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Image-guided radiotherapy for pelvic cancers: a review of current evidence and clinical utilisation

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Declaration of interest

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Keywords

Radiotherapy; Image-guided radiotherapy; Intensity modulated radiotherapy; Cancer; Pelvic cancer

Abstract

The meticulous selection and utilisation of image-guided radiotherapy treatment (IGRT) are essential for optimal radiotherapy treatment delivery when using highly conformal treatment techniques in pelvic radiotherapy. Pelvic IGRT has several general IGRT issues to consider (such as choice of match strategy, prioritisation between multiple treatment targets, and margin estimates) as well as issues specific to pelvic radiotherapy, in particular large interfraction organ variation. A range of interventions, including adaptive treatment strategies, have been developed to address these challenges. This review covers general considerations for clinical implementation of pelvic IGRT in routine practice and provides an overview of current knowledge regarding pelvic interfraction organ motion. Published IGRT evidence for each of the major tumour sites (gynaecological, prostate, bladder, rectal and anal cancer) is summarised, as are state-of-the-art adaptive approaches. General recommendations for implementation of an institutional pelvic IGRT strategy include

- Ensuring consistency between treatment intent and IGRT approach utilised.
- Ensuring minimum national and international IGRT guidance is followed whilst considering the benefit of daily volumetric IGRT.
- Ensuring the appropriate Allied Health Professionals (namely Therapy Radiographers/RTTs) lead on undertaking IGRT.
- Ensuring the IGRT workflow procedure is clear and includes an escalation process for difficult set-ups.
- Ensuring a robust IGRT service is in place before implementing advanced adaptive approaches.

Introduction

With the routine implementation of advanced radiotherapy techniques, image guidance is increasingly important. For most pelvic tumour sites, delineation guidelines have been published and implemented in clinical practice [1–6]. The current standard of using intensity modulated radiotherapy (IMRT) to reduce toxicity ensures tight dose conformity to target volumes. To fully realise the normal tissue toxicity reduction benefit of these two developments, treatment delivery uncertainty must be optimised. Multiple sources of uncertainty exist, compensated for by treatment volume margins, but day-to-day changes in internal pelvic anatomy relative to the planning imaging are possibly the largest source of error. In particular, bladder and rectum filling vary dramatically throughout treatment and can impact pelvic target volume position. Bladder and bowel preparations aim to reduce the daily variation [7–9] but far from eliminates it.

It is therefore essential in the era of modern targeted radiotherapy delivery that image-guided radiotherapy (IGRT) is incorporated into routine practice. IGRT should include the online and offline utilisation of all information acquired from imaging taken during radiotherapy. Volumetric imaging e.g. cone beam computed tomography (CBCT) should be considered. It allows for soft tissue visualisation; monitoring of bladder, bowel and rectum; and moreover a review of the target volume to ensure this remains within the high dose region.

General considerations

Match strategy

Deciding how to match the treatment images to the radiotherapy plan to ensure target coverage is relatively straightforward when a single clinical target volume (CTV) exists. However, many pelvic radiotherapy plans have multiple CTVs. The tumour volumes may move independently, while most nodal volumes are relatively fixed to bone. The prescribed dose to these volumes may also vary, leading to multiple dose levels. These complexities increase the importance but also the difficulties of implementing IGRT. Areas of tumour should in general take priority over elective target volumes, and organs at risk (OARs) need to be considered where dose is close to tolerance. It is vital to clearly define a robust prioritisation or match strategy before treatment starts. This match priority will depend upon whether/where gross tumour is present, relative risk of subclinical disease in elective volumes, inclusion of boost treatments (concurrent or sequential, including other treatment modalities), overall treatment strategy (radical or adjuvant), the therapeutic window (minimal required target dose versus maximum acceptable OAR dose), and the availability of trained health care professionals (HCPs), such as Therapy Radiographers (RTTs). This predefined strategy will also determine the anatomical location and frequency (e.g. daily versus weekly) of the CBCT. Daily CBCT aims to improve the set-up of the patient on every fraction. However, there is limited data suggesting a benefit of daily imaging when registering to bony structures only, compared to less intensive imaging protocols (e.g. no-action-limit protocols) for pelvic cancers. Based on Hurkmans et al [10], the reductions in systematic and random translational errors with daily image registration to bone are probably around 1.5mm and 2.5mm, respectively. It is important to note that rotations are rarely corrected, and generally only if they are above 3-5˚ [11]. Consequently, residual errors in bony structure setup will remain, even with daily imaging. Further tumour site specific discussion regarding match strategy including soft tissue match is found later within this manuscript.

Margins

Margins are added to treatment volumes to ensure that the planned dose gets delivered to the target [12]. They consider and compensate for uncertainties throughout the radiotherapy process. Many uncertainties stem from setup variation, and consequently margins are closely tied to the IGRT technique used. Treatment margins are tumour site and centre specific, and dependent on both the clinical scenario and local imaging match strategy. However, multiple aspects of the treatment process contribute to the overall treatment delivery uncertainty, including outlining, mechanical issues (e.g. kV / MV isocentre match), intra- and inter-observer image registration, and intrafraction patient movement. Therefore, the ability of IGRT and adaptive treatment strategies to reduce margins has inherent limitations. Each centre should optimally estimate their own treatment margins, using established approaches [12]. If this is not feasible, centres must carefully assess national, international or trial protocols, to ensure that the assumptions underlying any margin recommendations are appropriate for their local treatment and imaging process.

Clinical Implementation of IGRT

Centres should review national and international guidance on imaging modalities and frequencies for relevant tumour sites, prior to clinical implementation. IGRT protocols should be developed for each tumour site; defining the match-strategy, workflow procedure (including an escalation process for difficult set-ups), and documentation to be completed [13] (see Figure 1). RTTs should be at the core of undertaking the IGRT process, including online and offline reviews. RTTs (or similar staff groups) should have the relevant technical training, knowledge and are experienced in delivering radiotherapy treatment. Oncologist or Medical Physicist-led IGRT is resource intensive and not feasible or suitable for most clinics. Implementation of advanced IGRT requires clear guidance and training with defined learning outcomes [13] and with this appropriate training RTTs can safely and

effectively introduce such techniques [14–18]. Mixed methods and blended learning approaches have been successful at upskilling RTTs to be the HCPs leading the IGRT pathway [15,18,19]. Finally, IGRT must be closely aligned with the rest of the treatment process. Therefore, engagement, support, collaboration and feedback from the MDT is essential when implementing IGRT techniques [13,14], as is published evidence from IGRT implementation studies [14–18].

Adaptive treatment strategies

Following the introduction of volumetric IGRT, a range of differing complexity approaches for mitigating the impact of pelvic organ motion are currently in practice or under investigation [20,21]. The most straightforward and common strategies involve online repositioning based on 3D soft tissue imaging, rather than just bone imaging (as in 2D imaging). These common strategies will be the main focus of the current review, but may not fully account for the complex multifactorial variation seen. More involved adaptive strategies include (see Table 1):

- Individualised margins e.g. patient specific PTV or internal target volume (ITV): Combination of target contours from multiple scans including diagnostic imaging and/or pre-treatment planning scan and/or CBCTs acquired during the treatment course. This subsequent volume aims to cover all excursions of the target, over the chosen imaging time frames.
- 'Plan library' or 'Plan of the day' (POTD): Creation of multiple potential treatment plans for each patient, representing different 'likely anatomies' (e.g. different degrees of bladder filling) with the most appropriate plan selected daily based on on-treatment volumetric imaging.
- 'Planned adaptation' strategies, e.g. with re-scan and re-plan at one or more set timepoints throughout treatment: More beneficial in cases with significant primary tumour shrinkage.
- Daily re-optimisation or real time planning, with completely new treatment plans created online while the patient is on the treatment couch.
- Live tracking: Utilisation of fiducial markers/transponders for real time tumour tracking to account for intra-fraction target motion.

Ideally, unscheduled decisions to rescan and replan in case of systematic changes in anatomy should be unnecessary with implementation of these strategies, as they encompass assessment and interventions for day-to-day variations in internal anatomy (e.g. rectum and bladder filling). The most complex adaptive strategies (daily re-optimisation and live tracking) are currently only available in clinical practice on specialised, state-of-the art treatment delivery platforms. Very recently, platforms have been introduced which combine MV linear accelerators with on-line imaging and adaptive planning, based on MR as well as CT imaging. These may become more widely available over the coming years. As these complex technologies are not widely available on standard linear accelerators, they will not be covered by this review.

Pelvic organ motion

Inter-fraction variation is an issue in pelvic radiotherapy due to bladder, bowel and rectum filling, which can move the organ or surrounding pelvic structures in or out of the treatment field. Bladder, rectum and bowel filling varies greatly throughout the day, with impact from many factors including hydration and oral intake.

Intra-fraction motion is also an important issue and interventions such as actioning the online imaging within a reasonable timeframe and using rotational IMRT to reduce treatment time can

minimise this. However, addressing intra-fraction motion should not currently be the priority of IGRT implementation. Advanced techniques are utilised to mitigate intra-fraction motion, e.g. tracking/MR-linacs, but are not routine clinical practice.

Bladder

Bladder filling can vary considerably from day to day. Treatment with a full bladder can push bowel out of the pelvis (and thus out of the treatment fields), while an empty bladder may result in more bladder in the treatment field. There is evidence that bladder filling reduces throughout a course of radiotherapy [22] but this is not reported across all tumour sites. Drinking a set volume of water and waiting for a set time aims to achieve a similar bladder volume daily, but the actual impact of such a drinking strategy on bladder filling varies according to hydration status and other treatments (e.g. chemotherapy) [23]. Proposed methods of controlling this include regular bladder scanning with ultrasound [23], asking the patient to fill/void or compensating with adaptive methods (see Table 1).

Rectum

An empty rectum is most frequently preferred during radiotherapy. This can be simpler to reproduce and can reduce the volume overlapping with target if the rectum is an OAR. Variation in rectal filling is seen throughout the treatment course, with some evidence suggesting a trend towards a reduced volume [24,25]. To minimise variation, implementation of laxatives, enemas and dietary plans can be considered. Unplanned strategies also include removing the patient from the treatment couch and asking them to pass air or void.

Bowel

Small bowel may move several centimeters between fractions [26] and will often move in and out of the treatment fields, limiting the cumulative irradiation of any given bowel loop. However, interfraction movement is significantly reduced in the post-operative setting [27]. There are no known treatment interventions to reduce interfraction bowel motion or improve reproducibility. When planning, it is recommended to use a ‘potential bowel volume at risk’, (e.g. bowel bag or intestinal space structure) so that the plan is optimized to account for bowel motion [28]. For treatment regimens with very high boost doses delivered adjacent to small bowel structures daily monitoring of bowel loop position relative to the treatment target might be necessary.

Pelvic nodal volumes

Radiotherapy for many pelvic cancers includes irradiation of elective nodal volumes. The specific risk and pathway of nodal spread, and thus lymph node volumes to be treated, depend on the primary cancer. Relevant nodal volumes include inguinal, external iliac, internal iliac, obturator, pre-sacral, mesorectal, common iliac and para-aortic nodes. Movement observed relative to bony structures is highly dependent on specific anatomical sub-compartments, with high degree of anisotropy. Many of these volumes are partly fixed to bony anatomy and thus if the bony imaging indicates good positioning then CBCT provides little additional information. Margins in the region of 5-8 mm (depending on local setup and imaging policy) are typically adequate to ensure dose coverage in this case [29,30]. However, some volumes do exhibit more motion relative to pelvic bony structures, in particular rectal and mesorectal nodal volumes [31,32], and (to a smaller extent) inguinal nodes [33].

Evidence per tumour site

Gynaecological cancer

For gynaecological cancers, radiotherapy is most frequently used curatively in cervical and vaginal cancer and adjuvantly for endometrial and vulval cancer. Treatment is often 45-50.4Gy in 25-28# to a primary and nodal target. Simultaneous integrated boosts (SIBs) are applied to tumour or nodes as well as brachytherapy boosts at the end of the external treatment course. Primary tumour coverage usually takes priority over nodal regions but complexities such as gross nodal disease means case-by-case consideration is essential. Gaining accurate planning information regarding target movement is key to guide monitoring throughout treatment. Intensity of monitoring depends upon the resource and skill set available and patient selection e.g. identifying 'movers' with bladder filling [34].

Organ motion is most investigated in intact cervical cancer. A systematic review [22] reported patient-specific patterns which varied largely (5mm-40mm shifts). Consistent themes were non-linear shape changes, tumour volume decrease through treatment, and bladder volume moves uterus whilst rectum moves vagina/cervix. Tumour regression increases OARs within the high dose region and could theoretically increase cervical motion and therefore under coverage, but no evidence currently supports this. These findings support the need for consistent reproducible bladder and bowel preparation, as per trial protocols, e.g. INTERLACE or EMBRACE2, but few published recommendations exist [23]. They also emphasise the need for IGRT and adaptive strategies.

Adaptive strategies commonly applied include 'internal target volume' (ITV) and plan of the day (POTD); see Table 1. An ITV is created by combining CTVs from bladder full and empty imaging [35] or multiple pre-treatment imaging series (EMBRACE2, www.embracestudy.dk, NCT03617133) which may also account for rectal variation. This can result in large treatment volumes and increased OAR overlap. Therefore, POTD is preferred. POTD involves creation of individualised model-based ITVs to cover variable bladder filling [34,35]. This improves OAR sparing whilst ensuring CTV coverage, but backup 3D-conformal plans are necessary. Due to tumor shrinkage, scheduled replanning could be advantageous to further spare OARs, either at a preprogramed time, e.g. mid-treatment/ weekly, or dosimetrically triggered [36,37].

For post-operative endometrial or cervical cancer, the primary CTV moves similarly to the cervix. Vaginal cuff fiducial markers are feasible. Movements are related to both bladder and rectal filling but are patient specific [38–40]. Soft tissue imaging is therefore again vital.

Prostate cancer

Prostate cancer patients can receive radiotherapy in the primary/definitive or adjuvant (prostate bed radiotherapy) setting. This may also include the seminal vesicles or nodal target. The treatment schedules vary from delivering short course (hypofractionated) (5-7#s) to longer course treatments (37-39#s)

Throughout a course of radiotherapy, the prostate is prone to translational and rotational variation [41–43] and it may deform (mainly due to rectal volume variation) [44] or shrink (up to 24%)[45]. The seminal vesicles also move independently of the prostate itself [46]. Based on these variations, daily imaging should be implemented for all prostate radiotherapy schedules, as supported by multiple studies demonstrating IGRT benefit [47–54]. Registration to bony anatomy does not reflect the soft-tissue variation in the prostate and therefore fiducial markers should be considered as a minimum, but ideally volumetric imaging should be utilised. Fiducial markers can be surrogates for prostate position [55] when volumetric imaging is unavailable; however, the image registration to fiducials can differ from a volumetric prostate registration [56,57], and they do not represent the seminal vesicles [58].

In contrast to the multiple studies on primary prostate IGRT, the literature is more limited for prostate bed radiotherapy. There is no visible target to match to, but rectum and bladder filling can impact the target position [59,60] and there is inter-fraction variation [61,62]. The appropriateness of volumetric imaging should be considered, especially in the context of margin reduction [62].

The prostate will usually take priority over a nodal target. When correcting for prostate variation the nodal volume position may be compromised, but with bone registration, for nodal volumes, larger prostate margins may be required [63,64]. Therefore, margins, technique and match strategy in these cases must be considered carefully to ensure the target(s) remain within their prescribed dose region and the OARs are not.

Advanced techniques including real-time tracking [65–67] and adaptive radiotherapy [68,69] are being explored in prostate radiotherapy; however, these approaches are not currently utilised in routine radiotherapy practice [21].

Bladder cancer

Radiotherapy for bladder cancer may be delivered as an adjuvant treatment in early-stage bladder cancers (e.g. after TURBT), or as the primary treatment in patients not for surgery (either inoperable or wishing to avoid cystectomy). Radiotherapy is routinely delivered to the whole bladder, but the tumour area may also be treated alone or boosted, and radiotherapy may include nodal volumes. The treatment varies from long-course radical treatments (typically 20-32#s) to short course weekly treatments (in the more palliative setting). Full and empty bladder approaches have been utilised; there is little difference in inter- and intra-fraction variation when using either approach [8]. An empty bladder may be more difficult to achieve toward the end of treatment, however, due to toxicity [70]. Movement of the bladder wall by more than 1.5cm, in more than one direction, has been documented in up to 40% of patients [71].

When delivering whole bladder radiotherapy large PTV margins (1.5-3cm) have been standard practice for years [70,72] with weekly imaging [73]. However, this approach does not minimise the toxicity to the surrounding OARs, and margins can be reduced with more frequent volumetric imaging [74].

In recent times, tumour focused approaches - i.e. delivering a radical dose the bladder tumour and reducing/sparing the dose to the remaining uninvolved bladder - have been investigated. The complexity of delivering such an approach to a deformable organ has been investigated [75–77], and randomised controlled trials are ongoing (NCT02447549). Lipiodol may be utilised to visualise the tumour and assist matching [77].

To minimise OAR dose, while ensuring target coverage, adaptive radiotherapy has been studied. POTD is the most evidenced-based adaptive approach in bladder radiotherapy and has been assessed in single- and multi-centre studies, in the radical and palliative setting [78–82]. Usually a library of plans is generated based on PTVs of incremental increasing volumes. For whole bladder radiotherapy, the smallest plan may be the most desirable to limit OAR dose [83]. In contrast, for bladder sparing radiotherapy (using a tumour focused approach) larger plans may be more desirable [84]; limiting healthy bladder volume within the high dose region. Individualised margins using a patient-specific PTV covering all excursions of the bladder over a chosen timeframe [85–87] and daily re-optimisation [81,88,89] have also been explored but are not routine practice [21].

Rectal cancer

Rectal cancer radiotherapy is typically pre-operative with a small proportion receiving post-operative or definitive radiotherapy. Schedules are either standard chemoradiotherapy (45-54 Gy in 25-30 fractions) or hypofractionated short course radiotherapy (25 Gy in 5 fractions). The target volume includes the primary tumour, any pathologically enlarged nodes (usually mesorectal or pelvic sidewall), and mesorectal, presacral, internal iliac and obturator elective nodal compartments.

Soft tissue systematic changes are seen during long course chemoradiotherapy. Nodal volumes exhibit systematic errors 1.5-5.5mm and random errors 1.5-4.0mm [24,31,32]. Most result from soft tissue deformation, and 'simple' IGRT with no adaptive strategies cannot reduce margins substantially. Nijkamp et al (2012) provide CTV to PTV margin estimates with daily imaging, for short and long course radiotherapy; for most nodal compartments these are 0.7-1.5cm [24].

Rectal tumours can be highly mobile, especially if small. Bladder and rectum filling contribute to this motion, which is consequently highly dependent on location within rectum and is anisotropic. Estimates from repeat MRI scans [90] provide systematic errors (relative to bony structures) of 2.3-4.8mm and random errors of 1.5-3.3mm. Rectal tumours can be difficult to visualise on CBCT, and so primary tumour match is of limited use. Using the rectal wall as a surrogate does not improve match substantially relative to bony structures [91].

The plan library approach is the most evidence-based rectal cancer adaptive strategy. The most explored strategy uses multiple plans based on a single planning CT, with standardised CTV position variation towards the bladder, as most CTV motion is within the mesorectum and anteriorly [92–94]. This slightly increases target coverage, and significantly reduces bladder and rectum dose. The largest benefit is seen in long course radiotherapy [95]. Other adaptive strategies include individualised margins based on repeat imaging early in the treatment course [96] and planned treatment adaptation at set time points (particularly for boost strategies) [97–99]; but these have limited clinical evidence.

Anal cancer

Most anal cancers are treated with definitive chemoradiotherapy. IMRT using a SIB technique is considered standard-of-care, typically delivering 50-60Gy to primary tumour and involved nodes (nearly always inguinal nodes). There is very limited published data on IGRT in anal cancer. Two studies have examined setup errors for bony anatomy during tomotherapy and IMRT; they found systematic and random translational errors of 1-3mm and 3-4mm, respectively [100,101]. Brooks et al also studied primary tumour motion during IMRT, and found significant inter-fraction movement relatively to bony anatomy (>10 mm) [101]. The main cause of primary tumour movement appears to be a combination of bowel gas & filling variation (high tumours) and buttock displacement (low tumours). Finally, a single paper [33] reported on differential movement of primary tumour and involved (inguinal) node targets, and found considerable independent movement, highlighting the need for a target-specific match strategy in this patient group. There are no published studies on adaptive treatment strategies.

Summary and recommendations

IGRT is essential for the safe and appropriate implementation of highly conformal pelvic radiotherapy. Bladder, bowel and rectal variation can impact on target as well as OAR position within the high dose region. Thus, optimisation of IGRT requires a dedicated strategy. This strategy must take into account the entire treatment process, including pre-treatment imaging, planning and delivery. An overview of this workflow procedure is outlined in Figure 1. The available evidence for use of IGRT for pelvic radiotherapy vary considerably depending on tumour site, but some clear general recommendations can be made:

- There must be consistency between treatment intent, the pre-defined IGRT approach, treatment margins, and match prioritisation and strategy.
- Most patient groups will benefit from daily volumetric imaging. For minimum requirements, refer to national and international guidance on imaging modalities and frequencies (e.g. OnTarget in the UK).
- All RTTs, with relevant training, should be able to review volumetric imaging (e.g. CBCT) for pelvic radiotherapy; including a general sense check of overall anatomy (and changes), bone registration, and soft tissue review.
- Centres should ensure the workflow procedure is clear and moreover there is an identification process and escalation procedure for difficult set-ups, and ideally an available MDT for these cases.
- A robust IGRT service fully utilising volumetric CBCT imaging for daily setup and evaluation of soft tissue changes must be in place before implementing more advanced adaptive approaches, as these are not currently standard of care.

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Figure legends

Figure 1: Overview of image-guided radiotherapy (IGRT) workflow procedure. OAR: Organ At Risk. MDT: Multi-Disciplinary Team.

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