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REVIEW

# A review of the use of fiducial markers for image-guided bladder radiotherapy

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**ABSTRACT**

*Background*: Enhancing target visualization and reducing set-up errors in image-guided radiotherapy (IGRT) are issues faced when trying to implement more conformal and partial bladder techniques. This review examines the evidence available pertaining to the clinical use of Lipiodol and gold fiducials for IGRT for bladder cancer. *Material and methods*: Nine published articles relating to the feasibility of using Lipiodol injections or gold fiducial markers in IGRT for bladder patients were recruited from a database search strategy. Set-up errors were evaluated in addition to the stability and visibility of each on verification imaging. Adverse reactions from the insertion of each method were also assessed. *Results*: Both Lipiodol and gold fiducials have the potential to remain stable and visible in the bladder, however, fading, washout and seed loss was also reported. Set-up errors can be reduced by using Lipiodol or fiducial registration when compared to other registration techniques. Adverse reactions reported were minimal for each. *Conclusion*: Current evidence suggests that Lipiodol injections and gold fiducial markers present as promising and highly accurate methods of overcoming interfraction bladder motion in IGRT.

**HISTORY**

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Bladder cancer is somewhat of a rarity in radiation oncology accounting for just 3% of cancer cases worldwide [1]. Bladder preserving techniques commonly practiced include transurethral resection coupled with adjuvant radiotherapy and chemotherapy, as well as definitive chemoradiation [2,3]. Advances in radiotherapy are often hindered by the risk of normal tissue toxicity. In the case of bladder cancer, this is complicated by the issue of inter- and intrafraction target motion, where motion can be dependent on the location of the tumor in the bladder wall [4] and can vary up to 3 cm [5]. Whole bladder treatment coupled with large planning target volumes (PTVs) margins ranging from 15 mm to 20 mm act as a safety net for target motion and have been the standard of care for many years [5].

As advanced image-guided radiotherapy (IGRT) methods have come on stream in the last decade, an opportunity for increased accuracy in treatment delivery has been presented. However, even with use of these improved imaging modalities, target visualization still remains an issue. This problem becomes even more critical in the setting of partial bladder radiotherapy [6]. The combined use of IGRT, along with fiducial markers hopes to improve these uncertainties and provide greater sparing of normal structures. Furthermore, online adaptive radiotherapy aims to combat the issue of interfraction bladder filling variation. This combination of technological advances may in fact result in an increase in the number of patients receiving adjuvant radiotherapy. However, with many studies investigating partial bladder radiotherapy, coupled with dose escalation or boost delivery, accuracy remains paramount [6–8].

Gold seed fiducial markers present as a potentially accurate method of providing an easily visualized surrogate for the target in bladder patients. They have shown huge success in breast radiotherapy, allowing for reduced margins, partial breast treatments and dose escalation [9,10]. In prostate radiotherapy, they are used routinely for image guidance in many institutions leading to increased set-up accuracy, reduced target margins and dose escalation [11–13].

Lipiodol can be used as a radio opaque contrast agent in modern medicine. Similar to gold fiducials, it presents as a novel method of providing an easily visualized surrogate for the target and has a potential role to play in both target delineation and image verification for bladder radiotherapy.

Through the means of this review, the feasibility of the use of gold fiducial markers in comparison with Lipiodol injections for enhancing target visualization and image registration in bladder patients will be investigated. The insertion of both Lipiodol and gold fiducials is somewhat invasive for patients. There is also the potential for poor visibility due to fading and fall out, as well as migration. The ability of each method to reduce set-up errors and to remain stable and visible throughout treatment will be examined.

## Material and methods

The participant population of this research was all bladder cancer patients undergoing radical whole or partial bladder radiotherapy, of any age and performance status. It included

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patients of any disease stage and grade, along with any disease subtype. All radiotherapy techniques and verification imaging modalities were included in the research.

A database search using Pubmed, Embase, Science Direct and The Cochrane Library was carried out to establish articles published in English from 2004–2014. Search terms used were: 'Lipiodol AND bladder cancer'; 'Lipiodol AND bladder cancer AND IGRT'; 'IGRT AND bladder cancer'; 'Lipiodol AND IGRT'; 'fiducial AND bladder cancer'; 'fiducial AND bladder cancer AND IGRT; 'bladder cancer AND image AND verification.

The included studies were prospective and retrospective single and multi-institution cohort and observational studies that examined Lipiodol injections and gold fiducial markers in relation to reliability and the enhancement of target visualization. Any method of insertion of Lipiodol or gold fiducials was included. Studies with any population size were included. Published abstracts from oral presentations and poster presentations were excluded.

The recruited studies aimed to include set-up errors in two or more translational directions when using either Lipiodol injections or fiducial markers for image registration purposes. The number and visibility of Lipiodol spots and gold fiducials remaining throughout treatment were also included. They also aimed to report adverse reactions that occurred in patients due to the interventions used, i.e. Lipiodol or gold fiducials, using an internationally recognized toxicity scoring system. The studies also aimed to report the number and visibility of Lipiodol spots or gold fiducials remaining throughout treatment, to assess reliability.

## Results

Thirteen articles were recruited and analyzed for eligibility in the research based on the inclusion and exclusion criteria. Nine full text articles, including a total of 131 patients, were used. This included six studies with a total of 85 patients examining the set-up errors and reliability of Lipiodol spots and three studies with a total of 46 patients examining the set-up errors and reliability of fiducial markers.

### *Impact on reducing set-up errors and enhancing image registration*

Three studies reported the difference in set-up errors between using Lipiodol image registration and other registration techniques (Table I). Sondergaard et al., Chai et al., and Pos et al. all reported increased accuracy when using a Lipiodol registration on kV cone beam computed tomography (CBCT) compared to other conventional methods of registration [14–16]. One study reported on the accuracy of using a general mask registration (one large spot) and a sub mask registration (multiple spots) [15].

Considering the difference in set-up errors between using gold fiducial marker image registration and a bony match registration, on both kV two-dimensional (2D) and kV CBCT imaging (Table I), Della Biancia et al. reported increased accuracy when using fiducial match compared to a bony match, on kV CBCT [17]. It was found that the results of the fiducial match on kV CBCT were comparable to the same match on kV 2D images [17].

All studies used kV CBCT imaging only for Lipiodol image registration. Sondergaard et al. reported difficulty in the visualization of the Lipiodol spots on 2D kV images and did not report on accuracy of matches using this modality [14].

### *Visibility and accuracy for providing a stable surrogate for the target*

Five studies reported on the number of Lipiodol spots remaining visible during the course of radiotherapy from insertion to CT to kV CBCT (Table II). Lipiodol spots remained visible throughout treatment on kV CBCT [18]. Furthermore, the movement of the gold fiducials was consistent with the movement of the bladder wall [19] and in fact, Chai et al. found a strong correlation ($R = 0.86$) between bladder volume variation and Lipiodol marker movement [15].

Four studies reported on the percentage loss of visible Lipiodol spots by the final kV CBCT, which ranged from 5% to 24% [14–16,20]. All studies reported some degree of fading or washout of Lipiodol spots throughout the course of treatment with the exception of Meijer et al. [14–16,18,20,21] (Table III). Seed loss was also reported by all studies during treatment, ranging from 2% to 41%, when assessed on various imaging modalities (MV CBCT, kV CBCT and kV 2D images) [17,19,22]. In the case of the Garcia et al. study, this 2% loss was reported only for gold seeds not placed in the tumor area.

### *Toxicities associated with insertion*

Six studies reported on the side effects associated with the Lipiodol insertion technique. All studies reported that there were no adverse reactions experienced as a direct result of the Lipiodol, with any reactions being associated with cystoscopy or radiotherapy treatment [14–16,18,20,21].

Two studies reported on the adverse effects of the fiducial marker insertion technique. Garcia et al. reported hematuria and Mangar et al. reported mild dysuria, both resulting from the fiducial insertion procedure [19,22]. Mangar et al. reported difficulties in inserting gold fiducial markers into the dome of the bladder where disease was present [22]. Meijer at al. reported that Lipiodol could not be successfully injected to mark the tumor borders close to the bladder neck [21].

## Discussion

This review has examined the body of literature regarding the clinical use of Lipiodol and gold fiducials for image-guided bladder radiotherapy. Each method was successful in reducing the effects of interfraction target motion. However, the small number of studies available and low patient numbers result in low levels of evidence for the interventions in question.

Sondergaard et al. demonstrated that the difference in shifts between a bony match and a Lipiodol match was greater than 5 mm in over 50% of all treatment fractions [14]. Pos et al. showed registration accuracy of within 2 mm (SD), when compared to Gray scale registration [16]. Despite promising results, these studies are based on small populations of five

Table I. Set-up errors in fiducial matches (Lipiodol and gold fiducials) compared to alternative match types.

| Authors | No. of CBCT scans | Imaging protocol | Initial match type | Secondary match type based match type | Fiducial type | Difference in set-up errors between initial match and Lipiodol-based match |
|---|---|---|---|---|---|---|
| Pos et al. [16] | 80 | Online | Automatic Gray value registration | Automatic | Lipiodol | Mean Initial SD: 1.1, 0.9, 1.7(mm) LR, CC, APMean Lipiodol SD: 0.8, 0.9, 1.7(mm) LR, CC, AP |
| Pos et al. [16] | 80 | Online | Manual fiducial registration | Automatic | Lipiodol | Mean Initial SD: 1.8, 1.7, 2.1(mm) LR, CC, APMean Lipiodol SD: 0.8, 0.9, 1.7(mm) LR, CC, AP |
| Sondergaard et al. [14] | 114 | Offline | Pelvic bony match | Automatic | Lipiodol | Mean shift from Initial match to Lipiodol-based match (mm) SD:1(2), -2(3), 0(4) (LR, CC, AP) |
| *Chai et al. [15] | ~135 | Online | Fiducial registration-general maskchamfer algorithm | General mask | Lipiodol | *Mean and SD of the difference between twice general mask registrations were 0.01 mm and 0.05 mm, respectively |
| *Chai et al. [15] | ~135 | Online | Fiducial registration-sub maskchamfer algorithm | Sub mask | Lipiodol | *Mean and SD of the difference between twice average sub mask registrations were 0.06 mm and 0.18 mm, respectively |
| Della Biancia et al. [17] | 20 patients, 34–37 2D image pairs per patient | Online | 2D bony match | 2D gold fiducial match | Gold fiducial | Average difference (mm):LR: 0.5 ± 1.0 (range -2.0–+3.8)AP: 1.7 ± 4.4 (range -8.1–13.5)CC: -3.7 ± 5.8 (range -16.8–8.3) |
| Della Biancia et al. [17] | 5 patients, average 7 CBCT per patient | Online | 3D bony match | 3D gold fiducial match | Gold fiducial | Average difference (mm):LR: 0.3 ± 2.1 (range -2.4–5.1), AP: 3.1 ± 5.9 (range -2.9–13.3), CC: -4.8 ± 8.0 (range -16.4–9.5) |
| Della Biancia et al. [17] | Unknown | Unknown | 2D gold fiducial match | 2D gold fiducial match | Gold fiducial | Unknown. Results found to be comparable in LR, AP and CC by means of graph representation |

AP, anterior posterior; CC, cranial caudal; LR, left right; SD, standard deviation.
*An investigation into the accuracy of using a general mask registration (using all Lipiodol spots combined as one marker) and a sub mask registration (using individual spots as markers) was carried out in which the reproducibility of each was tested.

and 40 patients, respectively. With respect to potential margin reduction, Foroudi et al. showed that there was no advantage in using a bony match compared to a skin marker only set up, enforcing the advantage of the Lipiodol method over a bony match [23].

It was demonstrated that an automatic Lipiodol registration based on the chamfer algorithm is more accurate than a manual Lipiodol registration [16]. Furthermore, Chai et al. found that an automatic general mask registration (including all Lipiodol spots) was successful even if Lipiodol spots had faded or been lost. However, it is possible that larger spots would dominate the registration using this technique. A sub mask registration (including individual spots) was found not to be effective if spots were connected or lost. Therefore, implementing both procedures and using the difference between the two was suggested as a protocol to combat the possible shortcomings of both techniques. However, it was found that only 47% of patients were eligible for both techniques, questioning the feasibility of such a protocol and the necessity for the two techniques to work at the same time [15]. Overall, the Lipiodol registration can still be regarded as more accurate than a soft tissue registration.

Possible target displacements of up to 13.5 mm and 16.8 mm in the anterior direction and superior directions, respectively, when using a bony match compared to a fiducial match, were demonstrated [17]. The evidence for the use of fiducial marker registration is promising; however, the level of evidence provided is poor as these results are based on one observational study with 20 participants. Garcia et al. reported that the difference between a fiducial set up based on MV CBCT and a non-IGRT set up was 20 mm and 10 mm in the left/right and cranial/caudal dimensions, respectively [19]. However, inaccuracies in the technique used, which involved the clinician drawing dots on the patient to predict target location based on skin marker set up, result in these findings being questionable.

Lipiodol and fiducial matching are also appropriate for specialized techniques, such as IMRT and adaptive radiotherapy [14,17,18,21]. The superior set-up accuracy has translated into margin reduction, organ at risk sparing and also partial bladder treatment. Compared to the traditional 20–25 mm margin used when no Lipiodol demarcation is used [24,25], Sondergaard et al. reported that a 10–15 mm margin is needed when Lipiodol is used for tumor demarcation, and van Rooijen et al. report only a 5 mm margin is needed [14,26]. This presents promising outcomes for the use of Lipiodol for boost and partial bladder treatment delivery. Online adaptive radiotherapy acts in the interest of varying bladder sizes between fractions and has been deemed a viable method of treatment delivery in many studies [21,27–30]. Lipiodol and fiducial markers can both work well with adaptive planning, by providing enhanced visualization of the target as well as improved registration, which are fundamental to a successful online adaptive protocol.

The large variation in the number of Lipiodol spots injected (from 1 to 6 spots) may have had an impact on the differing set-up errors reported by three studies [14–16]. All six studies reported that 92% or more of the Lipiodol spots remained visible on CBCT, excluding Sondergaard et al. who reported

Table II. Visibility and percentage loss of Lipiodol spots from insertion to verification imaging.

| Author | No. of patients | Method of insertion | No. of Lipiodol spots per patient & ml of Lipiodol used | % Lipiodol spots visible at planning CT | % Lipiodol spots visible on kV CBCT | Fading of Lipiodol reported |
|---|---|---|---|---|---|---|
| Freilich et al. [18] | 5 | Cystoscopy, fluoroscopy guided. GA | 1 large spot, 10–15 ml per spot | *100% | *100% | No |
| Sondergaard et al. [14] | 5 | Cystoscopy, local gel anesthetic | 4–6 spots, 0.25–0.5 ml per spot | Unknown | 76% | Yes |
| Pos et al. [16] | 40 | Cystoscopy, no anaesthetics | 1 large spot, 0.25 ml per injection, 3–5 injections | 95% | 95% | No |
| Baumgarten et al. [20] | 5 | Cystoscopy, GA | 1 large spot 10–15 ml, 0.5 ml per injection | 95% | 95% | No |
| Meijer et al. [21] | 20 | Cystoscopy, fluoroscopy guided | Unknown | *100% | *100% | No |
| Chai et al. [15] | 15 | Cystoscopy | 2–4 spots, 0.25 ml per spot | Unknown | 92% | Yes |

GA, general anesthetic.
*Where no loss was reported by studies, 100% value was given for number of Lipiodol spots remaining.

Table III. Visibility and percentage loss of gold fiducial markers from insertion to verification imaging.

| Author | No. of patients | Method of insertion | No. of fiducial markers per patient | % fiducials visible at planning CT | % fiducials visible on verification imaging | Type of verification imaging used |
|---|---|---|---|---|---|---|
| Della Biancia et al. [17] | 20 | Cystoscopy | 2–4 | Unknown | Unknown | kV CBCT & 2D kV images |
| Garcia et al. [19] | 16 | Cystoscopy, fluoroscopy guided | 3–5, total 82 markers | 100% | 98% | MV CBCT & MV portal images |
| Mangar et al. [22] | 8 | Cystoscopy, GA, cystodiathermy | 5–6, total 44 markers | 75% | 59% | MV portal images |

GA, general anesthetic.

that only 76% remained visible [14–16,18,20,21]. Difficulties in injection techniques reported by Sondergaard et al. from the outset, undoubtedly, led to improved accuracy in Lipiodol insertion for the subsequent studies conducted, e.g. the use of fluoroscopy in the study by Meijer et al. [21]. This may explain the relatively consistent volumes of Lipiodol (0.25 ml per spot where multiple spots are used and 10–15 ml for one large spot) used to demark the tumor bed.

The visibility and stability of the fiducial markers within the bladder was also examined. Manger et al. reported that only 59% of gold fiducials inserted remained in place and visible on the MV portal images used for verification [22]. Design changes to the fiducial markers in subsequent studies, such as using micro-tines along their sides to help anchor into place achieved much higher levels of stability [17,19]. Garcia et al. reported that 98% of gold fiducials, when placed at the anatomical boundaries of the bladder, remained stable and visible on verification imaging and their representation of the movement of the target due to bladder filling was accurate [19]. Gold fiducials were easily visualized on all imaging modalities, both MV and kV.

Limitations to the Lipiodol method of registration lie in its dependence on kV imaging modalities. All studies used kV CBCT, and one reported difficulty in the visualization of the Lipiodol spots on 2D kV images. Artifact from pelvic bony anatomy had a large role to play in this and was reported to be worse on the lateral image [14]. This would restrict the use of such registration techniques in institutions that do not facilitate kV CBCT technology and would question its ability to be used on 2D kV imaging. No studies reporting on set-up accuracy in fiducial registration, compared to other registration techniques, used MV imaging modalities. One study reported that a Lipiodol spot was not visible in one patient due to artifact from a hip prosthesis, potentially deeming these patients unsuitable for this technique [15].

With Lipiodol fading reported by two studies, the accuracy of registrations based on this technique are debatable [14,15]. Poor visualization of the spots may lead to inaccuracies in image registration procedures. Dominance of clearer Lipiodol spots can occur, resulting in Lipiodol acting as an inaccurate surrogate for the target [15]. Sondergaard et al. also reported a loss of spots in one patient likely due to intravesical spillage during injection [14].

A study into the effects that gold fiducial markers can have on dose perturbation in patients undergoing photon beam therapy found that the maximum dose reduction was within 5% at 6 MV and 2% at 18 MV. It is important to take this into consideration especially when a large number of gold fiducials may be inserted.

A small proportion of bladder sites were deemed unsuccessful for demarcation in various studies. Mangar et al. reported difficulties in inserting gold fiducial markers into the dome of the bladder where disease was present [22]. Meijer et al. reported that in six patients with tumors close to the bladder neck, Lipiodol could not be successfully injected to mark the tumor borders due to restrictions of the cytoscope [21].

While most studies reported no adverse reactions from the insertion techniques used for both fiducial markers and Lipiodol, there were some isolated incidences of side effects experienced. Mild dysuria was reported post-insertion of fiducial markers, but this subsided after 24 hours [22]. Garcia et al. reported hematuria which resolved between 24 and

48 hours post-operatively with the aid of urinary catheterization [19]. Allergic reactions to the Lipiodol agent are possible, with institutions requiring appropriate facilities and personnel to deal with possible reactions.

While both insertion techniques involve a minimally invasive rigid or flexible cystoscopy insertion technique, general anesthetic was used in a number of studies and this may eliminate patients who would be unable to tolerate this. However, a number of studies also carried out the procedure with local gel anesthetic or no anesthetic. A cystodiathermy technique was also used in one study which can result in tissue necrosis and delayed marker fallout [19,22].

While this review has focused on Lipiodol and gold fiducials, it must be noted that the use of absorbable hydrogel has also been recently investigated as an upcoming marker type for this patient group. One multicenter study reported promising results with respect to ease of insertion and also visibility throughout a course of IGRT [31]. More recently, Lutkenhaus et al. published a comprehensive evaluation of the dose delivered during a course of adaptive radiotherapy for bladder cancer [32]. Of their patient cohort of 16, 31% had hydrogel inserted to assist in target localization and image matching, validating its use in routine clinical practice. There may also be scope to include the use of electromagnetic transponders, such as the Calypso tracking system for this patient population; however, this may be difficult for whole bladder treatments [33] and data here is limited.

Motion management certainly poses a difficult and complex challenge in bladder radiotherapy. Lipiodol injections and gold fiducial markers present as promising and accurate methods of overcoming interfraction bladder motion in IGRT treatment delivery. Combined with continuous image acquisition, such as fluoroscopy, these markers may also prove to be a valuable tool for the online assessment of intrafraction motion. Although fading and seed fall out is possible, they can remain stable and visible throughout treatment leading to high levels of accuracy and reliability. Furthermore, they act in the interest of improving partial bladder radiotherapy and online adaptive planning delivery methods. Further studies relating to accuracy of the image registrations achieved, with multi-institutional cooperation to achieve substantial patient numbers, are needed.

## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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