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

Chikae KAJITANI1,2, Isao ASAKAWA1, Fumiaki UTO3, Emiko KATAYAMA1, Kazuya INOUE1, Tetsuro TAMAMOTO1, Norihisa SHIRONE3, Hideyuki OKAMOTO4, Tadaaki KIRITA5 and Masatoshi HASEGAWA1,*

1Department of Radiation Oncology, Nara Medical University, 840 Shijo-cho, Kashihara 634-8522, Japan
2Department of Radiology, Yao Tokushukai General Hospital, 1-17 Wakakusa-cho, Yao 581-0011, Japan
3Department of Radiology, Takai Hospital, 461-2 Kuranosho-cho, Tenri, Nara 632-0006, Japan
4Department of Otorhinolaryngology – Head and Neck, Nara Medical University, 840 Shijo-cho, Kashihara 634-8522, Japan
5Department of Oral and Maxillofacial Surgery, Nara Medical University, 840 Shijo-cho, Kashihara 634-8522, Japan
*Corresponding author: Department of Radiation Oncology, Nara Medical University, 840 Shijo-cho, Kashihara 634-8522, Japan. Tel: +81-744-29-8908; Fax: +81-744-25-3434; Email: hasegawa@naramed-u.ac.jp

(Received 23 August 2011; revised 14 November 2012; accepted 3 December 2012)

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 18F-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 conformity 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]. 18F-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.

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 McNemar 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 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                 |
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, Table 2.

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

|                | CT-GTV | PET-GTV |
|----------------|--------|---------|
|                | n      | positive | Sensitivity | 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).
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).](image1)

![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).](image2)
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. 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).
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.

ACKNOWLEDGEMENTS

We thank Dr Takayuki Shinkai, Dr Hiroshi Okada, Dr Juichi TSUSHIMA, Dr Hitoshi Yoshimura and Prof. Kimihiko Kichikawa for their kind support and helpful advice. The results of this study were presented in part at the 51st Annual Meeting of the American Society for Therapeutic Radiology and Oncology, 1–5 November 2009, Chicago, IL, USA.

FUNDING

This study was partially supported by a Grant-in-Aid from the Ministry of Education, Science, Sports, and Culture of Japan (No. 22791216).

REFERENCES

1. Ling CC, Humm J, Larson S et al. Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality, Int J Radiat Oncol Biol Phys 2000;47:551–60.
2. Chapman JD, Bradley JD, Eary JF et al. Molecular (functional) imaging for radiotherapy applications: an RTOG symposium, Int J Radiat Oncol Biol Phys 2003;55:294–301.
3. Grosu AL, Piert M, Weber WA et al. Positron emission tomography for radiation treatment planning. Strahlenther Onkol 2005;181:483–99.
4. Nimmagadda S, Ford EC, Wong JW et al. Targeted molecular imaging in oncology: focus on radiation therapy, Semin Radiat Oncol 2008;18:136–48.
5. Paulino AC, Teh BS. PET-CT in Radiotherapy Treatment Planning. Philadelphia: Saunders Elsevier, 2005.
6. MacManus M, Nestle U, Rosenzweig KE et al. Use of PET and PET/CT for radiation therapy planning: IAEA expert report 2006–2007. Radiother Oncol 2009;91:85–94.
7. Devic S, Tomic N, Faria S et al. Defining radiotherapy target volumes using 18F-fluoro-deoxy-glucose positron emission tomography/computed tomography: still a Pandora’s box? Int J Radiat Oncol Biol Phys 2010;78:1555–62.
8. Conti PS, Lilien DL, Hawley K et al. PET and 18F-FDG in oncology: a clinical update. Nucl Med Biol 1996;23:717–35.
9. Di Martino E, Nowak B, Hassan HA et al. Diagnosis and staging of head and neck cancer: a comparison of modern imaging modalities (positron emission tomography, computed tomography, color-coded duplex sonography) with panendoscopic and histopathologic findings. Arch Otolaryngol Head Neck Surg 2000;126:1457–61.
10. Ahn PH, Garg MK. Positron emission tomography/computed tomography for target delineation in head and neck cancers. Semin Nucl Med 2008;38:141–8.
11. Nishioka T, Shiga T, Shirato H et al. Image fusion between 18FDG-PET and MRI/CT for radiotherapy planning of oro-pharyngeal and nasopharyngeal carcinomas. Int J Radiat Oncol Biol Phys 2002;53:1051–7.
12. Scarfone C, Lavelly WC, Cmelak AJ et al. Prospective feasibility trial of radiotherapy target definition for head and neck cancer using 3-dimensional PET and CT imaging. J Nucl Med 2004;45:543–52.
13. Paulino AC, Koshy M, Howell R et al. Comparison of CT- and FDG-PET-defined gross tumor volume in intensity-modulated radiotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2005;61:1385–92.
14. Schwartz DL, Ford EC, Rajendran J et al. FDG-PET/CT-guided intensity modulated head and neck radiotherapy: a pilot investigation. Head Neck 2005;27:478–87.
15. Riegel AC, Berson AM, Destian S et al. Variability of gross tumor volume delineation in head-and-neck cancer using CT and PET/CT fusion. Int J Radiat Oncol Biol Phys 2006;65:726–32.
16. Henriques de Figueiredo B, Barret O, Demeaux H et al. Comparison between CT- and FDG-PET-defined target volumes for radiotherapy planning in head-and-neck cancers. Radiother Oncol 2009;93:479–82.
17. Grégoire V, Chiti A. Molecular imaging in radiotherapy planning for head and neck tumors. J Nucl Med 2011;52:331–4.
18. Daisne J-F, Duprez T, Weynand B et al. Tumor volume in pharyngolaryngeal squamous cell carcinoma: comparison at CT, MR imaging, and FDG PET and validation with surgical specimen. Radiology 2004;233:93–100.
19. Troost EG, Schinagl DA, Bussink J et al. Clinical evidence on PET-CT for radiation therapy planning in head and neck tumours. Radiother Oncol 2010;96:328–34.
20. Schinagl DA, Vogel WV, Hoffmann AL et al. Comparison of five segmentation tools for 18F-fluoro-deoxy-glucose-positron emission tomography-based target volume definition in head and neck cancer. Int J Radiat Oncol Biol Phys 2007;69:1282–9.
21. Bradley J, Thorstad WL, Mutic S et al. Impact of FDG-PET on radiation therapy volume delineation in non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2004;59:78–86.
22. Uto F, Shiba E, Onoue S et al. Phantom study on radiotherapy planning using PET/CT – delineation of GTV by evaluating SUV. J Radiat Res 2010;51:157–64.
23. Wang D, Schultz CJ, Jursinic PA et al. Initial experience of FDG-PET/CT guided IMRT of head-and-neck carcinoma. Int J Radiat Oncol Biol Phys 2006;65:143–51.
24. Syed R, Bomanji JB, Nagabhushan N et al. Impact of combined 18F-FDG PET/CT in head and neck tumours. Br J Cancer 2005;92:1046–50.
25. Geets X, Daisne JF, Arcangeli S et al. Inter-observer variability in the delineation of pharyngo-laryngeal tumor, parotid glands and cervical spinal cord: comparison between CT-scan and MRI. Radiother Oncol 2005;77:25–31.
26. Ashamalla H, Rafla S, Parikh K et al. The contribution of integrated PET/CT to the evolving definition of treatment volumes in radiation treatment planning in lung cancer. Int J Radiat Oncol Biol Phys 2005;63:1016–23.
27. Fox JL, Rengan R, O’Meara W et al. Does registration of PET and planning CT images decrease interobserver and intraobserver variation in delineating tumor volumes for non-small-cell lung cancer? Int J Radiat Oncol Biol Phys 2005;62:70–5.
28. Hanna GG, McAleese J, Carson KJ et al. 18F-FDG PET-CT simulation for non-small-cell lung cancer: effect in patients already staged by PET-CT. Int J Radiat Oncol Biol Phys 2010;77:24–30.
29. Breen SL, Publicover J, De Silva S et al. Intraobserver and interobserver variability in GTV delineation on FDG-PET-CT images of head and neck cancers. Int J Radiat Oncol Biol Phys 2007;68:763–70.