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INVITED REVIEW

Fiducial markers: can the urologist do better?

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Abstract

Introduction Radiotherapy to the bladder has a risk of toxicity to pelvic structures, which can be reduced by using fiducial markers for targeting. Injectable contrast offers an alternative marker to gold seeds, which may fall out or exacerbate scarring. Combining contrast agents with tissue glue can minimize dispersion through tissue, enhancing its utility. We evaluated combinations of contrast agents and tissue glue using porcine bladder, for feasibility and utility as fiducial markers to aid image-guided radiotherapy.

Methods Different contrast agents (Lipiodol ultra or Urografin) were combined with different tissue glues (Histoacryl, Tisseal or Glubran2). The mixtures were endoscopically injected into porcine bladder submucosa to identify the area of interest with multiple fiducial markers. The porcine bladders were imaged within a phantom porcine pelvis using standard radiation therapy imaging modalities. The feasibility as an injectable fiducial marker and visibility of each fiducial marker on imaging were scored as binary outcomes by two proceduralists and two radiation therapists, respectively.

Results Lipiodol–glue combinations were successfully administered as multiple fiducials that were evident on CT and CBCT. Lipiodol with Histoacryl or Glubran2 was visible on kV imaging. The Lipiodol Glubran2 combination was deemed subjectively easiest to use at delivery, and a better fiducial on KV imaging.

Conclusion This study demonstrates the feasibility of mixing contrast medium Lipiodol with Histoacryl or Glubran2 tissue glue, which, injected endoscopically, provides discrete and visible fiducial markers to aid image-guided radiotherapy. Although promising, further study is required to assess the durability of these markers through a course of radiotherapy.

Keywords Fiducial markers · Prostate cancer · Bladder cancer · Endoscopy · Image-guided radiotherapy · Cone beam computed tomography · Iodized oil · Tissue glue

Introduction

Radiotherapy to the bladder is utilized in two common clinical situations. It is often used as adjuvant or salvage therapy following prostatectomy for the management of prostate cancer where the major radiotherapy targets include the vesicourethral anastomosis, posterior bladder and retro-vesical space [1]. It is also used to treat muscle invasive bladder cancer following transurethral resection of bladder tumour (TURBT) in the context of bladder preservation, pre-radical surgery or if radical surgery is not suitable [2]. Efficacy of radiation therapy is directly related to the dose received by the tumour. Similarly, radiation toxicity is directly related to the dosing of normal adjacent tissues. Specifically, bladder toxicity is associated with significant morbidity and is directly related to the proportion of the bladder to receive

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high radiation doses [3]. As such, the aim of modern radiotherapy is to accurately target the area of malignancy to maximize treatment dose while minimizing toxicity [4].

The use of fiducial markers in conjunction with image-guided radiotherapy (IGRT) allows for more accurate dose delivery of radiotherapy to the tumour or target - improving local control, while reducing dose and thus toxicity to the normal bladder and bowel. The requirements of any fiducial marker are visibility on a given imaging modality for use in IGRT, availability and reasonable cost [5]. This concept has been clearly demonstrated with the use of gold fiducial markers and IGRT for radiotherapy to an intact prostate [6]. Several studies have demonstrated that fiducial markers improve targeting of the prostate over use of bony landmarks [5]. Fiducial markers have also been demonstrated to be better than surgical clips for use in image-guided radiotherapy post-prostatectomy [7]. Solid fiducial markers are used in the bladder, but may be subject to migration, dislodgement or foreign body sequelae in the irradiated post-operative field [8]. The degree of migration of solid fiducial markers unrelated to bladder volume change has been documented to be as little as 1 mm over a course of treatment in a single patient [9], but needs further investigation and validation. Injectable contrast offers an alternative to potentially avoid these concerns [10]; however, dispersion of contrast through the bladder wall may impede its use [11].

A mixture of Lipiodol and cyanoacrylate tissue glue has been shown to be a safe and effective treatment of gastric and oesophageal varices [12]. Cyanoacrylate rapidly solidifies in the presence of weak bases such as water and blood. Lipiodol is an oily radiological contrast agent. The oil prevents the cyanoacrylate from polymerization until it contacts water or blood in tissue. It also enables the operator to visualize the process on X-ray imaging. We have previously successfully used a mixture of Lipiodol and cyanoacrylate glue as a fiducial marker for oesophageal cancer [13]. However, the use of glue fiducials has never been described in a water-filled organ such as the bladder.

The aim of the study was to test the technical and procedural aspects of combining and delivering liquid contrast agents with several types of tissue glues in a porcine pelvis bladder model. The objective was to create multiple reproducible discrete glue fiducial markers that could be visualized with standard radiotherapy imaging.

Materials and methods

Ethics approval was sought but not required according to the institutional HREC, as this study was conducted in vitro on isolated porcine bladder.

Six separate contrast–glue mixtures were tested by combining 2 contrast agents—Lipiodol Ultra liquid (esterized poppy seed oil, Aspen Medical) or Urografin 76% (amidotrizoate, Bayer Resources) with three different tissue glues: Histoacryl (monomeric *n*-butyl-2-cyanoacrylate, B Braun), Glubran2 (G-NB-2 NBCA-MS co-monomer, Baxter Healthcare) and Tisseal (fibrin sealant, Matrix Surgical), respectively, in a 1:1 ratio. For comparison, porcine bladders with no injection and single agent injection of Histoacryl, Glubran and Tisseal were used as controls. To create the mixtures, 1 ml of contrast agent was drawn up in a 2 ml syringe and 1 ml of tissue glue was drawn up in a separate 1 ml syringe. Mixing was performed using a luer-lock connector by plunging the agents back and forth between the syringes. Once adequately combined, the mixtures were immediately used.

A 17fr rigid cystoscope was used to endoscopically inspect the isolated bladders and fill the bladder with occlusion of the bladder neck against the scope itself by manual pressure to maintain continence. Using a William's needle (Cook Medical, Australia), contrast/glue combinations were injected submucosally to raise a bleb of 0.1 ml of mixture into the submucosal tissue (Fig 1). Injections were placed around the trigone to create discrete markers, to imitate marking out a small bladder tumour or the vesico-urethral anastomosis following a prostatectomy, as demonstrated in Fig. 2. Each individual mixture was tested in a separate bladder specimen.

The contrast/glue combinations were assessed for technical feasibility with regards to mixing and injection procedures on a binary rating system by the investigators carrying out the injections (NL & SS). After the injection was completed, the cystoscope was removed from the bladder with the needle kept beyond the scope to avoid occlusion of the working channel with the glue mixture. Once withdrawn from the bladder, the needle was disengaged from the cystoscope in a retrograde fashion (from the distal end) to protect

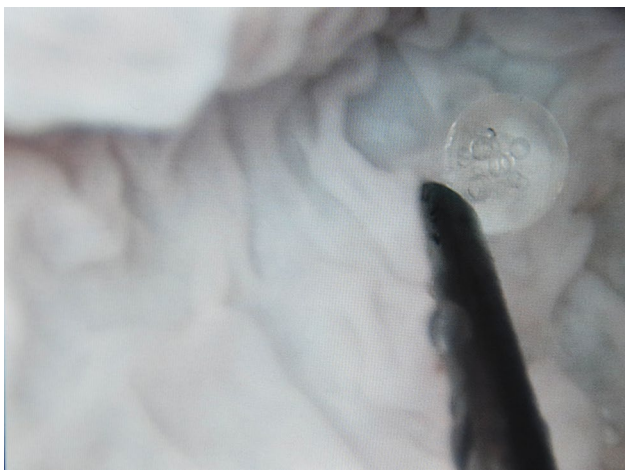

Fig. 1 Endoscopic ex vivo submucosal glue fiducial injection of fluid-filled pigs bladder

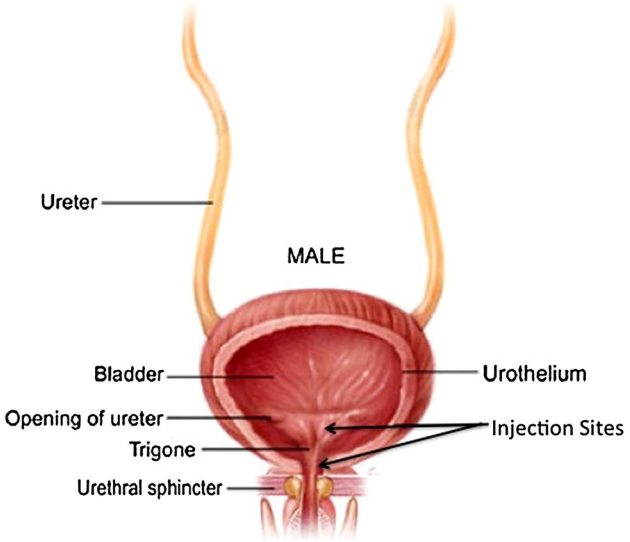

Fig. 2 Contrast/glue injection sites within the porcine bladder

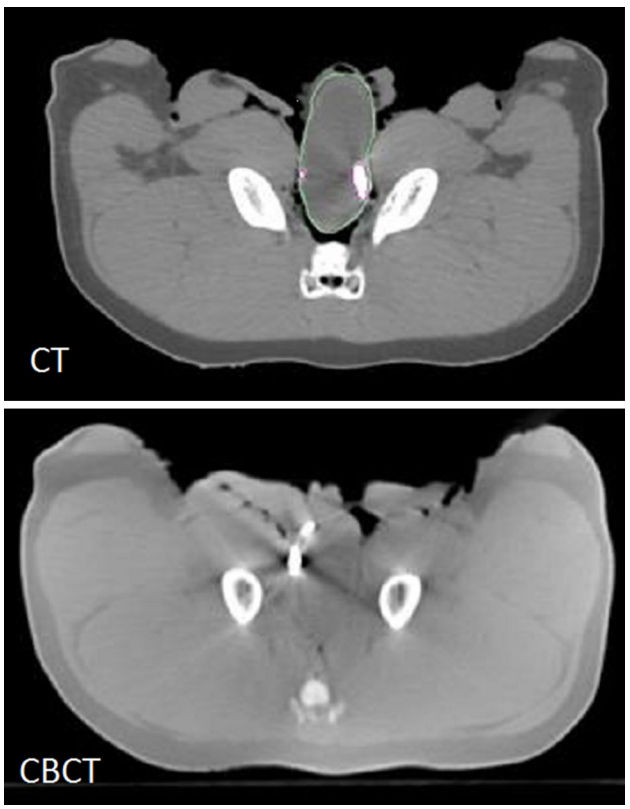

Fig. 3 Verification of lipiodol and glue fiducial marker on computed tomography (CT) and cone beam computed tomography (CBCT)

the scope from the glue mixture passing through the working channel of the cystoscope.

The bladders were then placed in a detached porcine pelvis positioned to imitate a human in a supine position. This also approximates the tissue densities in a human pelvis undergoing radiotherapy image guidance. The porcine pelvis and contained bladder were then imaged using typical radiotherapy modalities, i.e., cone beam computed tomography (CBCT), computed tomography (CT) and kilovoltage (KV) and megavoltage (MV) planar imaging (Fig. 3). The images were evaluated for visibility of contrast markers. The basis of the fiducial marker utilization during a course of radiotherapy is the accurate registration of the treatment images with the original planned images, so as to accurately deliver the radiation. This targeting and matching process is performed by trained radiation therapists or technicians. Therefore, if the markers were adequate to allow registration by the radiation technicians (consensus opinion of at least two investigators—RO, KB, ML) using standard imaging modalities for IGRT, the contrast–glue combination was considered to be visible on a binary rating system.

Results

Combining contrast with glue

Both contrast media were able to be mixed with the tissue glue in all combinations. However, since Urografin set quite quickly when combined with the tissue glue, only limited time was available for injection to be carried out. Ease of mixing was also subjectively better with the Lipiodol Ultra when compared with the Urografin. The rate of polymerization when Lipiodol Ultra was combined with Glubran2 was dependent on the ratio of the agents, with increased time to polymerization as the proportion of Lipiodol Ultra was increased.

Injection of contrast–glue combination

Urografin combinations could only be injected once as a single marker due to the rapid polymerisation of the mixture, as Urografin is a water-soluble contrast medium.

Lipiodol combinations with Glubran2, Histoacryl and Tisseal could be easily injected repeatedly into the bladder submucosa, raising multiple small blebs. The combination of Lipiodol with Glubran2 was assessed as being technically easiest to inject.

Imaging of porcine bladders

All markers were assessed with several typical imaging modalities to determine whether the markers were adequately visible to allow registration, recorded as a binary outcome being visible or not visible.

Urografin–glue combinations were each only able to produce a single fiducial that was visible on CT and CBCT, but not visible on KV or MV.

Lipiodol–tissue glue combinations were all able to deliver multiple fiducials that were adequately visualized on CT and CBCT. Lipiodol with either Histoacryl or Glubran produced visible fiducials on KV imaging. Subjectively, the Glubran 2 combination created a better marker. The Lipiodol with Tisseal combination was not visible on imaging. No combination produced sufficient contrast with MV planar imaging. These results are summarized in Table 1.

Discussion

This is the first study to demonstrate that Lipiodol Ultra can be easily combined with Glubran2 or Histoacryl tissue glue to create discrete injectable fiducial markers within the fluid-filled bladder wall. The combinations are visible on standard imaging modalities used in IGRT. They can be easily delivered using standard endoscopic injection techniques. The other combinations tested were not found to be suitable. Fiducials created with a mixture of Lipiodol and Tisseal were not visible on imaging, while Urografin mixtures with each tissue glue had practical limitations in creating more than one fiducial marker given rapid polymerization.

Several previous studies have demonstrated that Lipiodol is safe and effective for use in the bladder to demarcate tumours [10, 11, 14–18]. Success rates with Lipiodol alone have been variable, reported between 76 and 100% [10] as summarized in Table 2. No toxicity from Lipiodol has been reported. Notably, although Chai et al. report 92% of the markers remained in situ at the completion of the radiation course in their 15 patients, a further 16 patients could not be included in the series as the markers could not be registered for image-guided therapy due to splitting or joining [16]. Cyanoacrylic glues such as Histoacryl and the components of Glubran2 have been used in a range of urologic procedures including urethral tissue in animal models, and use in urinary fistulas without toxicity [19]. The use of a mixture of Lipiodol and Histoacryl glue has also been previously described for the treatment of persistent anastomotic urine leak after radical prostatectomy without toxicity at 23-week follow-up [20].

Despite the success in visibility of Lipiodol as described in the literature, our clinical experience in using Lipiodol alone has been variable. While discrete fiducials have been created, it was often hampered by the significant dispersion of Lipiodol through and beyond the bladder wall, limiting its specificity as a fiducial marker. This is reflected in the imaging included in each of the studies listed above that demonstrate good visibility on CT/kV imaging but highlight a lack of specificity in the location of the Lipiodol following injection [14]. Consequently, it may not be sufficient as the sole fiducial marker [11]. In addition, wide dispersion of contrast may significantly impact further imaging in these patients, which is commonly required for ongoing follow-up.

Placing a foreign body within an operative site during radiotherapy presents the potential risks of scarring and fistulae formation [21]. These concerns have prompted the consideration of options beyond the conventional gold seeds. Modified gold seeds have been used successfully in the bladder with endoscopic placement for targeting of radiotherapy for treatment of muscle invasive bladder cancer [22]; however, these seeds are not freely available. In contrast, Lipiodol and tissue glue (Glubran2 or Histoacryl) may be found in many hospitals, including regional centers. Notably, Lipiodol and Histocryl mixture is a cost-effective combination when compared to most other glues and fiducials.

The major limitation of this study is the evaluation of the fiducial markers at only a single time point immediately following the administration of the contrast–tissue glue combination. It does not address the stability, durability and migration of the marker. However, similar combinations used in other organs such as the upper gastrointestinal tract [23] suggest that these markers are likely to be stable. Further evaluation of the stability and reliability of Lipiodol–tissue glue markers through a standard course of radiotherapy is required by appropriate in vivo assessment.

Table 1 Injection visibility of Contrast/glue markers with multimodal imaging

Contrast agent	Urografin			Lipiodol		
Glue agent	Glubran	Histoacryl	Tisseal	Glubran	Histoacryl	Tisseal
Injection feasible	No	No	No	Yes	Yes	Yes
Visible	Yes[a]	Yes[a]	Yes[a]	Yes	Yes	No
	CT, CBCT, KV	CT only	CT and CBCT	CT, CBCT, KV		

CT computed tomography, *CBCT* cone beam computed tomography, *KV* kilovoltage planar imaging

[a]The single marker injected prior to polymerization of the Urografin–glue mixture was visible but re-injection was technically not feasible

Table 2 Current published series investigating as Lipiodol marker for image-guided radiotherapy

Study	Patient number	Trial type	Oncological outcome	Adverse effects	Visibility of Lipiodol markers on kv planar imaging (%)
Pos et al. 2009 [11]	40	Obs[a]	Difficulty controlling size of markers, with some lipiodol outside bladder wall, thus not feasible to use lipiodol alone as sole reference for delineation. Valuable aid, tumour would have been missed by radiation in some patients without lipiodol demarcation	No lipiodol toxicity. Lipiodol disappeared over 12 months on CT follow-up	95 (2 of 40 patients had no Lipidol present on imaging post-injection)
Chai et al. 2010 [16]	15	Obs[a]	15 of 32 patients injected with lipidol markers were included. 17 patients were not included, in 16 because markers had split or joined, in 1 because there was no contrast in the bladder wall No post-radiation follow-up	Not recorded	92 at 5 weeks (of included patients)
Sondergaard et al. 2010 [18]	5	Obs[a]	>50% of treatment fractions required moderate shift to match Lipiodol spots No post-radiation treatment follow-up	Adverse effects on cystoscopy + injection: 1 patient dysuria, 1 patient mild urinary frequency, both lasting < 24 h	76
Meijer et al. 2012 [17]	20	Obs[a]	Median follow-up 28 months, 9 patients died. 3 died of metastatic disease—no evidence local relapse; 2 patients died of local muscle invasive relapse and disease progression at 6 and 12 months post treatment; 4 died of MI[c] Remaining 11 patients had no evidence of disease	No adverse events from cystoscopy + injection. No G^b III toxicities, acute G^bII toxicities ~ 45%, at 36 months 25%	100
Baumgarten et al. 2014 [15] Freilich et al. 2014 [14]	5	Obs[a]	Follow-up 18 months In 2 of 5 patients tumour bed based on lipiodol extended outside planning target volume that would have been treated based on cystoscopy reports alone 3 no recurrence, 1 alive with metastatic disease, 1 died from metastatic disease	No adverse events from injection. No treatment related toxicities/infections	95
Kliton et al. 2017 [10] [in Hungarian]	3	Obs[a]	Total treatment time was shorted by 4 days. No oncological outcomes reported in English abstract	No toxicity to injection. 1 patient G^bII cystitis + proctitis, 1 patient G^bI cystitis	100

[a]Obs: observational trial, no randomization or control group comparison

[b]G: grade as per radiation therapy oncology group side effects grading recommendation

[c]MI: myocardial infarction

Conclusions

This model presents a Lipiodol–tissue glue combination as a feasible and potentially inexpensive alternative to solid fiducial markers or Lipiodol alone to overcome the respective difficulties with each. The technique has the advantages of utilizing standard stock available in most hospitals, and endoscopic injection techniques that are in widespread use. Further human trials are required [24], particularly to assess durability through a complete radiation treatment course.

Author contributions CB: data collection or management. KB: data collection or management. MC: protocol/project development. CD: Data analysis, manuscript writing/editing. FF: protocol/project development, data analysis. TJ: protocol/project development. DLJ: protocol/project development, data analysis, manuscript writing/editing. VK: manuscript writing/editing. ML: data collection or management. NL: protocol/project development, manuscript writing/editing. RO: data collection or management. SS: protocol/project development, manuscript writing/editing. AV: data collection or management. MW: protocol/project development.

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Compliance with ethical standards

Conflict of interest All of the authors declare that they have no conflict of interest.

Ethics This article does not contain any experimental studies with human participants or live animals performed by any of the authors. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. Ethics approval was sought from the institutional ethics committee but deemed redundant by the ethics committee, as porcine bladders were used in isolation.

Informed consent No patient data were included in this article.

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