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Efficacy of FDG-PET for defining gross tumor volume of head and neck cancer

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We analyzed the data for 53 patients with histologically proven primary squamous cell carcinoma of the head and neck treated with radiotherapy between February 2006 and August 2009. All patients underwent contrast-enhanced (CE)-CT and ^{18}F-fluorodeoxyglucose (FDG)-PET before radiation therapy planning (RTP) to define the gross tumor volume (GTV). The PET-based GTV (PET-GTV) for RTP was defined using both CE-CT images and FDG-PET images. The CE-CT tumor volume corresponding to a FDG-PET image was regarded as the PET-GTV. The CE-CT-based GTV (CT-GTV) for RTP was defined using CE-CT images alone. Additionally, CT-GTV delineation and PET-GTV delineation were performed by four radiation oncologists independently in 19 cases. All four oncologists did both methods. Of these, PET-GTV delineation was successfully performed in all 19 cases, but CT-GTV delineation was not performed in 4 cases. In the other 15 cases, the mean CT-GTV was larger than the PET-GTV in 10 cases, and the standard deviation of the CT-GTV was larger than that of the PET-GTV in 10 cases. Sensitivity of PET-GTV for identifying the primary tumor was 96%, but that of CT-GTV was 81% ($P < 0.01$). In patients with oropharyngeal cancer and tongue cancer, the sensitivity of CT-GTV was 63% and 71%, respectively. When both the primary lesions and the lymph nodes were evaluated for RTP, PET-GTV differed from CT-GTV in 19 cases (36%). These results suggested that FDG-PET is effective for defining GTV in RTP for squamous cell carcinoma of the head and neck, and PET-GTV evaluated by both CE-CT and FDG-PET images is preferable to CT-GTV by CE-CT alone.

Keywords: FDG-PET; gross tumor volume; target delineation; head and neck cancer

INTRODUCTION

Recent advances in radiation oncology and technology, such as 3D-conformal radiotherapy (3D-CRT) and intensity-modulated radiation therapy (IMRT), have improved the dose conformality of radiation treatment planning (RTP). Especially in the head and neck area, highly conformal RTP is very useful for escalating the tumor dose without increasing normal tissue injury, and precise identification of the target volume in RTP is essential. Most common RTP has been performed using anatomical images from CT scanning or MRI.

Functional or biological imaging by positron emission tomography (PET) is expected to provide more useful information than anatomical imaging alone so that more appropriate RTP can be performed [1, 2]. ^{18}F-fluorodeoxyglucose (FDG)-PET has recently been used to verify the target volume in RTP for various malignancies, especially non-small-cell lung cancer, head and neck cancer, etc. [3–6]; however, it has not been well established how FDG-PET can be utilized for actual treatment planning for many different types of malignancies, and various approaches for the suitable use of PET for RTP have been suggested.

In the present study, we evaluated the efficacy of FDG-PET for defining the gross tumor volume (GTV) of head and neck cancer to establish RTP using functional imaging.

MATERIALS AND METHODS

We analyzed the data for 53 patients with histologically proven primary squamous cell carcinoma of the head and neck treated with radiotherapy in Nara Medical University Hospital between February 2006 and August 2009. All patients underwent routine contrast-enhanced (CE)-CT and FDG-PET for staging and defining the GTV. PET images were acquired about 60 min after intravenous administration of 3 MBq/kg FDG. If FDG-PET could not be performed before RTP, patients were excluded from this study. Plain CT simulation for RTP of patients in the supine position, immobilized with a head-rest and thermoplastic mask, was also performed.

Table 1. Patient characteristics

Characteristics	Number of patients
Gender	
Male	39
Female	14
Stage	
I	0
II	13
III	13
IVA	27
IVB	0
Tumor site	
Oral cavity	31
tongue	14
gingiva	8
buccal mucosa	4
mouth floor	4
others	1
Pharynx	13
oropharynx	8
hypopharynx	5
Nasal cavity/Paranasal sinus	7
Others	2
Total	53

RTP of the head and neck cancer was performed based on CT simulation using both CE-CT and FDG-PET images with a visual method [5, 7], according to the institute definition of the target volume for PET-based RTP. The definition is as follows: CE-CT-based GTV (CT-GTV) for RTP is defined using conventional CE-CT images alone. PET-based GTV (PET-GTV) for RTP is defined using both CE-CT and FDG-PET images. The CE-CT volume corresponding to a positive FDG-PET image was regarded as the PET-GTV, and RTP was performed using the GTV, with inflammatory FDG accumulation being excluded by a nuclear radiologist. If PET images were regarded as inappropriate for RTP due to false-positive or false-negative, CT-GTV was used predominantly for RTP.

In the present study, PET-GTV was compared with CT-GTV to evaluate the importance of FDG-PET information on target definition in RTP. The sensitivity of CE-CT alone for identifying primary lesions, and that of the combination of CE-CT and FDG-PET was calculated, comparing the histologically proven lesions as the standard of reference; however, the specificity was not assessed because of the bias of the patients in this study, i.e. exclusively patients with histologically proven squamous cell carcinoma of the head and neck. Statistical significance of the difference in sensitivity was assessed by the McNemer test (StatMate IV for Windows V4.01; ATMS, Tokyo).

The PET-GTV for each case was then compared with the CT-GTV in order to evaluate the importance of the FDG-PET information in identifying lymph node metastases for RTP. However, the sensitivity and the specificity of PET-GTV and CT-GTV were not assessed for lymph nodes, because most of the lymph nodes had not been histologically studied in these cases, although every primary squamous cell carcinoma was histologically confirmed.

In addition to the above study, CT-GTV delineation and PET-GTV delineation in 19 cases (13 patients with tongue cancer and 6 patients with oropharyngeal cancer) were performed by four radiation oncologists independently to evaluate the difference in volume due to interobserver variability in the GTV delineation. The statistical significance of the difference in GTV was assessed by the Wilcoxon signed-ranks test (StatMate IV for Windows V4.01; ATMS, Tokyo).

RESULTS

Patient characteristics for the 53 cases are shown in Table 1. Of the 53 primary tumor sites, 51 lesions showed positive accumulation of FDG; the sensitivity of PET-GTV for identifying the primary site was 96% (Table 2 and Figures 1–5). The margins of the tumors on PET and PET/CT images were relatively ill-defined and not always

Table 2. Sensitivity (%) of CT-GTV and PET-GTV for identifying primary tumors

	n	CT-GTV positive	Sensitivity %	PET-GTV positive	Sensitivity %
Oral cavity	31	24	77	29	94
tongue	14	10	71	13	93
gingiva	8	6	75	7	88
bucca	4	4	100	4	100
mouth floor	4	4	100	4	100
others	1	0	0	1	100
Pharynx	13	10	77	13	100
oropharynx	8	5	63	8	100
hypopharynx	5	5	100	5	100
Nasal/Para	7	7	100	7	100
Others	2	2	100	2	100
Total	53	43	81	51	96

Nasal/Para = Nasal cavity/Paranasal sinus

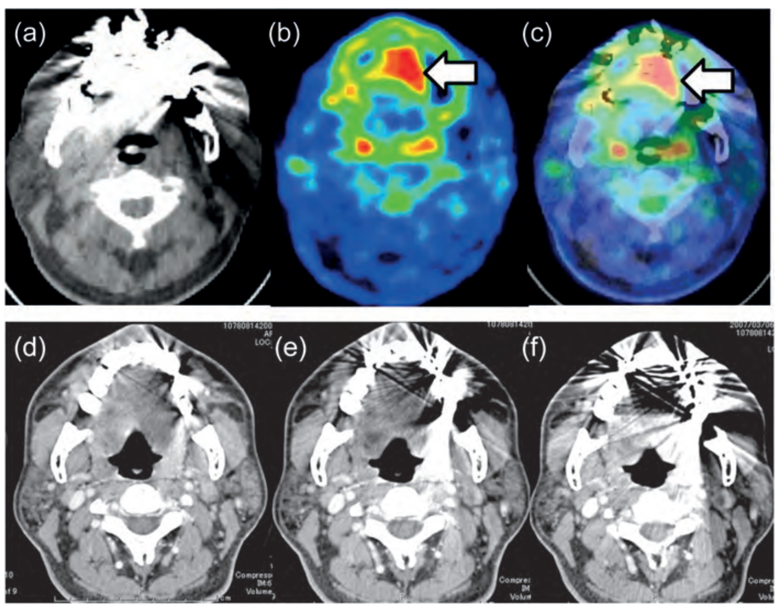

Fig. 1. A case of squamous cell carcinoma of the tongue. The primary tumor lesion was not evident on plain CT (a) and CE-CT (d-f) images due to artifacts induced by artificial teeth, but the lesion was evident on FDG-PET (b) and FDG-PET/CT (c) images (arrows).

clear. The PET-GTV was smaller in some cases and larger in other cases than the CT-GTV. In two cases (tongue cancer and gingiva cancer), it was difficult to determine the GTV by PET (Table 2 and Fig. 4).

In contrast, the GTV of 10 cases was not clear (that of 43 cases was evident) on CE-CT images; the sensitivity of CT-GTV for identifying the primary tumor site was 81% (Table 2) and was significantly lower than that of PET-GTV ($P < 0.01$). In 43 cases, no significant difference was found between PET-GTV and CT-GTV when they were compared to identify the localization of the primary lesions.

In 14 patients with tongue cancer, 10 tumors were evident on CE-CT images, but 4 primary lesions were not clear and 3 of these were due to artifacts induced by bones, teeth, or artificial teeth; sensitivity of CT-GTV to a primary site on the tongue was 71% and that of PET-GTV was 93% (Table 2, Figures 1 and 2). In 8 patients with gingival cancer, 6 tumors were evident, but 2 primary lesions were not clear due to artifacts; sensitivity of CT-GTV to the primary site was 75% and that of PET-GTV was 88% (Table 2, Figures 3 and 4). In 8 patients with oropharyngeal cancer, 3 primary lesions were not obvious; sensitivity of

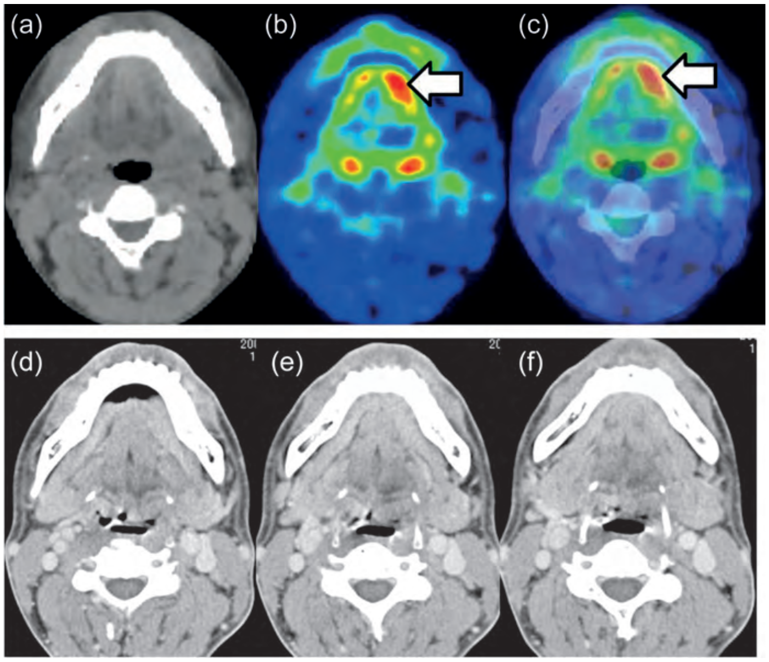

Fig. 2. A case of squamous cell carcinoma of the tongue. The primary tumor lesion was not evident on plain CT (a) and CE-CT (d–f) images regardless of slight artifact, but the lesion was evident on FDG-PET (b) and FDG-PET/CT (c) images (arrows).

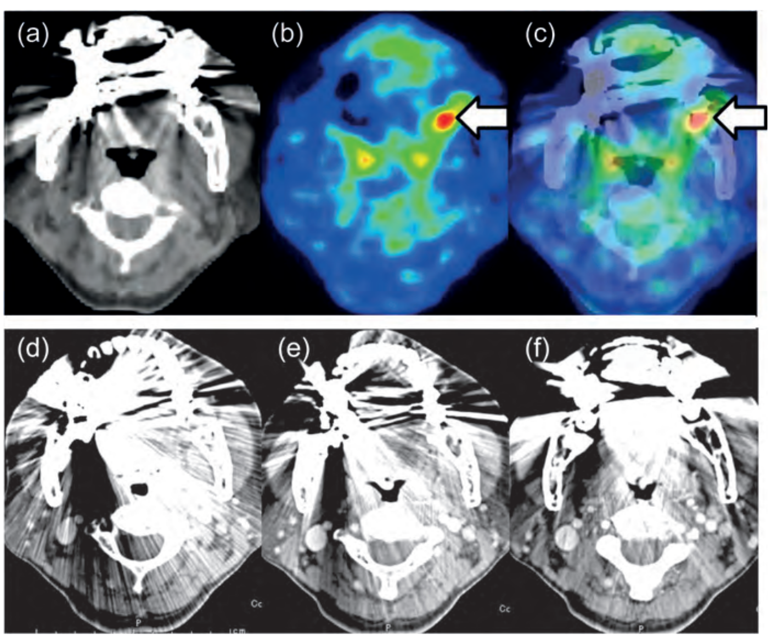

Fig. 3. A case of squamous cell carcinoma of the gingiva. The primary tumor lesion was not evident on plain CT (a) and CE-CT (d–f) images due to artifacts induced by artificial teeth, but the lesion was evident on FDG-PET (b) and FDG-PET/CT (c) images (arrows).

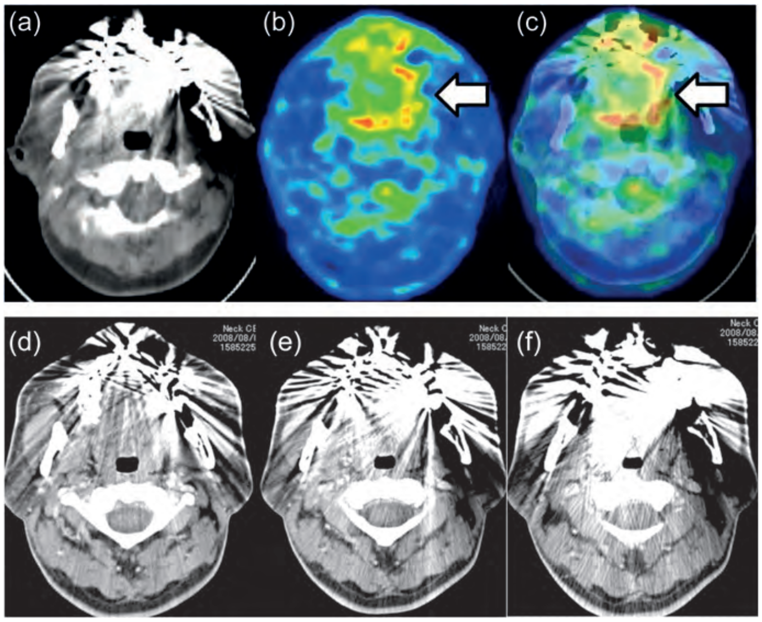

Fig. 4. A case of squamous cell carcinoma of the gingiva. The primary tumor lesion was not evident on plain CT (a) and CE-CT (d–f) images due to artifacts induced by artificial teeth. FDG-PET (b) and FDG-PET/CT (c) images showed positive FDG accumulation (arrows), but it was difficult to determine the GTV because the accumulation was not specific to the tumor.

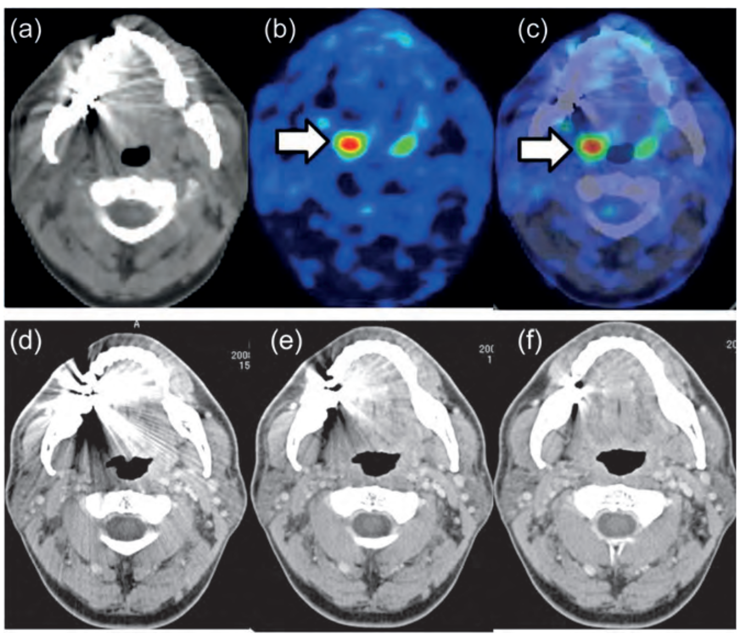

Fig. 5. A case of squamous cell carcinoma of the oropharynx. The primary tumor lesion on plain CT (a) and CE-CT (d–f) images was not as obvious as on FDG-PET (b) and FDG-PET/CT (c) images (arrows).

CT-GTV to the primary site was 63% and that of PET-GTV was 100% (Table 2 and Fig. 5).

Lymph node metastases were suggested in 41 cases (77%) by CE-CT and in 32 cases (60%) by FDG-PET. Neither CE-CT nor FDG-PET showed evident metastases in 11 cases (21%). The PET-GTV differed from the CT-GTV in 11 cases (21%) when we evaluated lymph nodes for RTP. Swollen but FDG-negative lymph nodes were not regarded as the PET-GTV according to the definition of the target volume for PET-based RTP. In 10 cases

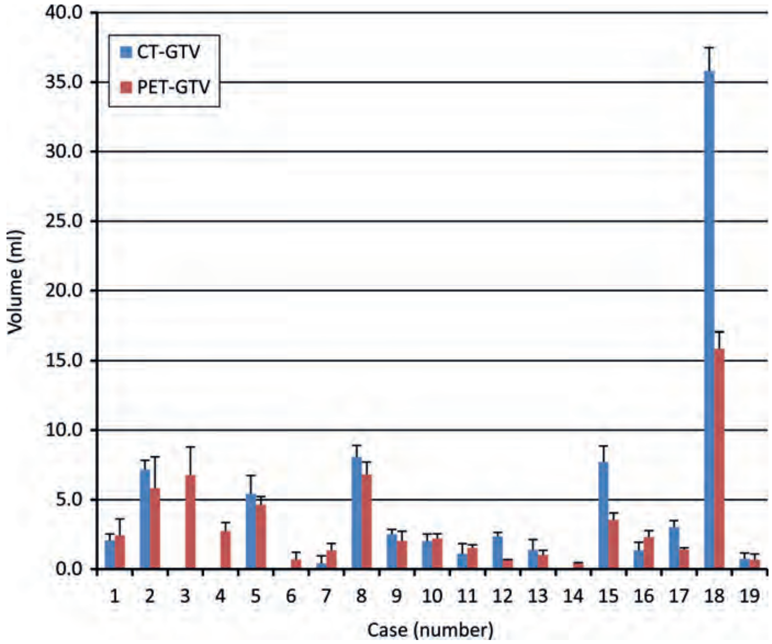

Fig. 6. Comparison of gross tumor volume (GTV) delineated by four radiation oncologists (mean + standard deviation): It was difficult to delineate CT-GTV in four cases (No. 3, 4, 6 and 14). In the other 15 cases, the mean CT-GTV was larger than PET-GTV in 10 cases, and the standard deviation of CT-GTV was larger than that of PET-GTV in 10 cases.

(19%), lymph nodes were regarded as the CT-GTV but they were FDG-negative. In contrast, in only one case, lymph nodes were not swollen significantly, but showed evident accumulation of FDG.

When both the primary lesions and the lymph nodes were evaluated for RTP, the PET-GTV differed from the CT-GTV in primary lesions, lymph nodes, or both in 19 cases (36%) and no significant difference was found between the PET-GTV and the CT-GTV in the other 34 cases (64%).

In comparison of the CT-GTV and the PET-GTV as delineated by 4 radiation oncologists, PET-GTV delineation was successfully performed in all 19 cases, but CT-GTV delineation was not performed in 4 cases by any radiation oncologists due to unclear tumor images (Fig. 6). We evaluated the differences in the CT-GTV and the PET-GTV in the other 15 cases. The CT-GTV was larger than the PET-GTV in 10 of 15 cases, but the difference was not significant ($P = 0.12$). The standard deviation (SD) for the CT-GTV was larger than that for the PET-GTV in 10 cases, and the difference was statistically significant ($P < 0.01$).

DISCUSSION

FDG-PET has been used as a very useful imaging modality for detecting malignant primary lesions and lymph node metastases. Very high sensitivity of the primary lesions, and the high sensitivity and specificity of lymph node metastases of the head and neck have often been reported [8–10]. RTP using FDG-PET has recently been performed in anticipation of more appropriate target planning [5, 6]. Many studies of lung cancer and head and neck cancer have been reported during the past decade [5–7, 10–17]; however, the efficacy of FDG-PET for RTP for various malignancies has not been well established [18]. Recently, Troost *et al.* [19] concluded that PET can characterize tumors for radiotherapy, which is a promising prospect, but unresolved issues remain and the applications are not yet ready for introduction into routine clinical practice.

Schinagl *et al.* [20] suggested that FDG-PET may be important for GTV definition, but the choice of a segmentation tool for target-volume definition based on PET images is not trivial and the absolute PET volume is dependent on the segmentation method. Several different threshold techniques for delineating tumors on PET have been used, and the choice of technique leads to large differences in target volume [5, 10].

In our institute, RTP is performed based on CT simulation using both CE-CT and FDG-PET or FDG-PET/CT images with a visual method [5, 7], and fusion of FDG-PET images and CT simulation is not performed. The institute definition of the target volume for PET-based RTP has been used for the past five years. PET-based GTV for RTP is defined using both CE-CT and FDG-PET images. When PET images are regarded as inappropriate for RTP due to false negatives or false positives, the GTV for RTP are determined using CE-CT images predominantly.

The present study has shown the utility of FDG-PET for RTP of head and neck cancer in patients with histologically proven squamous cell carcinoma. The addition of FDG-PET image information to the CE-CT image resulted in significant changes to the GTV for RTP in 19 cases (36%). The sensitivity of PET-GTV for the 53 primary tumor sites was 96%; however, that of CT-GTV was 81%; in patients with oropharyngeal cancer and those with tongue cancer, the sensitivity of CT-GTV was no more than 63% and 71% respectively, due to false negatives for artifacts, etc. Changes in the GTV using FDG-PET have been reported in several studies of head and neck cancer [5, 11–13], varying from 11% to 93%, and the PET-GTV was smaller in some cases and larger in other cases than the CT-GTV.

These results suggest that the additional use of FDG-PET is more effective for RTP than CE-CT alone and this will be recommended for defining the GTV for RT; however, the specificity for the identification of lesions could not be evaluated in this study because the cases were limited to patients with histologically proven cancer who had been referred to the Department of Radiation Oncology for RT.

Target delineation, or automated tumor contouring for RTP by FDG-PET, has often been demonstrated [5, 6, 10], but tumor contouring by PET was outside the scope of the present study. Target delineation for RTP by defining the percentage of the maximum standardized uptake value (SUV) of FDG has been reported [12, 13, 21]; however, this method may have limitations [22]. Tumor delineation using an SUV of 2.5 has been considered insufficient in other studies [20, 23]. Visual comparison of FDG-PET images and CT simulation [5, 7] was utilized in this study, and the visual correlation of FDG-PET and CT simulation yielded higher sensitivity for the identification of primary lesions of the head and neck cancer regardless of exact tumor contouring, as suggested above.

It has often been indicated that interobserver variability in target volume delineation of both head and neck cancer and lung cancer is reduced by using PET [24–28]; however, Breen *et al.* [29] reported that the addition of PET-CT to primary site GTV delineation of head and neck cancer did not change the GTV defined by expert observers and CE-CT would be more reliable than PET-CT. The present study suggests that the interobserver difference in target delineation will be decreased by using FDG-PET due to its excellent ability to identify primary gross tumors of the head and neck.

CONCLUSION

In conclusion, the results of this study have shown that FDG-PET is effective for defining the GTV in RTP for squamous cell carcinoma of the head and neck, and the sensitivity of FDG-PET for defining the primary tumor is higher than that of CE-CT alone. PET-GTV evaluated by both CE-CT and FDG-PET images is indicated to be preferable to CT-GTV by CE-CT alone, but further studies will be necessary to establish the standard use of FDG-PET for RTP. In particular, it would be desirable to perform more accurate GTV delineation by using other methods different from those mentioned above.

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