Radiotherapy and Oncology 117 (2015) 412–418

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Setup verification

Marker-based quantification of interfractional tumor position variation and the use of markers for setup verification in radiation therapy for esophageal cancer

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ARTICLE INFO

Article history:
Received 15 June 2015
Received in revised form 30 September 2015
Accepted 4 October 2015
Available online 20 October 2015

Keywords:
Esophageal cancer
Radiation therapy
Fiducial markers
Interfractional position variation
Setup verification

ABSTRACT

Purpose: The aim of this study was to quantify interfractional esophageal tumor position variation using markers and investigate the use of markers for setup verification.
Materials and methods: Sixty-five markers placed in the tumor volumes of 24 esophageal cancer patients were identified in computed tomography (CT) and follow-up cone-beam CT. For each patient we calculated pairwise distances between markers over time to evaluate geometric tumor volume variation. We then quantified marker displacements relative to bony anatomy and estimated the variation of systematic (Σ) and random errors (σ). During bony anatomy-based setup verification, we visually inspected whether the markers were inside the planning target volume (PTV) and attempted marker-based registration.
Results: Minor time trends with substantial fluctuations in pairwise distances implied tissue deformation. Overall, $\Sigma(\sigma)$ in the left–right/cranial–caudal/anterior–posterior direction was 2.9(2.4)/4.1(2.4)/2.2(1.8) mm; for the proximal stomach, it was 5.4(4.3)/4.9(3.2)/1.9(2.4) mm. After bony anatomy-based setup correction, all markers were inside the PTV. However, due to large tissue deformation, marker-based registration was not feasible.
Conclusions: Generally, the interfractional position variation of esophageal tumors is more pronounced in the cranial–caudal direction and in the proximal stomach. Currently, marker-based setup verification is not feasible for clinical routine use, but markers can facilitate the setup verification by inspecting whether the PTV covers the tumor volume adequately.
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With the most rapidly increasing incidence [1,2], esophageal cancer has been estimated globally as the eighth most common cancer and the sixth most common cause of death from cancer [3]. Neoadjuvant and definitive chemoradiation therapy are the preferred treatment modalities for resectable and unresectable/inoperable (gastro-)esophageal cancer patients [4–6]. Currently, in clinical image-guided radiation therapy (IGRT) for esophageal cancer, it is common to rigidly register the 3-dimensional (3D) planning computed tomography (pCT) or 2-dimensional (2D) digitally reconstructed radiographs (DRRs) with the kilo-/megavoltage (kV/MV) cone-beam CT (CBCT) or 2D fluoroscopy images on bony anatomy (i.e., the vertebrae) for patient setup verification [7–11]. Although the actual tumor volume-based registration is preferred, it is virtually impossible due to the limited soft-tissue contrast in CT and CBCT. Hence, delineation uncertainties and intra-/interfractional tumor position variation relative to bony anatomy currently prompt the use of large isotropic safety margins for uncertainty compensation [5]. However, this can lead to potential toxicities in organs at risk [5,12] and hamper the use of dose-escalation for improving locoregional control of definitive chemoradiation therapy [13].

For a number of tumor sites, fiducial markers have successfully aided delineation, tumor position variation quantification, and tumor-based setup verification [14–17]. For esophageal tumors, endoscopy-/endoscopic ultrasound (EUS)-guided marker placement was also found feasible and useful for accurately projecting the gross tumor volume (GTV) extent onto the planning CT [11,18,19]. However, few studies have quantified the intra-/interfractional position variation of esophageal tumors using fiducial markers [10,20]. Moreover, the potential benefit of using

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http://dx.doi.org/10.1016/j.radonc.2015.10.005
0167-8140/

markers for patient setup verification in IGRT for esophageal cancer has not yet been investigated.

In this study, we included esophageal cancer patients with markers placed in the tumor volume and manually identified these markers in the pCT and follow-up CBCT scans. We aimed to quantify the interfractional position variation of esophageal tumors relative to bony anatomy using the markers. In addition, we investigated the use of markers for patient setup verification.

Materials and methods

Patient and marker characteristics

From March 2013 to May 2014, we consecutively included 30 esophageal cancer patients (24 males and 6 females) aged 45–84 (average: 66) years in our study. This patient population is identical to the one in a pilot study concerning the feasibility of marker placement [11]. For one patient, markers failed to be placed due to a manufacturing error in the preloaded needle system; all other 29 patients underwent successful endoscopy-/EUS-guided marker placement prior to pCT acquisition. The medical ethics committee of our institute approved the marker implantation and all patients gave written informed consent [11]. Table 1 lists the patient and marker characteristics. Two different types of gold markers and one gel-based marker were used: solid marker (Cook Medical, Limerick, Ireland; or in-house manufactured), flexible coil-shaped marker (Visicoil; IBA Dosimetry, Bartlett, TN, USA), and hydrogel marker (TraceIt; Augmenix, Waltham, MA, USA). For each patient, we placed at least 2 markers of the same type, preferably in the submucosal layer at the cranial and caudal border and in the center of the primary tumor, as described in [11]. For 5 patients, no markers were identified in any of the CBCT scans, due to marker detachment after the placement, too short hand-cut flexible coil-shaped marker, or absorption/dissolution of hydrogel in the tissue [11]. Therefore, 24 patients with in total 65 markers with clear visibility in CBCT were included in our data analysis (Table 1). The 65 markers were classified, according to the American Joint Committee on Cancer manual [21], into four subgroups based on their locations in the esophagus: 12, 11, 31, and 11 markers, in the proximal esophagus, middle esophagus, distal esophagus, and proximal stomach, respectively (Fig. 1).

Image acquisition and target delineation

For each patient, a 3D pCT scan was acquired within 0–5 days (average: 1 day) after marker placement. During pCT acquisition (LightSpeed RT 16 CT; General Electric Company, Waukesha, WI, USA), all patients were positioned supine with arms up above their

Table 1
Overview of patient and marker characteristics.

Patient	Tumor type	Tumor location	Marker type	Marker length/ volume	Dose scheme (Gy)	No. of CBCTs	No. of markers		
							At placement	Visible in pCT	Visible in CBCTs
1	AD	Lower	Solid	5 mm	23 × 1.8	7	2‡	1	1
2	AD	Lower	Solid	5 mm	23 × 1.8	7	3‡	2	1
3	AD	Lower	Solid	5 mm	23 × 1.8	7	3‡	3	1
4	PDC	Lower	Solid	5 mm	23 × 1.8	7	3	3	3 → 2
5	SCC	Lower	–	–	28 × 2.2	8	0	0	0*
6	SCC	Lower	Solid	5 mm	28 × 1.8	8	4	4	4
7	AD	Lower	Flexible	5–10 mm	23 × 1.8	8	4	4	4
8	AD	Lower	Flexible	3 mm	28 × 1.8	28	5	5	0*
9	SCC	Middle	Flexible	4 mm	23 × 1.8	8	4	3	3
10	AD	Lower	Solid	5 mm	23 × 1.8	7	3	2	0*
11	SCC	Lower	Flexible	2–10 mm	23 × 1.8	12	3	2†	2†
12	SCC	Upper	Flexible	10 mm	28 × 1.8	8	3	3	3
13	SCC	Middle	Flexible	7–8 mm	23 × 1.8	23	4	4	4
14	SCC	Upper	Hydrogel	0.40 ml	28 × 1.8	25	3	3	1
15	SCC	Lower	Hydrogel	0.40 ml	23 × 1.8	8	6	5	0*
16	AD	Lower	Hydrogel	0.40 ml	28 × 1.8	8	3	3	3 → 1
17	AD	Lower	Flexible	10 mm	23 × 1.8	8	3	3	3
18	AD	Lower	Hydrogel	0.40 ml	23 × 1.8	23	3	3	0*
19	AD	Lower	Flexible	8 mm	23 × 1.8	7	3	3	3 → 2
20	AD	Lower	Flexible	8 mm	23 × 1.8	11	3	2†	2†
21	AD	Lower	Flexible	8 mm	28 × 1.8	8	4	4	3
22	AD	Lower	Flexible	8 mm	23 × 1.8	9	4	4	4
23	AD	Lower	Flexible	10 mm	23 × 1.8	12	3	3	3
24	AD	Lower	Flexible	10 mm	23 × 1.8	12	4	4	2
25	AD	Lower	Flexible	10 mm	23 × 1.8	8	4	4	4
26	SCC	Lower	Hydrogel	0.40 ml	23 × 1.8	8	3	2	0*
27	SCC	Upper	Solid	5 mm	28 × 1.8	8	3	3	3
28	SCC	Middle	Solid	5 mm	28 × 1.8	9	5	4†	4
29	SCC	Lower	Solid	5 mm	23 × 1.8	9	3	2	2
30	AD	Full	Solid	5 mm	23 × 1.8	7	3	3	2
Total						318	101	91	65 → 61

Diameter of gold markers: solid: 0.43–0.64 mm or 0.35–0.50 mm; flexible: 0.35 mm.
Arrow (→) means marker went missing during the treatment course.
Tumor location: upper = upper third of esophagus; middle = middle third of esophagus; lower = lower third of esophagus; full = full coverage of esophagus.
Abbreviations: AD = adenocarcinoma, SCC = squamous cell carcinoma, PDC = poorly differentiated carcinoma. pCT = planning computed tomography, CBCT = cone-beam computed tomography.

* No marker was visible in CBCT; therefore these patients were excluded from data analysis.
† Compared to the pilot study [11], there is a difference of 1 in the number count because we excluded a metal clip (patient 11), a marker located in the lung in the pCT and CBCT (patient 20), or a marker that detached between implantation and acquisition of the pCT and was therefore located in the stomach in the pCT (patient 28).
‡ Two markers placed in the same location by accident have been counted as one marker [11].