

Cine-magnetic resonance imaging for assessment of larynx motion in early glottic cancer radiotherapy

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Introduction

Radiation therapy is an essential component of early glottic cancer treatment. Radical radiotherapy outcomes for early glottic cancer are excellent with reported 5-year local control (LC) rates reaching 95% and 85% for T1 and T2 lesions respectively, and 5-year overall survival (OS) exceeding 90% [1–5]. In recent years, increasing interest in reducing radiation treatment volumes has emerged, with the objective of reducing toxicity while maintaining LC. Although surgical approach involves the resection of tumor-bearing vocal cord, radiotherapy currently involves irradiation of the entire larynx. In an era of intensity modulated radiotherapy (IMRT) and image guided radiotherapy (IGRT), the rationale for this discrepancy becomes difficult to justify – it is therefore appealing to mirror surgical approaches and migrate towards partial larynx irradiation.

The group from Erasmus Medical Center Cancer Institute have previously reported feasibility [6] and, more recently, excellent LC outcomes from a retrospective analysis of 30 patients with T1aN0 glottic cancer treated with single vocal cord IMRT [7]. However, internal motion of the larynx is generally associated with fear of geographical miss with the use of IMRT and tighter treatment margins. Internal larynx motion includes swallowing, respiration as well as isolated, more sudden movements, attributed to tongue motion [9]. In the context of conventional radiotherapy using lateral opposed fields, previous studies have evaluated laryngeal motion and found a negligible dose reduction of 0.5% with swallowing [9, 10]. In the era of IMRT and partial larynx irradiation, it becomes crucial to adequately select planning margins. Use of cine magnetic resonance imaging (MRI) is an opportunity to capture the swallowing and breathing motion of the larynx of each patient. Cine-MRI can be acquired over a prolonged period of time at no radiation cost, it is therefore most representative of the natural motion that can occur in the larynx over a given duration of time.

Cine-MRI can be used to determine personalized internal target volume (ITV) margin based on individual motion. If cine-MRI cannot be obtained for each patient, populational internal target margin can be generated for use in the clinic. In this study, we use cine-MRI for assessment of larynx motion in a cohort of patients treated with IMRT for early glottic larynx cancer.

Material and methods

Study population

A total of 20 patients were prospectively enrolled in this study from August 2014 to January 2016. Eligibility criteria included:

1. histologically proven glottic cancer,
2. stage TisN0, T1a-bN0 or T2N0 as per the American Joint Committee on Cancer 7th edition,
3. Eastern Cooperative Oncology Group performance status 0–2.

Patients with prior radiation to the head and neck region were excluded.

The protocol and patient consent form were reviewed and approved by our institutional ethics committee.

Planning CT and MRI

All patients had a 1.5 mm slice thickness planning computed tomography (CT) scan (SOMATOM Definition Flash, Siemens Healthcare, Forchheim, Germany) from the vertex to the carina with and without intravenous contrast injection in supine position. Immobilisation device included a thermoplastic mask of the head and shoulder fixed to the treatment table. Patients were instructed not to swallow during acquisition of planning CT.

Patients underwent planning MRI on a RT-dedicated 1.5 Tesla system (MAGNETOM Aera, Siemens Healthcare, Erlangen, Germany). Transverse T2-weighted Turbo Spin Echo (TSE), T1-weighted TSE and post-gadolinium

T1-weighted fat saturated TSE sequences were obtained for planning purposes. Cine-MRI used for motion assessment consisted in sagittal non-enhanced true fast imaging with steady state precession (TrueFISP) sequences acquired using a rapid acquisition protocol (10 mm thickness extending cranio-caudally, temporal resolution of 3.8 images per second). These cine-MRI sequences were acquired pre-treatment as well as mid-treatment, to assess changes in motion over time. MRI sequences were acquired in treatment position, using a Spine matrix coil posteriorly and a large flex coil anteriorly (Siemens Healthcare, Erlangen, Germany). TrueFISP sequence parameters were as follow: TR = 262 ms, TE = 1.2 ms, field-of-view = 256 mm, and spatial resolution = 2 x 2 x 10 mm. To capture the natural frequency of swallowing and the impact of the treating team’s instruction not to swallow, a first 2-minute acquisition with the patient given no particular instruction was followed by a 2-minute acquisition with the patient instructed not to swallow. Laryngeal motion analysis on cine-MRI was performed on a MimVista workstation (version 6.2, MimVista software Inc, Cleveland, OH, USA). In addition to extent of motion, cine-MRI was used to assess swallowing frequency and time (Fig. 1).

Results

Patient characteristics

In total, the study included 17 males (85%) and 3 females (15%) and the median age was 67 (51–77). Tumors were stage Tis, T1 and T2N0 in 3 (15%), 5 (25%) and 12 (60%) patients, respectively. 17 lesions (85%) were unilateral, 2 lesions (10%) were bilateral and 1 involved the anterior commissure. For the entire cohort, median gross tumor volume was 1 cm³ (1–2). Median dose was 65.25 Gy in 29 fractions (63–65.25).

Dynamics of laryngeal motion

Swallowing frequency and time

On pre-treatment cine-MRI, mean swallowing frequency over 2-minutes was 1 (0–5) and was significantly reduced

to 0 (0–1) when patients were instructed not to swallow (p = 0.03). This translated into a reduction in percentage of time spent swallowing from 2.3% (0–10%) with no instruction to 0.5% (0–2.5%) with instruction (p = 0.06.) Mid-treatment cine-MRI showed mean swallowing frequency of 0, with or without instruction not to swallow.

Detailed laryngeal motion dynamics

Mean amplitudes of swallowing motion in the superior, inferior, anterior and posterior directions on cine-MRI are presented in table 1. Greatest extent of motion was observed in the superior direction with a mean exceeding 20 mm, and in the anterior direction with a mean of 6 mm. Mean swallowing motion in the inferior and posterior directions were ≤ 1 mm (Table 1). In addition, when the larynx was in resting position, a mean respiratory motion of 4 mm (1–6) and 2 mm (1–2) in the supero-inferior (SI) and antero-posterior (AP) directions was demonstrated.

Discussion

Swallowing was associated with an important motion that was typically beyond 20 mm in the superior direction and within 6 mm in the anterior direction, consistent with previous studies [10–13]. Swallowing motion was typically minimal in both posterior and inferior directions. As was previously well shown in the context of conformational radiotherapy [9–12], our results demonstrate that swallowing motion is rapid, rare over a 2 minute period and further decreased with instruction not to swallow. Swallowing motion is therefore unlikely to be a concern in larynx irradiation. Whether patients were given instructions or not, swallowing frequency was significantly reduced mid-treatment compared to pre-treatment; possible explanations include increasing radiation-induced swallowing discomfort over time, or simply that patients may become more at ease with the treatment procedure over time. Similarly, in the context of opposed wedge fields, van Asselen et al. reported swallowing to occur over 0.45% of the total irradiation time (typically delivered over less

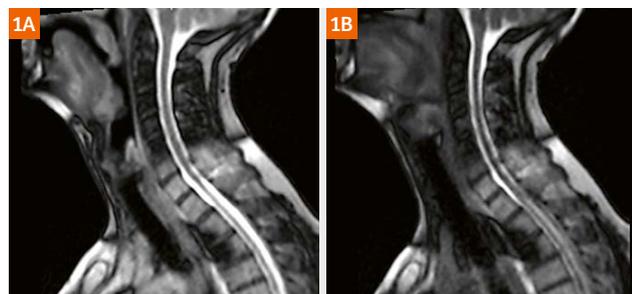


Figure 1: Sagittal TrueFISP MRI sequences for assessment of laryngeal motion showing most inferior (1A) and most superior (1B) larynx position during swallowing.

Motion (mm)	Swallowing		Resting	
	Pre-Tx MRI	Mid-Tx MRI	Pre-Tx MRI	Mid-Tx MRI
Sup (M ± SD)	23 ± 5	22 ± 6	4 ± 2	3 ± 2
Inf (M ± SD)	1 ± 1	1 ± 1		
Ant (M ± SD)	6 ± 2	6 ± 2	2 ± 1	1 ± 1
Post (M ± SD)	1 ± 1	0 ± 1		

Table 1: Summary of larynx motion dynamics on dynamic 2D MRI.

Pre-tx = Pre-treatment, Mid-tx = Mid-treatment, Sup = superior, Inf = inferior, Ant= anterior, Post = posterior, M = mean, N = number, SD = standard deviation

than 1 minute) [9] and Hamlet et al. [10] reported an average dose reduction of 0.5% due to swallowing.

If swallowing motion unlikely impacts dose delivery to the tumor in the context of partial larynx irradiation, respiratory larynx motion reaching 6 mm in the superior-inferior direction and 2 mm in the antero-posterior direction was observed in the context of this study. Van Asselen et al. previously reported non-swallowing motion to occur at varying frequency (reaching up 20 times per minute) and associated with displacement reaching 11 mm and 6 mm in SI and AP directions, respectively, attributed to respiration as well as occasional occurrence of isolated tongue motion [9]. Brady et al. [13] also described a respiratory larynx motion on dynamic MRI reaching 3 mm. Importantly, such intra-fraction motion cannot be addressed by means of daily image guidance. Although current margins used in whole larynx irradiation are largely sufficient to include respiratory motion, regular and consistent respiratory motion can be associated with a risk of marginal miss in partial larynx irradiation if not properly taken into account. In the context of partial larynx IMRT, it is therefore of crucial importance to include an internal motion margin that accounts for respiration. This margin can be personalized, using a cine-MRI for each patient at time of treatment planning. This would represent the best case scenario to minimize unnecessary irradiation in patients with minimal motion and ensure safe treatment delivery in patients with larger range of motion. Alternatively, as suggested by the results of our study, maximum respiratory motion observed was within 6 mm for all patients. In order to derive a safe population-based margin to be generalized to any patient, assessment of respiratory motion in a large sample of patients is currently on-going at our institution.

Conclusion

Although swallowing motion is associated with large larynx excursion reaching beyond 2 cm in the superior direction, swallowing motion was reported to be rare, rapid and easily suppressed by patients, and is therefore considered to have negligible impact on RT dose delivery.

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On the other hand, respiratory motion reaching 6 mm in the superior-inferior direction and 2 mm in the antero-posterior direction was revealed on cine-MRI studies. When considering partial larynx IMRT, an internal motion margin should be used to account for this respiratory motion. Cine-MRI can be used to derive a personalized margin based on observed larynx motion of individual patients. Assessment of respiratory motion in a large cohort of patients using cine-MRI is currently on-going, and will help determine safe generalizable internal motion margin in the absence of cine-MRI.

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