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A radiopaque polymer hydrogel used as a fiducial marker in gynecologic-cancer patients receiving brachytherapy

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ABSTRACT

PURPOSE: We assessed a novel Food and Drug Administration–approved hydrogel, synthesized as absorbable iodinated particles, in gynecologic-cancer patients undergoing computed tomography (CT) or magnetic resonance (MR) based brachytherapy after external beam radiation.

METHODS AND MATERIALS: Nineteen patients underwent CT-guided (n = 13) or MR-guided (n = 6) brachytherapy for gynecologic cancers. Seventy-seven hydrogel injections were placed. The hydrogel material was injected into gross residual disease and/or key anatomic landmarks in amounts ranging from 0.1 to 0.4 mL. The visibility of the tracer was scored on CT and on MR images using a 5-point scoring scale. A Cohen's kappa statistic was calculated to assess interobserver agreement. To assess the unadjusted effects of baseline parameters on hydrogel visibility, we modeled visibility using a linear mixed-effect model.

RESULTS: Injections were without complication. The kappa statistic was 0.77 (95% confidence interval [CI], 0.68–0.87). The volume of hydrogel injected was significantly associated with visibility on both CT ($p = 0.032$) and magnetic resonance imaging ($p = 0.016$). We analyzed visibility by location, controlling for amount. A 0.1-cc increase in volume injected was associated with increases of 0.54 (95% CI = 0.05–1.03) in the CT visibility score and 0.83 (95% CI = 0.17–1.49) in the MR visibility score. Injection of 0.4 cc or more was required for unequivocal visibility on CT or MR. No statistically significant correlation was found between tumor type, tumor location, or anatomical location of injection and visibility on either CT or magnetic resonance imaging.

CONCLUSIONS: In this first report of an injectable radiopaque hydrogel, targets were visualized to assist with three-dimensional–based brachytherapy in gynecologic malignancies. This marker has potential for several applications, is easy to inject and visualize, and caused no acute complications.

Keywords: Fiducial; Radiopaque polymer hydrogel; Brachytherapy

Introduction

Fiducial markers are composed of radiopaque materials, most commonly gold or a metal alloy, and are used for the clinical and radiographic localization of normal and malignant tissues. These markers have been used in gynecologic radiation therapy to confirm daily setup position, assess target motion during external beam radiation therapy (EBRT), and to identify the tumor or cervix location during brachytherapy (1–3). Fiducial markers have also been used to assess intrafraction organ motion during therapy (4). In the modern era of three-dimensional (3D) image-guided therapy (5), accurate delineation of target volumes (6) is feasible and allows a greater understanding of organ- and tumor-motion management and allows the assessment of intrinsic patient setup uncertainty. These advancements have led to dose escalation of the primary tumor and dose reduction to nearby organs at risk (7–9).

Traditionally, fiducial markers have been composed of inert metals (2). The ability to successfully implant fiducial

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markers into gynecologic organs is known (1–3). Novel fiducial-marker gel compounds may offer advantages over metallic markers including decreased image artifact, decreased migration in tissue, absorbability, and the ability to create 3D structures of varying sizes (10).

The novel fiducial marker used in this series was a Food and Drug Administration (FDA)-approved polyethylene glycol (PEG) hydrogel micro particles containing covalently bound iodine (TraceIT Tissue Marker; Augmenix, Waltham, MA). PEG hydrogels are well-suited as fiducial markers as they are well-tolerated with minimal immunogenicity (11). A small risk of side effects is noted in drug delivery (12, 13), medical sealants and barriers (14–16) that use hydrogels. Additionally, because of its high water and iodine content, the hydrogel can be visualized using magnetic resonance imaging (MRI), computed tomography (CT), and/or ultrasound. The hydrogel is water-soluble and is visible for 3 months, after which the gel is slowly absorbed into the body over approximately 6 months, and subsequently excreted through the renal filtration system (10). We performed a prospective clinical evaluation of this novel hydrogel fiducial marker, assessing its visibility in patients receiving brachytherapy for gynecologic malignancies.

Methods and materials

Nineteen patients with gynecologic cancers treated with high-dose-rate brachytherapy were prospectively enrolled in this protocol, which was approved by the institutional review board.

Clinical information

The 19 patients underwent brachytherapy for primary or recurrent cervical or endometrial carcinoma. Twelve patients had primary cervical cancer, three had primary vaginal cancer, three had recurrent endometrial cancer at the vaginal cuff, and one had recurrent cervical cancer. All patients underwent 3D image-based brachytherapy. Seven patients had CT-planned tandem and ring, six had CT-planned interstitial, four had MR-planned interstitial, and two had MR-planned tandem and ring.

Imaging and implantation of fiducial markers

Before EBRT, all 19 patients had a diagnostic CT and eight also had a diagnostic MRI. After external beam, patients were placed under anesthesia. With the patient in the lithotomy position before brachytherapy applicator insertion, the hydrogel material was injected using a transvaginal approach through an 18-gauge spinal needle into the target with direct visualization of the injection site. The injection marked gross residual disease and/or key anatomic landmarks. The injected amount ranged from 0.1 to 0.4 mL. Post-implantation CT imaging was completed on all patients. The six patients whose procedure was done in the MR suite also underwent T1- and/or T2-weighted MRI (Siemens Magnetom Verio 3T) after implantation.

Materials

The Food and Drug Administration–approved hydrogel was synthesized as microbeads impregnated with iodine contrast material (TraceIT Tissue Marker; Augemenix, Co). This polymer is an absorbable tissue marker that remains visible for approximately three months. It is composed primarily of water and iodinated cross-linked PEG.

Interobserver variability

Two physicians separately scored the visibility of the radiopaque hydrogel on CT and on MRI using a 5-point scoring scale. Physicians had pretreatment imaging and postinjection CT and/or MR imaging available for review. At the time of scoring, neither physician had access to the other's scores nor was scoring performed under time constraints. The values were predetermined as follows: (*1*) not visualized; (*2*) faint or trace visibility (shadow or haze); (*3*) visible but indistinct borders (definable entity, not just haze); (*4*) partially distinct border, partial haze; and (*5*) clearly visualized, unequivocal. Cohen's Kappa statistic and the associated standard error were calculated to assess interobserver agreement (17). Standard nomenclature for the agreement levels associated with the kappa values was used: poor (kappa < 0), slight (kappa 0.01–0.2), fair (kappa 0.21–0.3), moderate (kappa 0.41–0.6), substantial (kappa 0.61–0.8), and almost perfect (kappa 0.81–1).

Statistical analysis

All statistical analysis (including the computation of the kappa statistics) was performed using R version 3.0.1. To assess the unadjusted effect of baseline parameters of anatomic differences and their relationship to hydrogel visibility, we fit a series of linear mixed-effect models to predict the visibility score based on the volume. Volume was treated as a fixed effect, and patient ID was treated as a random effect. Separate models were fit for CT visibility and MRI visibility. A second version of each model was also calculated that included a second fixed effect for tumor type (classified as cervical, vaginal, or endometrial). The coefficient for each model was used to estimate the increase in visibility for a 0.1-cc increase in the volume injected.

Results

Successful submucosal implantation of the radiopaque gel was accomplished without significant bleeding or interprocedure loss of the hydrogel marker. Ensuring minimal movement after insertion of the needle was critical to prevent the