



HOKKAIDO UNIVERSITY

Title	Can hybrid FDG-PET/CT detect subclinical lymph node metastasis of esophageal cancer appropriately and contribute to radiation treatment planning? A comparison of image-based and pathological findings
Author(s)	Shimizu, Shinichi; Hosokawa, Masao; Itoh, Kazuo et al.
Citation	International Journal of Clinical Oncology, 14(5), 421-425 https://doi.org/10.1007/s10147-009-0893-4
Issue Date	2009-10
Doc URL	https://hdl.handle.net/2115/56599
Rights	The final publication is available at link.springer.com
Type	journal article
File Information	Int J Clin Oncol_14_421-425.pdf



Can Hybrid FDG-PET/CT Detect Subclinical Lymph Node Metastasis of Esophageal Cancer Properly And Contribute to the Radiation Treatment Planning? – A Comparison of Image-Based And Pathological Findings —

Shinichi Shimizu, M.D.,^{*1,2} Masao Hosokawa, M.D.,^{*2} Kazuo Itoh, M.D.,^{*2} Masahiro Fujita, M.D.,^{*2} Hiroaki Takahashi, M.D.,^{*2} Hiroki Shirato, M.D.^{*1}.

1) Hokkaido University, Graduate School of Medicine, Department of Radiology, Sapporo, Japan

2) Keiyukai Sapporo Hospital, Sapporo, Japan

Correspondence: Shinichi Shimizu, M.D., Hokkaido University, Graduate School of Medicine, Department of Radiology, North 15 West 7, Kita-Ku, Sapporo 060-8638, Japan.

Tel. +81-11-706-5977; Fax +81-11-706-7876

e-mail: sshimizu-rad@umin.ac.jp

All authors have no financial disclosures

Abstract

Background.

To determine the appropriateness of appending FDG-PET to CT and other pre-existing diagnostic imaging modalities by comparing images from these modalities with the results of histopathological analysis.

Methods.

Twenty patients who received radical surgery for squamous cell carcinoma of the esophagus were examined by computed tomography (CT), positron-emission tomography with computed tomography (PET-CT), and endoscopic ultrasound (EUS) examination before surgery. Based on these diagnostic modalities, the clinical target volume (CTV) was set as the gross tumor volume (GTV) plus a 1-cm margin. Histopathological diagnosis was performed in all patients immediately after resection.

Results.

Fifty-three (3.0%) out of 1764 nodes in the 20 patients were histopathologically positive for cancer cells. The CTV was not adequate to cover these histopathologically detected positive lymph nodes in 8 of 20 (CT), 5 of 20 (CT+EUS), 7 of 20 (PET-CT) and 5 of 20 (PET-CT+EUS) patients.

Conclusion.

The detection rate of subclinical lymph node metastasis did not improve with the use of PET-CT either for the cervical and supraclavicular, mediastinal, or abdominal regions. It is not recommendable to use FDG-PET or PET-CT alone as the diagnostic tool to determine CTV if pathologically involved lymphatic regions are to be included in the CTV in the treatment protocol. The accuracy of PET-CT must be further improved in order to better detect positive nodes and improve the definition of the CTV.

Mini-abstract

For esophageal cancer, the detection rate of subclinical lymph node metastasis did not improve with the use of PET-CT. It is not recommendable to use PET-CT alone to determine CTV.

Key words: FDG, PET-CT, Esophageal cancer, radiotherapy

Introduction

Many institutions are using large radiotherapy fields for elective nodal irradiation in chemoradiotherapy for esophageal cancer. However, it has been suggested that locoregional recurrence due to missed targets and treatment-related toxicities caused by large fields of radiation still occur in a substantial proportion of patients, and thus more accurate radiotherapy targeting is needed to improve locoregional control and reduce toxicity (1). ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) is frequently used to detect the primary tumor and metastasis to lymph nodes, and is reported to be useful to supplement computed tomography (CT) in the staging of esophageal cancer (2-6). However, Yoon et al. reported that this imaging modality had limited efficacy for pre-surgical diagnosis. In their study, they compared CT- and FDG-PET-based clinical diagnoses with the pathological diagnoses after surgery and reported that both FDG-PET and CT had low sensitivity for depicting nodal metastasis (7). Recently, Yuan et al. reported that PET/CT was more effective than PET alone for assessing the involvement of locoregional lymph nodes in thoracic esophageal squamous cell carcinoma (8).

In a prospective trial of preoperative chemoradiotherapy for esophageal cancer, FDG-PET was shown to be useful in the staging and prediction of prognosis by detecting occult metastasis (9). However, Vrieze et al. showed that FGD-PET alone cannot be used for the treatment planning because the chance of a false-negative result on FGD-PET is not negligible, and thus the target volume should not be reduced based on a negative FDG-PET finding in a region with nodes that are suspect by other modalities (10). It has been shown that CT and FDG-PET image fusion has an impact on treatment planning and management of esophageal carcinoma by altering the choice of gross tumor volume (GTV) (11). Similarly, Gondi et al. suggested that a hybrid FDG-PET/CT scanner had an impact on the radiotherapy planning of esophageal cancer and non-small cell lung cancer (12).

In this study, we investigated the appropriateness of hybrid PET/CT for determining the clinical target volume (CTV) by comparing the radiological diagnosis before surgery and the pathological diagnosis. We also compared the efficacy of hybrid PET/CT to that of CT alone, FDG-PET alone, and the combination of CT and endoscopic ultrasound (EUS) for the CTV determination.

Methods and Materials

Twenty patients (15 male and 5 female; median age: 61 years; range: 47-75 years) with

squamous cell carcinoma of the esophagus who consented to receive surgical esophagectomy were the subjects of this study. There were 3 stage I (UICC 6th edition, 2002), 8 stage II, and 9 stage III patients (13). Written informed consent was obtained from all patients.

All patients received a diagnostic work-up consisting of CT, endoscopy and EUS, and FDG-PET within 2 weeks. A high-speed multi-detector raw CT scan (ROBUSTO; Hitachi Medical Corporation, Tokyo, Japan) was used with a slice thickness and interval of 5 mm and 5 mm, respectively. An endoscopist performed the EUS (EU-M2000; Olympus Medical Systems Corp., Tokyo, Japan) and provided a written report of the EUS results for all patients. F-18 FDG was purchased from Nihon Medi-Physics Co., Ltd. (Tokyo, Japan). It was intravenously injected to patients who were instructed to fast for at least 4 hours before PET imaging. Sixty minutes after FDG injection, an attenuation-corrected whole body image (3D-mode) from the top of the skull to the proximal thighs was obtained at 1 bed position per 2.0 minutes using PET/CT (GEMINI-GXL; Philips, Amsterdam, Netherlands).

Diagnostic specialists reviewed each image independently without reference to the other images. A radiologist examined each node and diagnosed it positive if the maximum diameter was larger than 1.0 cm without calcification on transaxial CT. On PET-CT each node was diagnosed as positive if the node showed increased FDG uptake relative to around tissue. Standardized uptake value (SUV) was used only for a reference. The cutoff SUV was not set. On EUS, an endosonographer diagnosed it positive if the visible lymph node showed in size > 5mm and its shape round or oval, mixed/hyperechoic internal texture.

A radiation oncologist determined the clinical target volume (CTV) by adding a 1.0 cm margin around the gross tumor volume (GTV) including local tumor and lymphatic involvement based on either CT-alone, CT with EUS, PET-CT alone, or PET-CT with EUS (Figure 1). No other parameters were used other than the gross tumor volume determined by each diagnostic image. The Japanese Guidelines for esophageal cancer was used to describe the location of the lymphatic involvement (Table 1)(14). Analysis of the results was performed by grouping these lymphatic locations into the cervical and supraclavicular (A), mediastinal (B), and abdominal (C) regions.

Surgery was performed within 3 weeks after the end of the diagnostic work-up in principle. A pathological diagnostic report was made by a pathologist for each surgical specimen regarding local extent and lymphatic spread. The positivity of metastasis to the lymph nodes was examined histopathologically.

We first calculated the diagnostic accuracy, sensitivity, and specificity of CT and

PET-CT. Fisher's exact test was used to compare categorical data. Adequacy of the CTV to cover the subclinical pathological positive lymph node metastasis was examined among the different diagnostic work-ups after pathological investigation. The portal size of each RT plan was also examined.

Results

The surgical specimens of the 20 patients contained 1764 lymph nodes. 53 (3.0%) of the 1764 nodes were histopathologically positive for cancer cells. The number and location of the lymph nodes are shown in Table 2. The accuracies of thin-slice CT and conventional PET-CT according to the location of the lymph nodes were 0.95 and 0.85 for the cervical and supraclavicular region (A), 0.95 and 0.6 for the mediastinal region (B), and 0.65 and 0.6 for the abdominal region (C).

The sensitivities were 1.0 and 0.5 (A), 0.86 and 0.14 (B), and 0.22 and 0.11 (C) for thin-slice CT and conventional PET-CT, respectively. The specificities were 0.94 and 0.94 (A), 0.69 and 0.85 (B) and 1.0 and 1.0 (C) for thin-slice CT and conventional PET-CT, respectively.

The number of patients with subclinical positive lymph node metastasis that were not detected in the pre-surgical work-up but were detected in the histopathological examination was determined for each of the combinations of imaging modalities. Out of 20 patients, subclinical positive lymph node metastasis were not detected in 8 patients by CT alone (CT), in 5 patients by CT and EUS (CT+EUS), in 7 patients by PET-CT (PET-CT) and in 5 patients by PET-CT and EUS (PET-CT + EUS).

To cover the subclinical pathological positive lymph node metastasis, enlargement of the CTV was required for region (A) in 1/8 (CT), 1/5 (CT+EUS), 2/9 (PET-CT), and 1/5 (PET-CT + EUS) patients, for region (B) in 0/8 (CT), 0/5 (CT+EUS), 1/9 (PET-CT), and 0/5 (PET-CT + EUS) patients and for region (C) in 7/8 (CT), 4/5 (CT+EUS), 6/9 (PET-CT), and 4/5 (PET-CT + EUS) patients, respectively (Table 3). There were no statistically significant differences among the regions on each modalities, but enlargement of CTV was suggested to be required for region (C) more frequently than for regions (A) and (B).

Discussion

The accuracy, specificity, and sensitivity of FDG-PET for lymphatic metastasis of esophageal cancer in the present study were consistent with those of previously reported series (15-18). Meltzer et al. have reported that FDG-PET had 35-41% sensitivity and 90% specificity, versus 63-87% sensitivity and 14-43% specificity for CT

(15). Räsänen et al. have shown that the sensitivity for local peritumoral lymph node metastasis was 37% for PET and 89% for EUS, and the specificity for local lymph node metastasis was 63% for PET, 66% for CT, and 75% for EUS (16). A systematic review showed that the pooled sensitivity and specificity for the detection of locoregional metastases were 0.51 (95% CI, 0.34 to 0.69) and 0.84 (95% CI, 0.76 to 0.91), respectively (17). Katsoulis et al. reported in a prospective study that the CT had 29% sensitivity and 67% specificity, whereas FDG-PET had 71% sensitivity and 67% specificity ($P=0.0412$) (18). In one of the largest series on squamous cell carcinoma (81 patients), Yoon et al. showed that the sensitivity, specificity, and accuracy, respectively, of CT were 11%, 95%, and 83%, whereas those of FDG PET were 30%, 90%, and 82% (P values: <0.001 , 0.009, and 0.382, respectively)(7). Although there is some variation in the literature, the sensitivity of PET should be considered insufficient, although the specificity may be better than that of a CT scan.

Yuan et al. reported that PET/CT improves the sensitivity, accuracy, and negative predictive value of ^{18}F -FDG imaging in the assessment of locoregional lymph nodes in thoracic esophageal squamous cell cancer (8). The sensitivity, specificity and accuracy of PET/CT were 93.90% (77/82 nodal groups), 92.06% (290/315), and 92.44% (367/397), respectively, whereas those of PET were 81.71% (67/82), 87.30% (275/315), and 86.15% (342/397), respectively ($P = 0.032$, 0.067, and 0.006, respectively). However, our results did not show that the detection rate of subclinical lymph node metastasis improved with the addition of PET-CT for the cervical and supraclavicular, mediastinal, or abdominal regions. The PET-CT used in this study was a state-of-the-art machine, and thus the same results would be expected even if we would have used one of the other PET-CT machines available now.

Previous studies have reported that the use of FDG-PET resulted in a change of CTV margin around the gross tumor volume compared with that determined by CT (1, 19). However, these same authors noted that determination of the CTV for the lymphatic region was a challenge even when using PET. Our results were consistent with their findings. The detection rate of subclinical lymph node metastasis did not improve with the addition of PET-CT for either cervical and supraclavicular nodes, mediastinal, or abdominal regions. In clinical practice, a larger CTV including larger lymphatic regions is often used to cover unpredictable widespread lymphatic metastasis in esophageal cancer treatment (1). Radiological examinations such as CT, PET, EUS, and CT-PET are not yet sufficient for determination of the CTV for the lymphatic region. Although it is not conclusive whether we should treat all cervical, mediastinal and abdominal lymphatic regions for a majority of patients, this is a subject better left for future

investigations.

Enlargement of the CTV is required more frequently in abdominal region (Table 3.). EUS has its potential to visualize a small lymph node metastasis located around the oesophageal and gastric wall, though EUS has also limitation or penetration depth about 5cm. PET-CT is expected to perform superiority than CT in the detection of lymph node metastasis. In our study the result is not sufficient. It may not be enough the amount of altered tissue glucose metabolism included in the subclinical lymph node metastasis that can be well visualized through extra-body PET detectors. FDG-PET/CT also has its limitation to point out the lymph node metastasis in the deep abdominal lesion.

Our results suggested that PET-CT requires further improvement of its accuracy for the detection of positive nodes to improve the accuracy in determining CTV. Recently, a new PET with semiconductor detectors has been developed and is expected to have potential for precise detection of small cancer metastasis (20). We need to continue to improve the various imaging modalities so that they can be used as reliable guides for radiotherapy.

In conclusion, it is not recommendable to use FDG-PET or PET-CT alone to determine CTV when all pathologically involved lymphatic regions are to be included in the CTV as a treatment strategy.

References

1. Gao XG, Qiao X, Wu F, et al. (2007) Pathological analysis of clinical target volume margin for radiotherapy in patients with esophageal and gastroesophageal junction carcinoma. *Int J Radiat Oncol Biol Phys* 67:389 – 396
2. Block MI, Patterson GA, Sundaresan RS, et al. (1997) Improvement in staging of esophageal cancer with the addition of positron emission tomography. *Ann Thorac Surg* 64:770-776
3. Luketich JD, Schauer PR, Meltzer CC, et al. (1997) Role of positron emission tomography in staging esophageal cancer. *Ann Thorac Surg* 64:765 – 769
4. Luketich JD, Friedman DM, Weigel TL, et al. (1999) Evaluation of distant metastases in esophageal cancer: 100 consecutive positron emission tomography scans. *Ann Thorac Surg* 68:1133 – 1136
5. Flanagan FL, Dehdashti F, Siegel BA, et al. (1997) Staging of esophageal cancer with 18F-fluorodeoxyglucose positron emission tomography. *Am J Roentgenol* 168: 417 – 424

6. Flamen P, Lerut A, Van Cutsem E, et al. (2000) Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. *J Clin Oncol* 18:3202-3210
7. Yoon, YC, Lee KS, Shim YM, et al. (2003) Metastasis to regional lymph nodes in patients with esophageal squamous cell carcinoma: CT versus FDG PET for presurgical detection - prospective study *Radiology* 227:764 – 70
8. Yuan S, Yu Y, K.S. Chao C, et al. (2006) Additional value of PET/CT over PET in assessment of locoregional lymph nodes in thoracic esophageal squamous cell cancer. *J Nucl Med* 47:1255 – 1259
9. Blackstock AW, Farmer MR, Lovato J, et al. (2006) A prospective evaluation of the impact of 18-F-fluoro-deoxy-D-glucose positron emission tomography staging on survival for patients with locally advanced esophageal cancer. *Int J Radiat Oncol Biol Phys* 64:455 – 460
10. Vrieze O, Haustermans K, De Wever W, et al. (2004) Is there a role for FDG-PET in radiotherapy planning in esophageal carcinoma ? *Radiother Oncol* 73:269 -275
11. Moureau-Zabotto L, Touboul E, Lerouge D, et al. (2005) Impact of CT and ¹⁸F-deoxyglucose positron emission tomography image fusion for conformal radiotherapy in esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 63:340 – 345
12. Gondi V, Bradley K, Mehta M et al. (2007) Impact of hybrid fluorodeoxyglucose positron-emission tomography/computed tomography on radiotherapy planning in esophageal and non–small-cell lung cancer. *Int J Radiat Oncol Biol Phys* ;67: 187 – 195
13. Sobin LH, Wittekind CH. (2002) UICC: TNM classification of malignant tumors. 6th ed. New York: Wiley-Liss
14. The Japanese Society for Esophageal disease. (2001) Guidelines for clinical and pathologic studies on carcinoma of the esophagus, the ninth edition. Tokyo: Kanehara Publishing, p. 8–10
15. Meltzer CC, Luketich JD, Friedman D, et al. (2000) Whole-body FDG positron emission tomographic imaging for staging esophageal cancer : comparison with computed tomography. *Clin Nucl Med* 25:882 – 887
16. Räsänen, JV, Sihvo EIT, M. Knuuti, MJ, et al. **(2003)** Prospective Analysis of Accuracy of Positron Emission Tomography, Computed Tomography, and Endoscopic Ultrasonography in Staging of Adenocarcinoma of the Esophagus and the Esophagogastric Junction. *Ann Surg Oncol* 10:954 -960
17. van Westreenen HL, Westerterp M, Bossuyt PMM, et al. (2004) Systematic Review of the Staging Performance of 18F-Fluorodeoxyglucose Positron Emission

Tomography in Esophageal Cancer. J Clin Oncol 22:3805 – 3812

18. Katsoulis IE, Wong WL, Mattheou AK, et al. (2007) Fluorine-18 fluorodeoxyglucose positron emission tomography in the preoperative staging of thoracic oesophageal and gastro-oesophageal junction cancer: a prospective study. Int J Surg 5:399 – 403
19. Leong T, Everitt C, Yuen K, et al. (2006) A prospective study to evaluate the impact of FDG-PET on CT-based radiotherapy treatment planning for oesophageal cancer. Radiother Oncol 78:254 – 261
20. Shiga T, Morimoto Y, Kubo N, et al. A new PET scanner with semiconductor detectors enables better identification of intratumoral inhomogeneity. J Nuc Med, in press.

Figure Legends

Fig.1.

An example of the change in the treatment field due to difference in CTV determined by various imaging modalities to cover primary lesion and subclinical positive lymph node metastasis (case4). The field I, II, III, and IV corresponds to CTV determined by using CT, CT + EUS, PET-CT, and PET-CT + EUS.

Table

Table 1.

Numbering of lymph nodes according to the guidelines for clinical and pathologic studies on carcinoma of the esophagus (extracted from (14)).

Group	Number	Description
(A) Cervical and supraclavicular region	101	Cervical paraesophageal lymph nodes
	102	Deep cervical lymph nodes
	104	Supraclavicular lymph nodes
(B) Mediastinal region	105	Upper thoracic paraesophageal lymph nodes
	106	Thoracic paratracheal lymph nodes
	107	Bifurcational lymph nodes
	108	Middle thoracic paraesophageal lymph nodes
	110	Lower thoracic paraesophageal lymph nodes
	111	Supradiaphragmatic lymph nodes
	112	Posterior mediastinal lymph nodes
(C) Abdominal region	1	Right cardiac lymph nodes
	2	Left cardiac lymph nodes
	3	Lesser curvature lymph nodes
	7	Left gastric artery lymph nodes
	9	Celiac artery lymph nodes
	19	Infradiaphragmatic lymph nodes

Table 2.
Patient characteristics and findings.

Pat.No /Age		Primary	Sta ge	CT (Ln>10mm)	EUS	PET	Pathology findings	
1	50M	Lt	3	-	101	Lt.cervical, upper mediastinum,lower esophagus	2/101	3
2	59M	Mt	3	101,104,110, 3	101, 108		3/122	101, 108, 3
3	49M	Mt	3	101, 106, 107	101	Rt.mediastinum, paratrachea	1/94	101
4	56M	Mt	2	106	106	Upper mediastinum	1/82	106
5	62F	Mt	2	-	-	Upper mediastinum	0/113	-
6	61M	Mt	1	105,106	-		0/63	-
7	62M	Mt	3	-	108		0/103	-
8	71M	Ut	2	-	-		0/60	-
9	55M	Mt	2	101,105,106	105, 106		2/96	101, 106
10	65M	Mt	3	101,105,106,110	101, 7		1/94	9
11	66M	Mt	1	106,107	-		0/53	-
12	63M	Lt	1	-	-		0/102	-
13	56M	Lt,Ae	3	106, 9	7	Ln adhare to primary tumour	17/183	1, 2, 110
14	60M	Lt	2	110	2, 110		8/32	2, 19,110,112
15	66M	Mt	2	-	-		2/108	7
16	68F	Ce	3	104	-	Upper mediastinum	2/46	101, 102, 104-
17	57F	Lt,Ae	3	106	-		3/93	2, 7
18	75M	Lt,Ae	2	-	-		7/50	1, 3, 7, 19, 110, 111
19	47F	Lt	2	108	-		3/68	108
20	61F	Lt	3	-	1		1/101	1

Table 3.

Number of patients requiring CTV enlargement to cover subclinical positive lymph node metastasis.

	No. of patients	(A) Cervical + supraclavicular	(B) Mediastinal	(C) Abdominal
CT only	8	1	0	7
CT + EUS	5	1	0	4
PET-CT	9	2	1	6
PET-CT + EUS	5	1	0	4

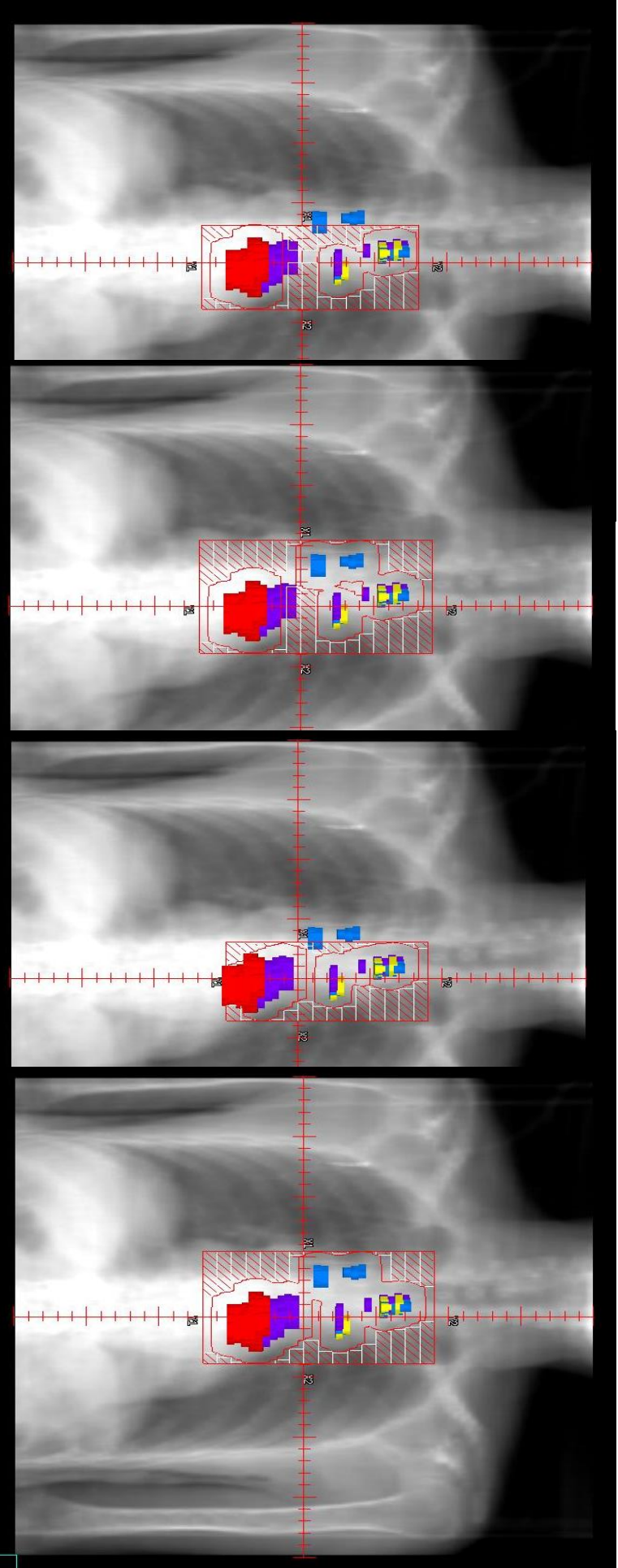


Fig. 1