Title:

Evaluation of dynamic tumour tracking radiotherapy with real-time monitoring for lung tumours using a gimbal mounted linac

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This paper consists of 21 pages and 2 tables. There are 2 supplementary figures.

Running head:

Dynamic tracking with real-time monitoring

Keywords: stereotactic body radiotherapy; lung cancer; dynamic tumour tracking; real-time monitoring; feasibility study

Abstract:

Purpose: To evaluate feasibility and acute toxicities after dynamic tumour tracking (DTT) irradiation with real-time monitoring for lung tumours using a gimbal mounted linac.

Materials and Methods: Spherical gold markers were placed around the tumour using a bronchoscope prior to treatment planning. Prescription dose at the isocentre was 56 Gy in 4 fractions for T2a lung cancer and metastatic tumour, and 48 Gy in 4 fractions for the others. Dose-volume metrics were compared between DTT and conventional static irradiation using in-house developed software.

Results: Of twenty patients enrolled, DTT radiotherapy was successfully performed for 16 patients, except 4 patients who coughed out the gold markers, one who showed spontaneous tumour regression, and one where the abdominal wall motion did not correlate with the tumour motion. Dose covering 95% volume of GTV was not different between the two techniques, while normal lung volume receiving 20 Gy or more was reduced by 20%. A mean treatment time per fraction was 36 minutes using DTT. With a median follow-up period of 13.2 months, no severe toxicity grade 3 or worse was observed.

Conclusions: DTT radiotherapy using a gimbal mounted linac was clinically feasible for lung treatment without any severe acute toxicity.

Introduction

Lung cancer is the leading cause of cancer-related deaths in most countries, including the US[1] and Japan[2]. There have been two trends in lung cancer in recent years. The first is the shift in the patient population to older ages[1,2], and the second is the gradual increase in the ratio of early stage lung cancer[3,4]. Thus, development of a new treatment modality that is appropriate for elderly patients with early stage lung cancer is desirable.

Stereotactic body radiotherapy (SBRT) was developed as a new treatment modality for early stage lung cancer in the late 1990s. Many retrospective studies and several multi-institutional prospective trials have demonstrated that excellent local control is obtained by SBRT, with acceptable toxicity[5–7]. Thus, SBRT is now an important treatment option for patients with early stage non-small-cell lung cancer who are medically inoperable and those who are elderly and relatively unfit for surgery.

The next innovation expected for lung SBRT is four-dimensional (4D) radiotherapy, which can cope with tumour movement. The lung expands periodically according to respiration and a lung tumour moves mainly in the craniocaudal direction. The amplitude of craniocaudal tumour motion is around 1 cm in mean, but can be 3-4 cm in some patients[8]. When the whole trajectory of a moving tumour is included in the irradiation field, larger volumes of healthy tissues are irradiated. The latter leads to a risk of toxicity[9–11], and accordingly, that might limit the indication of SBRT to smaller tumours. A new 4D

irradiation technique that permits delivery of a dose to the tumour and limiting that to normal tissues by coping with respiratory motion,may have the potential to improve the outcomes and to expand the indications of SBRT.

The Vero4DRT (formerly called the MHI-TM2000; Mitsubishi Heavy Industries Ltd., Tokyo, Japan, and BrainLab AG, Feldkirchen, Germany)[12] has two special features that allow dynamic tumour tracking (DTT) with real-time monitoring. One is two sets of kilovoltage (kV) x-ray imagers, that can monitor the three-dimensional position of the tumour in real-time via implanted fiducial markers, and the other is a gimbal mounted linac, enabling DTT. Extensive evaluation of the characteristics of this DTT system demonstrated high accuracies in treatment delivery to a moving target[13–17]. Previous experimental validation offered the required confidence for clinical implementation of DTT treatment of lung tumours. The purpose of this study was to evaluate feasibility and acute toxicities after DTT radiotherapy with real-time monitoring in SBRT for lung cancers using the Vero4DRT system.

Materials and Methods

Patients

Eligibility criteria were as follows: (1) a single lung tumour with a diameter of 50 mm or less, (2) no nodal or distant metastasis, (3) respiratory tumour movement of 5 mm or more, (4) age of 20 years or

above, (5) performance status of 0-2, (6) arms could be held over the head for 30 min or more, (7) doses to adjacent organs not exceeding the pre-determined constraints, which were the same as in the Japan Clinical Oncology Group protocol 0403[18], and (8) written informed consent. This study was approved by the institutional review board. It was registered with the UMIN Clinical Trials Registry in Japan (UMIN000005324).

Pre-planning procedures

Prior to treatment planning, spherical gold markers with a diameter of 1.5 mm (FMR-201CR; Olympus Medical Systems, Tokyo, Japan) were placed around the tumour under bronchoscopic guidance as an internal surrogate for the tumour position. Treatment planning was carried out 1 week after insertion of the gold markers. At least 3 markers were required for the DTT irradiation to be performed.

On the simulation day, the patient was fixed in a supine position with both arms raised using an individualized vacuum pillow (BodyFIX; Elekta AB, Stockholm, Sweden, or ESFORM; Engineering System, Matsumoto, Japan). Ten respiratory phases of 4D CT were acquired in axial cine mode using a 16-slice CT scanner (LightSpeed RT16 or BrightSpeed Elite; GE Healthcare, Little Chalfont, UK) and a real-time positioning management system (Varian Medical Systems, Palo Alto, US). Immediately after the 4D CT scan, a breath-hold CT scan was also acquired at the end of exhalation. The breath-hold CT

was sent to iPlan RT image (ver. 4.1; BrainLab AG) as a reference image. The coordinate for each phase image from the 4D CT was modified so that its centroid of the fiducial markers was matched with that in the breath-hold CT. Then, the 10 phase images were fused onto the breath-hold CT. After the CT scan, the patient was moved to the Vero4DRT to perform a 4D modelling[14], which correlates the external abdominal motion and the internal fiducial motion. The purpose of the modelling was to estimate the 4D modelling error and the peak-to-peak amplitude of tumour motion.

Treatment planning

Gross tumour volumes (GTVs) were delineated on the breath-hold CT and 10 phase images. An internal target volume for tracking (ITV) was defined as a composite of the eleven GTVs from the breath-hold CT and the 10 phase images (Supplementary Fig. 1). Because the phase images were registered based on the marker centroid, the ITV was supposed to compensate for tumour deformation and uncertainty in the positional relationship between the tumour and fiducial makers during respiration[19]. Planning target volume (PTV) for tracking was defined as the ITV plus setup error and additional margins to compensate the 4D modeling error, baseline drift of the abdominal position, and mechanical errors of the system. The setup error was estimated to be 2.5 mm in each direction as an inter-fraction positional variation between the fiducials and the tumour[19]. A margin for the 4D modelling error was defined as

a mean plus 2 times of standard deviation in the 4D model on the simulation day. A margin for the baseline drift was estimated as 10% of the tumour motion amplitude. The mechanical errors were defined as 0.5 mm[12]. The PTV margin was defined as a linear sum of these errors. At least 5 mm was required for the margin.

Monitor units (MUs) for the treatment beams were calculated using the X-ray voxel Monte Carlo algorithm in iPlan RT dose (ver. 4.5.1; BrainLab AG) on the breath-hold exhale CT. The prescription dose was 48 Gy in four fractions for stage IA lung cancer, and 56 Gy in four fractions for stage IB lung cancer and metastatic lung tumour. This dose was prescribed at the isocentre. We typically arranged seven beams: four non-coplanar and three coplanar beams. 6-MV x-ray beams were collimated to the PTV plus 5-mm margin with a multi-leaf collimator. A static SBRT plan with non-tracking beams, based on the motion-encompassing method[8], was also prepared as a backup if DTT irradiation could not be achieved for some reason. Dose distributions were evaluated with an in-house developed software that allows 4D dose calculation considering with the gimbal mounted linac[20]. The calculated dose distributions for the 10 phase CT images were accumulated into the exhale breath-hold CT with deformable image registration using MIM Maestro (ver. 5.2; MIM Software Inc., Cleveland, OH). If the dose-volume metrics in the tracking plan were diagnosed to be superior to those in the static plan, the patient underwent DTT irradiation.

Irradiation of treatment beams

First, the patient was laid on the pre-formed vacuum pillow. Set-up error was corrected for bony structures using the ExacTrac X-ray system. Second, a 4D model was built to correlate the infra-red markers on the abdomen with the internal fiducial markers. Then, irradiation could start in dynamic tracking mode with the beam following a location predicted by the 4D model based on the infra-red markers placed on the patient's abdominal wall. During irradiation, the tumour and the internal fiducials were monitored visually every second with EPID and the kV imagers. If the fiducial markers displaced from the predicted positions by 3 mm or more in 3 consecutive frames on the kV images, the irradiation was interrupted and rebuilding the 4D model was considered.

Follow-up after treatment

Follow-up visits were planned at 2, 4, 6, 9, and 12 months within the initial year after SBRT and every 3 months thereafter. A CT scan was performed at each visit. The follow-up period was defined as the duration between the first day of treatment and the last follow-up visit or the date of death. Acute toxicity was defined as any treatment-related toxicities during the initial 6 months after the treatment. Toxicity grading was according to the Common Terminology Criteria for Adverse Events v.4.0.

154

155 **Results**

156 Twenty-two patients were enrolled into this study between August 2011 and July 2013. No patients
157 experienced toxicities related to the insertion of fiducial markers. Twenty-two of the 101 inserted
158 markers were coughed out before the CT simulation. Consequently, the number of remaining makers in
159 4 patients decreased to two, which is insufficient for DTT to be performed. The planning procedures for
160 DTT could not be performed in another two patients. One patient showed thoracic breathing that
161 prevented the Vero system from tracking a tumour based on the abdominal motion (Supplementary Fig.
162 2). In the other patient with histology-unproven primary lung cancer, the tumour spontaneously
163 regressed during 10 days between the fiducial insertion and the simulation. For the remaining 16 patients,
164 the CT simulation for DTT was successfully performed. Characteristics of the 16 patients are shown in
165 Table 1.

166 The mean PTV volume reduced from 56.2 cm^3 to 39.6 cm^3 for the static and tracking plans, respectively
167 (Table 2). GTV doses were not spoiled by the tracking method (dose covering 95% volume of GTV,
168 93.4% vs. 93.7% of the prescription dose; $p = 0.323$ by paired *t*-test). Doses to the normal lung and liver
169 were reduced in the 16 patients. Lung V20, the relative volume receiving 20 Gy or more, was reduced by
170 19.5%, from 5.5% to 4.4%. The tracking plan showed a higher maximal dose to the spinal cord than the

171 static plan in 5 patients. However, the difference did not exceed 0.3 Gy and was considered to be
172 clinically acceptable.

173 The DTT irradiation was completed for all 64 fractions for the 16 patients. Mean and standard deviation
174 in treatment time per fraction were 36.2 and 8.8 minutes (range, 19-70 minutes), respectively. The
175 treatment time exceeded 50 minutes in 5 fractions because of communication failures between the
176 tracking system and the gimbal system requiring a restart of the tracking procedure. The gold markers
177 were well recognized with kV x-ray imagers throughout all treatment fractions. The 4D modelling was
178 performed a mean of 1.9 times per fraction (range, 1 to 4).

179 With a median follow-up period of 13.2 months (range, 3.4–26.5 months), one patient experienced grade
180 2 radiation pneumonitis. No severe toxicity grade 3 or worse has been observed in any of the patients.
181 Two patients died of cancer, and one died of infectious pneumonia. Local tumour control was achieved
182 except one patient who developed local recurrence at 12.0 months.

183

184 **Discussion**

185 The Vero4DRT system has two major advantages. The first is that tumour position can be monitored in
186 real time using kV imagers and an EPID. The second is that no extra treatment time over static SBRT
187 and no special training for breath control are needed for the 4D treatment, which is clinically beneficial

both for patient comfort and the throughput of the treatment system.

Several uncertainties are associated with 4D irradiation, including tumour position prediction errors and mechanical errors in beam delivery, which are problems to be overcome. In the Vero4DRT, kV imagers can ensure that the positions of the tumour and fiducial markers correspond to the predicted sites. EPID can be used to verify the tumour position in complement to the kV imagers[21]. Furthermore, log files allow retrospective confirmation of the accuracy in the delivery of tumour tracking after treatment. Our previous study, which evaluated the initial 10 patients from the present study cohort, confirmed high accuracies in the tracking performance. The 95th percentiles of overall tracking errors were 1.3 mm, 2.4 mm and 1.4 mm in left-right, cranio-caudal and anterior-posterior directions, respectively[22].

The Task Group 76 of the American Association of Physicists in Medicine classified motion management methods into five types: motion-encompassing, respiratory gating, breath-hold, forced shallow breathing with abdominal compression, and real-time tumour-tracking methods[8]. The motion-encompassing method is the most conventional and well-established. However, it uses the largest field of the five methods, with a large PTV. The breath-hold technique and abdominal compression are not always suitable for frail and elderly patients. Respiratory gating needs a longer treatment time than motion-encompassing methods. With a dynamic tracking method, patients do not need to hold or limit their breath, and the tumour is always irradiated by the treatment beams without intermittence, leading to

205 a shorter treatment time than the breath-hold methods or the gating methods, and a comparable treatment
206 time to the motion-encompassing methods. Dynamic tumour tracking is considered to be the favourable
207 method among the five motion management methods from the patient compliance and comfort points of
208 view. According to a Japanese survey of SBRT in 2009[23], the most frequent response regarding the
209 time needed for a single daily fraction was 30 min, followed by 40 min. Our result of 36.2 min for a
210 single fraction was thus comparable with standard times for SBRT in Japan. In addition to patient
211 comfort, a few studies have suggested that prolongation of the treatment time for a single fraction may
212 reduce its biological effectiveness[24,25]. Unfortunately, considerable prolongation of treatment time
213 over 50 minutes occurred in 5 fractions in the present study. The cause for the prolongation was
214 immaturity of the tracking system including software. To realize DTT irradiation, the tracking software
215 needed to communicate with other systems in real time and to command several operations including
216 control of the gimbal motion, process of signals from the infra-red camera and analysis of images from
217 the kV x-ray imagers. The tracking system had initial instability in the communication process where the
218 system could not simultaneously execute such different tasks. Some adaptations to the tracking system
219 have been introduced after the present study with the aim of improving stability. Volumetric modulated
220 arc therapy, which can reduce total MUs and consequently reduce treatment time, is being applied to
221 SBRT for the lung[26]. Arc irradiation application to DTT is needed for reduction of treatment time with

222 the Vero4DRT. The Vero4DRT achieved the same level of geometric and dosimetric accuracy with
223 conformal arc DTT irradiation as that with fixed-port DTT[27]. A treatment planning system capable of
224 VMAT plan is under development for the Vero4DRT.
225 The disadvantages of the current Vero4DRT system are its dependence on 4D modeling and fiducial
226 marker insertion. If no appropriate 4D model is acquired, dynamic tracking cannot be performed, as
227 occurred in one patient. One solution for this issue is to track a tumour based on real-time stereo
228 fluoroscopy without any 4D model. However, this method introduces another problem of skin doses due
229 to the continuous fluoroscopy during a treatment time. Another way to improve the 4D model is a
230 training to encourage for patients to perform periodical abdominal breathing[28].
231 The Vero4DRT currently requires fiducial markers with x-ray fluoroscopy monitoring to detect the
232 tumour position and create the 4D model. Two types of fiducials are applicable to the Vero4DRT: one is
233 a spherical marker, and the other is a cylindrical marker. We used the spherical gold markers that were
234 inserted into a peripheral bronchiole under bronchoscopy. This method was reported in more detail by
235 Imura et al. from Hokkaido University[29]. All 57 patients in their report tolerated the marker
236 implantation procedure and only one experienced pneumothorax, which resolved with bed rest. The
237 toxicity rate was much lower than those of percutaneous insertion methods[30,31]. Trade-offs, however,
238 for the reduced toxicity are marker dislocation between insertion and radiotherapy, and positional

uncertainty between the tumour and makers. Imura et al. reported that 25% of the inserted markers could not be detected throughout the treatment period. Indeed, 22% of the markers in this study were coughed out before the CT simulation, and 4 of 22 (18%) patients could not undergo the DTT due to the marker dislocation. The reason why the Vero4DRT system requires 3 markers or more in the use of spherical markers is to detect the marker dislocation. Regarding the positional uncertainty between the tumour and markers, Ueki et al. evaluated intra- and interfractional variations[19]. Root mean squares in the intrafractional variations were 0.6 mm, 0.9 mm and 1.5 mm in the right-left, anteroposterior and craniocaudal directions, respectively. Moderate correlations of the intrafractional variation with tumour motion amplitude and tumour-marker distance were observed with correlation coefficients of 0.549–0.780. However, the intrafractional error did not always distribute symmetrically around zero, but often distributed in one side above or below zero. The direction and amplitude of the intrafractional variations varied between patients. Base on the results, we judged that a uniform isotropic margin was inadequate to cover the intrafractional variations, and that the fused CT approach as in the Method section was suitable for DTT planning. The interfractional variation could be covered by a 2.5-mm margin.

In conclusion, DTT radiotherapy with real-time monitoring using a gimbal mounted linac was clinically feasible for the lung without any severe acute toxicity.

Conflict of interests:

T.M., M.K. and M.H. have consultancy agreements with Mitsubishi Heavy Industries Ltd., Japan. A sponsored research program is provided by Mitsubishi Heavy Industries Ltd.

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Figure legend:

Supplementary figure 1. A schema for definition of an internal target volume (ITV) for tracking

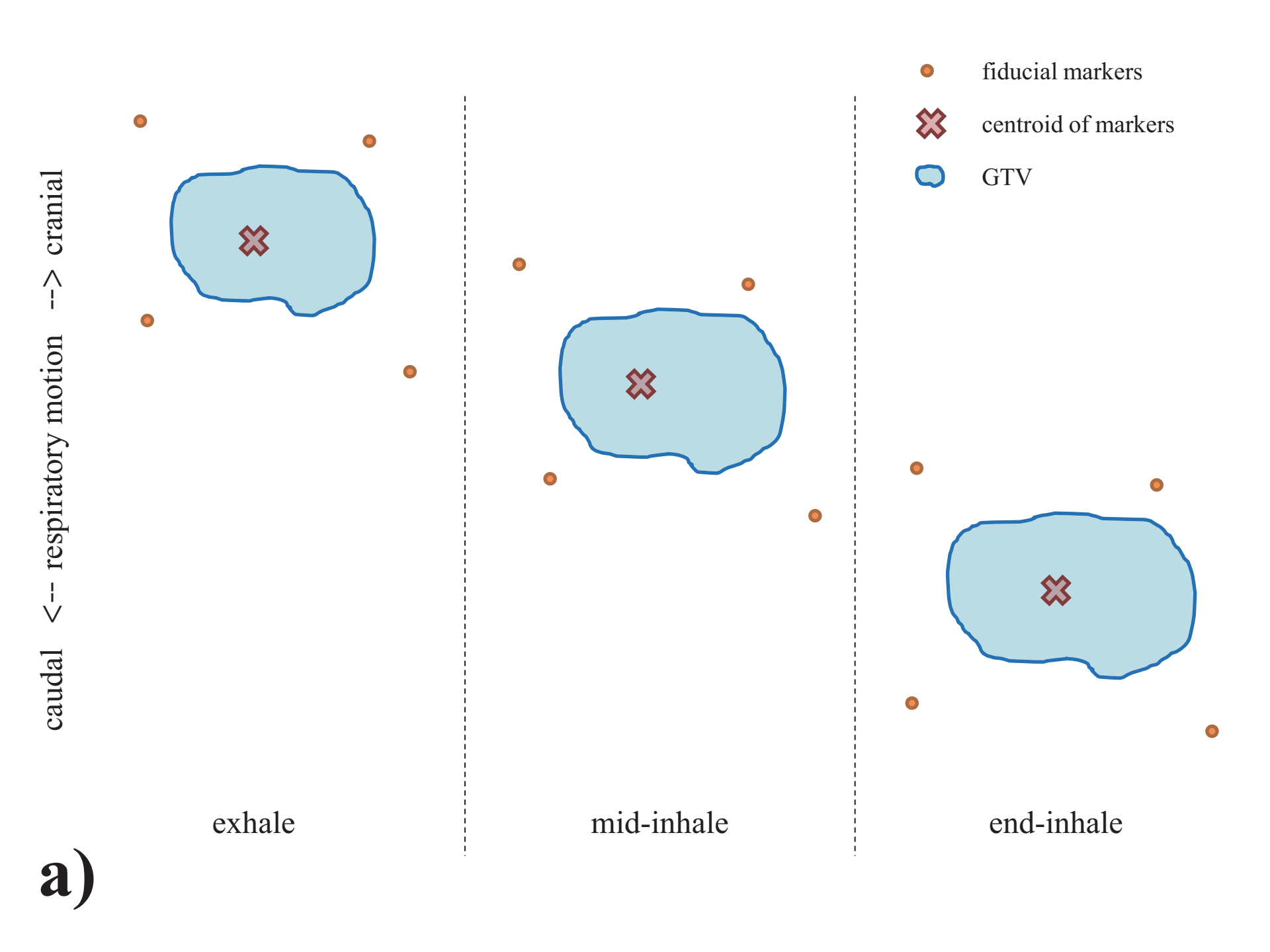
a) An example of intrafractional change in alignment of gross tumour volume (GTV) and fiducial markers, and intrafractional tumour deformation.

b) Definition of ITV for tracking. The GTVs are fused based on the marker centroids. Then, an ITV for tracking (the thick red line) is defined as a composite of the fused GTVs.

c) A screenshot from a case. Several lines with various colours are shown around the tumour, which indicate GTVs from phase images of 4D CT. An ITV (not shown) is defined as a volume including all the GTVs. The outermost pink line indicates a planning target volume for the ITV.

Supplementary figure 2. A patient who showed thoracic breathing

The tumour position in the superior-inferior (SI) direction and the abdominal wall position in the anterior-posterior (AP) direction are shown in blue and red lines, respectively. Note that the patient showed thoracic breathing where the tumour moved without any abdominal motion during the initial 10 seconds. Thoracic breathing was the dominant respiratory pattern in the patient so that the Vero system could not create an appropriate 4D model for the patient.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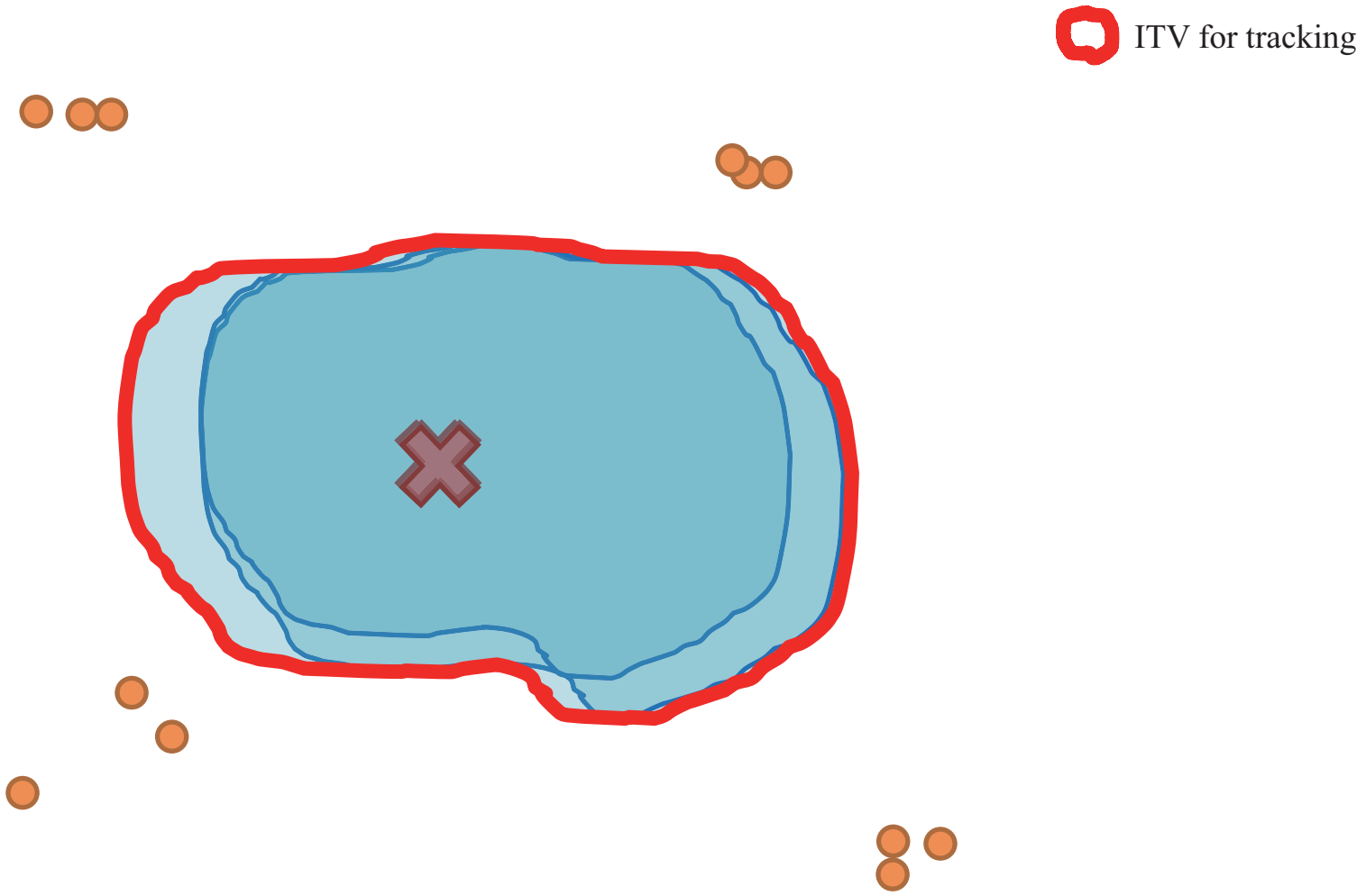
a)



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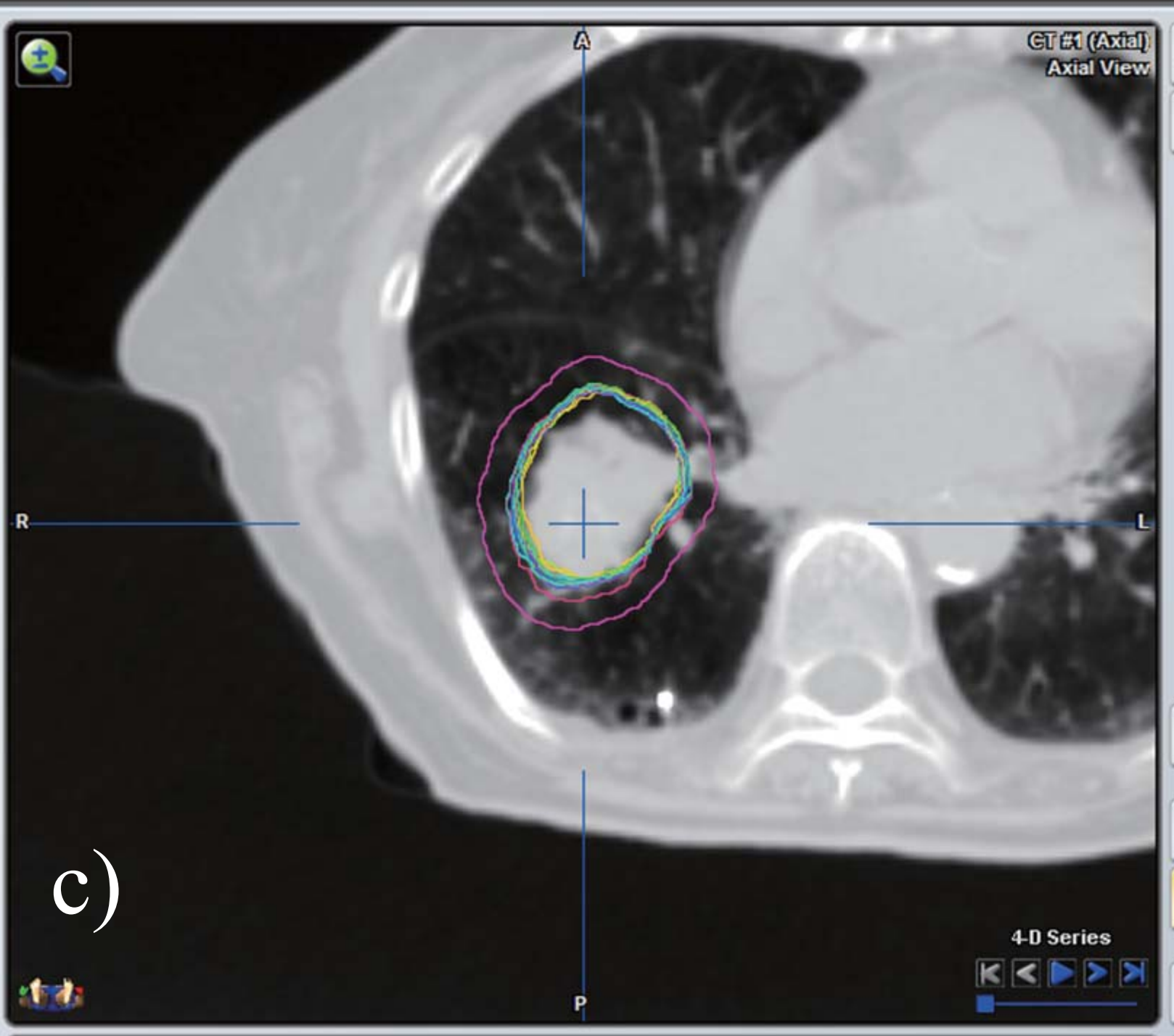

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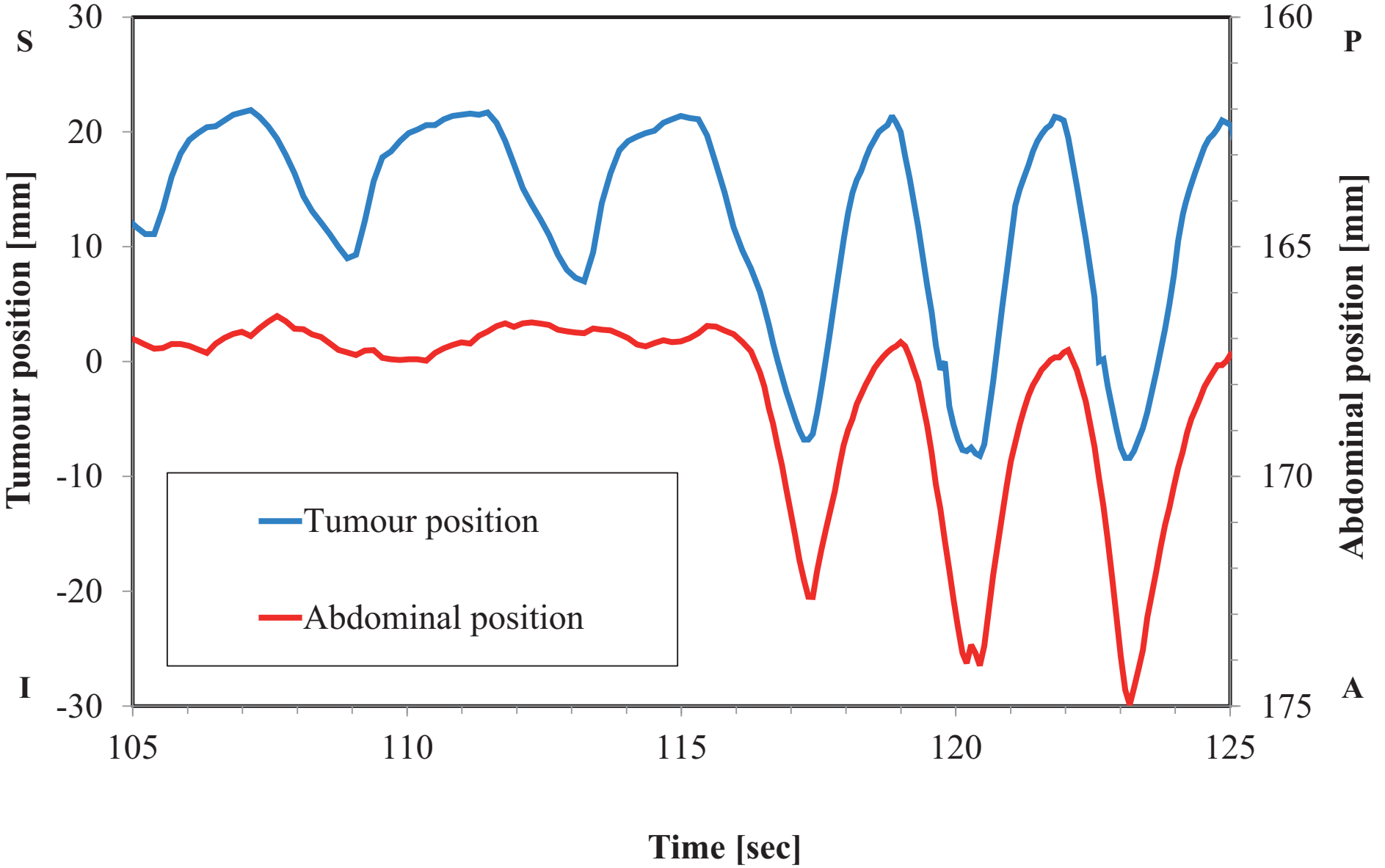
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