A novel endoscopic marker for radiological localization and image-guided radiotherapy in esophageal and gastric cancers (with video)

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Background and Aims: Radiotherapy is an accepted modality in the treatment of esophageal cancers and is currently being evaluated in conjunction with chemotherapy for the neoadjuvant treatment of gastric cancers. Our aim was to assess whether a novel endoscopically inserted marker can be used to improve radiological assessment of the primary cancer and allow for image-guided radiotherapy.

Methods: A phase II feasibility study was conducted at a tertiary-care center. Twenty-six consecutive adult patients with esophagogastric cancers underwent endoscopic marking of the tumor margins with a novel radiopaque marker (mixture of lipiodol and n-butyl 2-cyanoacrylate). The main outcome measure was the successful insertion of the marker based on a combination of radiological, endoscopic, and histological assessment.

Results: A total of 92 markers were inserted in 26 patients. Twenty-two (88%) had follow-up imaging to assess the 81 markers inserted, 79 of which (97.5%) were visible. There were no postprocedural adverse events noted in our cohort. Radiological assessment of tumor size improved such that it was in line with the endoscopic evaluation after marker placement in 18 of 21 patients (85.7%) who had appropriate follow-up radiology imaging. Ten patients (38.5%) from our cohort underwent image-guided radiotherapy (IGRT) by using the endoscopically inserted markers.

Conclusion: Within the limitations of our small pilot study, endoscopic placement of our novel marker was successful in the majority of our cohort without significant adverse events. Marker placement resulted in improved radiological localization in the majority of our cohort and allowed for IGRT. (Australian New Zealand Clinical Trials Registry: ACTRN12613000239763.) (Gastrointest Endosc 2016;83:309-17.)

Esophagogastric cancers are the sixth most common cause of cancer-related death in Australia and the fourth worldwide, with the 5-year survival rates of esophageal and gastric cancers being 35% and 33%, respectively.[1,2] Factors that contribute to this include ineffective therapies and late detection.[3-5] Radiotherapy is an accepted modality in the treatment of esophageal cancers and is currently being evaluated in conjunction with chemotherapy for the neoadjuvant treatment of gastric cancers.[3]

One of the limitations to the delivery of radiotherapy to patients with upper GI malignancies relates to the mobility of the esophagus and stomach, which results in the requirement of large target volumes with generous margins to account for this.[6,7] Recent literature on a novel

Abbreviations: AU$, Australian dollars; IGRT, image-guided radiotherapy; PET, positron emission tomography.

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technique of fiducial placement under EUS guidance that includes a study reported by our group[8] suggests that this may allow for improved radiological localization of the primary malignancy and the opportunity for image-guided radiotherapy (IGRT). Although this technique was successful in the majority of our cohort, we found substantial limitations to this procedure that may limit the implementation of it across our patient population.[8] These included the financial impact of this technique (Australian dollars [AU$]1752.50–2352.50) and the cumbersome method of loading the fiducial onto the delivery needle, which is time-consuming in addition to the risk of misplacement with the associated cost. Finally, access to EUS, which has led to its limited role in the staging of esophagogastric cancers in Australia.

Fiducial placement is well established in the management of prostate and breast cancer for its role in IGRT, and there is emerging literature on its role in upper GI cancer.[9,10] However, given the issues that were identified in our previous study, we searched for an alternative marking method to address the limitations of EUS-guided fiducial insertion in the management of upper GI cancers. We chose lipiodol in combination with n-butyl 2-cyanoacrylate, given our experience with it in the management of gastric varices. In addition, the utility of lipiodol alone has been studied in the setting of bladder cancer for image-guided radiotherapy and more recently in lung cancer and has been shown to be a useful radiopaque marker.[11-13] However, the drawbacks of using lipiodol alone have been extravasation and the difficulty in producing a consistent marker size.[11-14] Lipiodol has been readily identifiable on radiographic and CT imaging modalities with no major adverse events noted in the lung and bladder cancer setting.[11-14] Its stability in bladder cancer can be variable, with a reported loss of lipiodol volume of up to 24% over a 6-week course of radiotherapy.[11] However, in the lung cancer setting, lipiodol was reported to be stable in relation to the primary cancer on follow-up imaging in a small case series.[13] With regard to its histopathological effect on tissue, a study in the lungs of rats indicated that it can induce an acute injury pattern that is at its most severe 24 hours after injection, which subsequently disappeared at 1 week.[15]

METHODS

Study protocol

A phase II feasibility study of a novel endoscopically inserted marker in esophagogastric cancers was conducted from June 2013 to December 2014 at Austin Health in Melbourne, Victoria, Australia. Consecutive patients with biopsy-proven adenocarcinoma or squamous cell carcinoma of the esophagus or adenocarcinoma of the stomach who were discussed at the upper GI multidisciplinary team meeting were considered eligible if they fulfilled the inclusion criteria. Inclusion criteria were expected survival of at least 3 months, older than 18 years of age, and medically suitable for radiotherapy. Exclusion criteria were contraindications to CT and/or positron emission tomography (PET)/CT.

The 3 study endoscopists included 2 interventional gastroenterologists and 1 endoscopy fellow.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, in compliance with good clinical practice and according to local regulations. All patients who were enrolled in the study signed a patient information and consent form. With institutional board approval (Austin Research Ethics Committee: H2013/04975), data were collected by using standardized report forms that captured patient details, endoscopic findings, procedure time, procedural findings, and successful marker placement on follow-up imaging. Adverse events were reported to and recorded by the site investigators. The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12613000239763).

Design and definitions

All patients with esophageal or gastric cancer who fulfilled the inclusion criteria were enrolled. The marker used in our study was a combination of iodized oil (Lipiodol Ultra-Fluid; Aspen Pharmacare, St. Leonards, New South Wales, Australia) and n-butyl 2-cyanoacrylate (Histoacryl; B. Braun Australia, Bella Vista, New South Wales, Australia), which was used to minimize the risk of extravasation of lipiodol, which was observed in a previous pilot study of lipiodol marking in the prostate.[16] Enrolled patients underwent a gastroscopy with deep sedation administered by an anesthesiologist. An adult gastroscope (GIF-H190; Olympus, Melbourne, Victoria, Australia) was used in our cohort. After an initial examination and assessment of the upper GI malignancy, markers were placed at the superior and inferior margin of the tumor via a standard injecting needle. Markers were not routinely placed at the lateral margins as superior and inferior margins were deemed sufficient based on the literature (both local and international) indicating that 2 fiducials are equivalent to 3 for target alignment within the prostate, which traditionally used 3 markers.[17] The first 5 enrolled patients had their procedure performed with the assistance of fluoroscopy to determine the optimal injection volume of the marker. We started at 0.5 mL based on the original case series on the use of iodized oil marking in the prostate[16] and subsequently found that the use of 0.2 mL provided a marker of more consistent size on subsequent radiology. Although there was no extravasation or embolization with the 0.5-mL volume, it produced a marker that was too large and affected the size assessment of the primary cancer. The 0.2-mL volume was then used for the following