation) with few fractions, for instance five, and using technology allowing a continuous monitoring and correction of intra-fraction rigid motion. In this case, intrinsic uncertainty and residual intra-fraction error are the only remaining uncertainties and may be of the same order of magnitude, although this depends on the rapid evolution of the tracking technology. The major error is the residual rigid intra-fraction shift between two consecutive corrections. For a robotic system with two orthogonal X-ray detectors, an average time of 70 s between two consecutive corrections (including both translations and rotations) resulted in a residual SD of about 1 mm [97]. The impact of such an error on the dose delivered to the prostate is clearly not Gaussian but may be adequately covered with margins of 2–3 mm in combination with robot translations and rotations up to 5° [98,99]. However, the combined impact of this rigid residual component of intrafraction error and of local prostate deformations has not been yet fully investigated leading to set the plausible range of margins between 2 and 4 mm.

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Table 4
ESTRO ACROP recommendations on prostate IGRT:

1. IGRT for prostate cancer needs to be based on the position of the prostate itself, IGRT based on bony anatomy is considered inadequate for prostate only treatments
2. IGRT to account for interfractional prostate movement for conventionally fractionated and moderately hypofractionated EBRT as a minimum standard must be based on either fiducial markers or CT-based approaches with soft-tissue matching. A combination of fiducial markers with CT-based approaches is preferred
3. While US is a viable option for prostate IGRT, for now it must be considered less accurate compared to visualization of implanted fiducial markers or CT-based image guidance
4. Daily on-line correction is preferred for conventionally fractionated radiotherapy and recommended in case of hypofractionated radiotherapy.
5. For a treatment of both the prostate and pelvic lymph nodes (PLN), IGRT is preferentially based the position of the prostate. IGRT based on the bony structures may be considered but margins for prostate should then be enlarged compared to the sizes suggested in Table 3, in order to accommodate prostate organ motion
6. A distended rectum in the planning CT should be prevented as it may deform the prostate
7. Bowel regimens (including evacuation techniques, dietary interventions, laxatives, and enemas) are not recommended as routine practice. However, for patients with a high degree of intrafractional motion, they may be indicated
8. Bladder filling protocols have no clear effect on positioning stability of the prostate, but may ensure a dosimetric advantage in terms of bladder and bowel sparing as they move the bowel and parts of the bladder out of the high-dose volume
9. Monitoring and ideally tracking of intrafraction motion of the prostate may be considered for extreme hypofractionation
10. Margins for the three most popular IGRT scenarios have been suggested as examples in Table 3. Centers should however make an effort to estimate the residual error in their own institution and derive safe margins from these estimates

Summary of recommendation

Based on the discussed issues, a summary of the relevant recommendations for prostate cancer IGRT is shown in Table 4. The Table includes methods and procedures that are recommended as well as more advanced methods/procedures that, while not strictly recommended, are encouraged as further improvements of clinical practice. Margins for the three most popular IGRT scenarios have been suggested as examples in Table 3. Centers should however make an effort to estimate the residual uncertainties in their own institution and derive safe margins from these estimates.

CONCLUSION

IGRT is an important component in modern prostate cancer EBRT. The ESTRO ACROP consensus defines methods and procedures recommended for IGRT to guide clinicians in daily practice. More advanced methods and procedures were described that the committee encourages as further improvements to clinical practice.

DISCLAIMER

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DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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