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1 **Title:**

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

4

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26

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

28

29 **Running head:**

30 Dynamic tracking with real-time monitoring

31

32 **Keywords:** stereotactic body radiotherapy; lung cancer; dynamic tumour tracking; real-time monitoring;

33 feasibility study

34

35 **Abstract:**

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

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

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

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

50

51

52 **Introduction**

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

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

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

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

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

81

82 **Materials and Methods**

83 *Patients*

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

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

91

92 *Pre-planning procedures*

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

97 On the simulation day, the patient was fixed in a supine position with both arms raised using an
98 individualized vacuum pillow (BodyFIX; Elekta AB, Stockholm, Sweden, or ESFORM; Engineering
99 System, Matsumoto, Japan). Ten respiratory phases of 4D CT were acquired in axial cine mode using a
100 16-slice CT scanner (LightSpeed RT16 or BrightSpeed Elite; GE Healthcare, Little Chalfont, UK) and a
101 real-time positioning management system (Varian Medical Systems, Palo Alto, US). Immediately after
102 the 4D CT scan, a breath-hold CT scan was also acquired at the end of exhalation. The breath-hold CT

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

109

110 *Treatment planning*

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

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

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

137

138 *Irradiation of treatment beams*

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

147

148 *Follow-up after treatment*

149 Follow-up visits were planned at 2, 4, 6, 9, and 12 months within the initial year after SBRT and every 3
150 months thereafter. A CT scan was performed at each visit. The follow-up period was defined as the
151 duration between the first day of treatment and the last follow-up visit or the date of death. Acute
152 toxicity was defined as any treatment-related toxicities during the initial 6 months after the treatment.
153 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 markers 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 cm³ to 39.6 cm³ 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

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

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

197 The Task Group 76 of the American Association of Physicists in Medicine classified motion
198 management methods into five types: motion-encompassing, respiratory gating, breath-hold, forced
199 shallow breathing with abdominal compression, and real-time tumour-tracking methods[8]. The
200 motion-encompassing method is the most conventional and well-established. However, it uses the largest
201 field of the five methods, with a large PTV. The breath-hold technique and abdominal compression are
202 not always suitable for frail and elderly patients. Respiratory gating needs a longer treatment time than
203 motion-encompassing methods. With a dynamic tracking method, patients do not need to hold or limit
204 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

239 uncertainty between the tumour and markers. Imura et al. reported that 25% of the inserted markers could
240 not be detected throughout the treatment period. Indeed, 22% of the markers in this study were coughed
241 out before the CT simulation, and 4 of 22 (18%) patients could not undergo the DTT due to the marker
242 dislocation. The reason why the Vero4DRT system requires 3 markers or more in the use of spherical
243 markers is to detect the marker dislocation. Regarding the positional uncertainty between the tumour and
244 markers, Ueki et al. evaluated intra- and interfractional variations[19]. Root mean squares in the
245 intrafractional variations were 0.6 mm, 0.9 mm and 1.5 mm in the right-left, anteroposterior and
246 craniocaudal directions, respectively. Moderate correlations of the intrafractional variation with tumour
247 motion amplitude and tumour-marker distance were observed with correlation coefficients of 0.549–
248 0.780. However, the intrafractional error did not always distribute symmetrically around zero, but often
249 distributed in one side above or below zero. The direction and amplitude of the intrafractional variations
250 varied between patients. Base on the results, we judged that a uniform isotropic margin was inadequate
251 to cover the intrafractional variations, and that the fused CT approach as in the Method section was
252 suitable for DTT planning. The interfractional variation could be covered by a 2.5-mm margin.

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

255

256 **Conflict of interests:**

257 T.M., M.K. and M.H. have consultancy agreements with Mitsubishi Heavy Industries Ltd., Japan. A
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259

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265

266

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353

354 **Figure legend:**

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

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

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

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

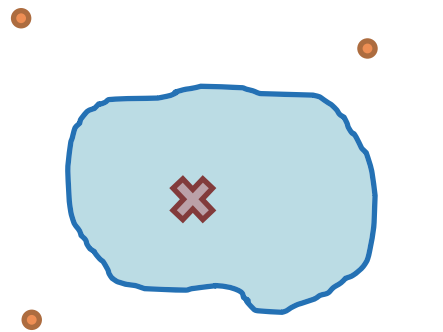
365

366 **Supplementary figure 2. A patient who showed thoracic breathing**

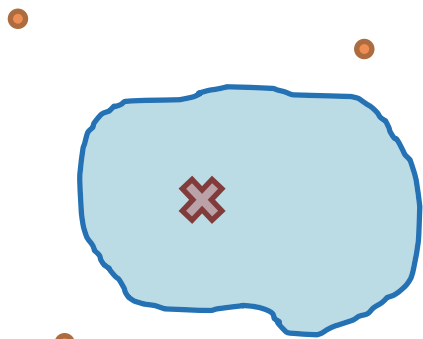
367 The tumour position in the superior-inferior (SI) direction and the abdominal wall position
368 in the anterior-posterior (AP) direction are shown in blue and red lines, respectively. Note
369 that the patient showed thoracic breathing where the tumour moved without any
370 abdominal motion during the initial 10 seconds. Thoracic breathing was the dominant
371 respiratory pattern in the patient so that the Vero system could not create an appropriate
372 4D model for the patient.

a)

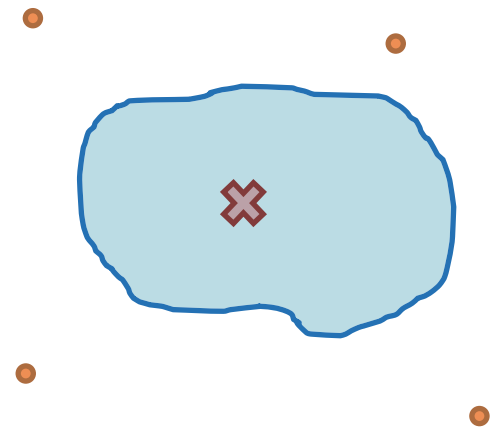
caudal <--- respiratory motion ---> cranial



exhale



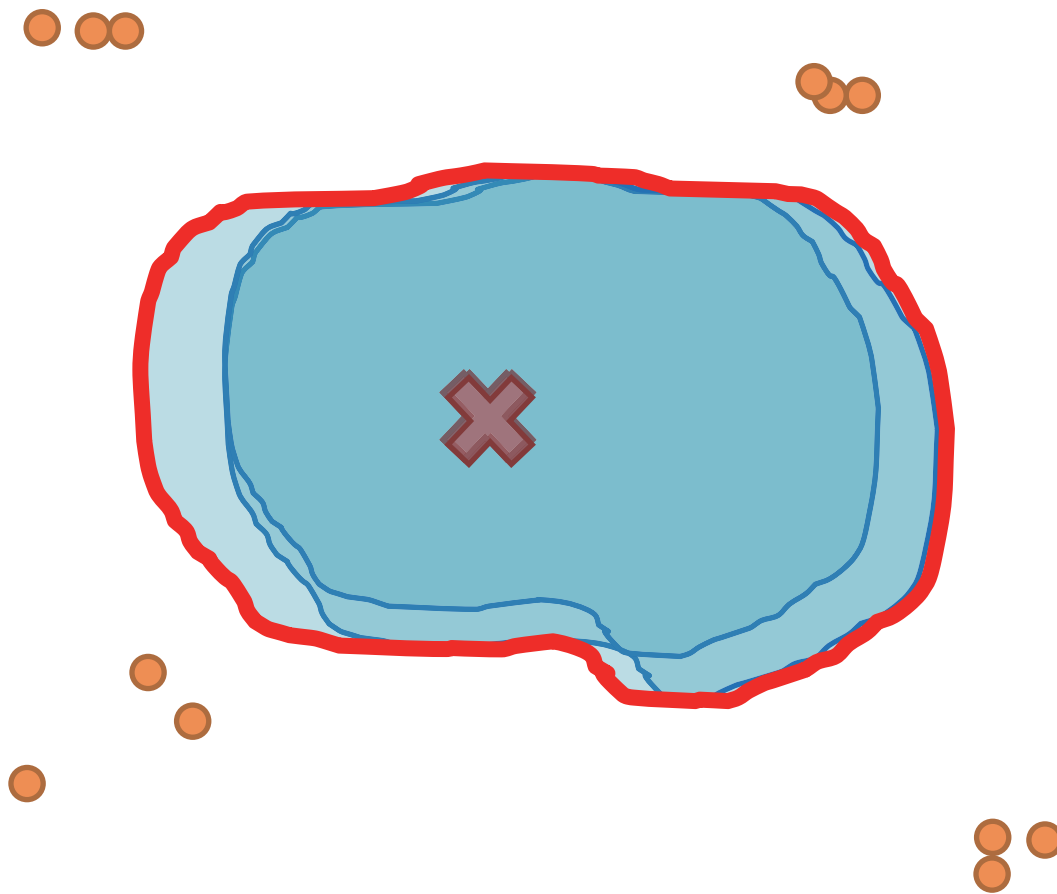
mid-inhale



end-inhale

- fiducial markers
- ✕ centroid of markers
- GTV

 ITV for tracking



b)



R

L

A

P

c)

4-D Series

