

Title: Comparative evaluation of respiratory-gated and ungated FDG-PET for target volume definition in radiotherapy treatment planning for pancreatic cancer

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Running head: ITV definition from 4D-PET

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1 Abstract

2 Objective

3 The purpose of this study was to evaluate the usefulness of respiratory-gated positron emission
4 tomography (4D-PET) in pancreatic cancer radiotherapy treatment planning (RTTP).

5 Materials and Methods

6 Fourteen patients with 18F-fluorodeoxyglucose (FDG)-avid pancreatic tumours were evaluated between
7 December 2013 and March 2015. Two sets of volumes were contoured for the pancreatic tumour of each
8 patient. The biological target volume in three-dimensional RTTP (BTV3D) was contoured using
9 conventional respiratory un-gated PET. The BTV3D was then expanded using population-based margins
10 to generate a series of internal target volume 3D (ITV3D) values. The ITV 4D (ITV4D) was contoured
11 using 4D-PET. Each of the five phases of 4D-PET was used for 4D contouring, and the ITV4D was
12 constructed by summing the volumes defined on the five individual 4D-PET images. The relative
13 volumes and normalized volumetric overlap were computed between ITV3D and ITV4D.

14 Results

15 On average, the FDG-avid tumour volumes were 1.6 (range: 0.8–2.3) fold greater in the ITV4D than in
16 the BTV3D. On average, the ITV3D values were 2.0 (range: 1.1–3.4) fold larger than the corresponding
17 ITV4D values.

18 Conclusion

19 The ITV generated from 4D-PET can be used to improve the accuracy or reduce normal tissue irradiation
20 compared with conventional un-gated PET-based ITV.

21

1 Introduction

2 Pancreatic cancer is the fifth most common cancer and the fourth leading cause of cancer-related
3 mortality worldwide. In the United States, 46,420 people are expected to be diagnosed with pancreatic
4 cancer, and 39,590 are expected to die of the disease in 2014 [1]. Approximately 30% of patients with
5 pancreatic cancer are diagnosed with unresectable, locally advanced pancreatic cancer (LAPC), and their
6 prognosis is poor, with a 5-year survival rate <5% [2]. Local relapse with or without distant metastasis
7 occurs in 30 to 50% of patients receiving definitive chemoradiotherapy (CRT) for LAPC [3–6], and the
8 causes of death in patients with LAPC are often related to locally destructive complications [7].

9 The latest technological innovations in RT, including intensity modulated radiation therapy (IMRT) or
10 stereotactic body radiation therapy (SBRT), allow precise local dose conformation, resulting in selective
11 tumour irradiation and dose sparing of normal adjacent organs and dose escalation of RT or concurrent
12 chemotherapy [8–10]. Thus, RT could play an important role in the local control of LAPC, although PC is
13 relatively radio-resistant, and neighbouring organs such as the duodenum, stomach, and intestines are
14 highly sensitive to radiation. Therefore, minimization of the dose to the normal neighbouring organs is a
15 critical issue, and the tumour must be accurately recognized to be used for RT planning. On the other
16 hand, the target definition is difficult in LAPC, because the pancreatic tumour moves during respiration.
17 According to previous studies using several modalities including fluoroscopy, ultrasound, magnetic
18 resonance imaging, and four-dimensional computed tomography (4D-CT), the magnitude of the
19 respiratory motion is as large as 20 mm [11–14]. The margins to account for the motion of pancreatic
20 tumours vary by institution and range from 1 to 2 cm or more. Feng et al. suggested that small 1-cm
21 margins may not provide complete geometric coverage [14]. However, the indiscriminate use of such
22 population-based margins could result in excessive irradiation of normal tissues in many cases.

23 The usefulness of positron emission tomography (PET) with ¹⁸F-fluorodeoxyglucose (FDG) has been
24 reported in pancreatic cancer RT planning [15]. They mentioned the need for respiratory-gated PET (4D-
25 PET), because pancreatic tumours move throughout the breathing cycle. Several authors have reported on
26 the benefit of 4D-PET for target volume delineation in various cancers [16–22]. Lamb et al. reported on
27 the clinical usefulness of 4D-PET for RT planning [20]. They concluded that 4D-PET can be used to

improve the accuracy and reduce normal tissue irradiation compared with conventional respiratory ungated PET (3D-PET). To the best of our knowledge, no data are available to evaluate 4D-PET in pancreatic cancer RT planning.

The purpose of this study was to evaluate the usefulness of 4D-PET in pancreatic cancer RT planning.

Materials and methods

Patients

Twenty-one consecutive patients who underwent 4D-PET for histologically proven pancreatic tumours from September 2013 to May 2015 were recruited for the present study. Among the recruited patients, seven patients whose tumours did not show metabolic activity were excluded. The remaining 14 patients with FDG-avid pancreatic tumours were considered eligible for the present study. All of the patients underwent 4D-PET before treatment. The patient characteristics are summarized in Table 1. The patients consisted of six females (43%) and eight males (57%), and the median age was 67 years (range, 53–78 years). Histological confirmation for adenocarcinoma was performed for all of the patients. The tumour clinical stage was III, called LAPC, in 11 patients (79%) according to the 7th edition of the Union Internationale Contre le Cancer. The clinical stages of the other tumours were IIA in 1 patient (7%), IIB in 1 patient (7%), and IV in 1 patient (7%). We also included these tumours in the present study, because this study did not focus on the clinical outcome after CRT for LAPC but rather RT treatment planning.

This study was approved by the Institutional Review Board of the Kyoto University, Kyoto, Japan (approval number R0151).

4D-PET protocol

4D-PET was performed using a combined PET/CT scanner (Discovery ST Elite; GE Healthcare Waukesha, WI, USA). All of the patients fasted for at least 6 hours before the administration of FDG. The plasma glucose level was checked immediately before the injection of FDG and was confirmed to be less than 120 mg/dL in all of the patients. Data acquisition started approximately 60 min after the injection of

a standard dose of 200–250 MBq. Low-dose CT scans were acquired during shallow breathing initially starting at the level of the thigh using a 16-detector row scanner with the following parameters: 20–100 mAs, 120 kV, 0.6-second tube rotation, 3.75-mm section thickness, 512×512 matrix, and a pitch of 1.75. Immediately after the CT scans were acquired, whole-body 3D-PET scanning was performed using an acquisition time of 2 min per bed position and respiratory-gated PET thereafter. The respiratory-gated PET was applied to the upper abdomen, including the pancreas. Data acquisition was performed for 10 min without holding the breath. The same CT scan data were used for attenuation correction and registration for both PET scans, and images were reconstructed using a 3D iterative reconstruction algorithm VUE Point Plus. The respiratory gating system consisted of the Real-time Position Management (RPM) system respiratory gating hardware (Varian Medical Systems Inc., Palo Alto, CA, USA). The respiration cycle was divided into five phases, and 2-min acquisition images were reconstructed for each respiratory phase. These five respiratory data sets were reconstructed using a phase-sorting algorithm.

Target volume delineation

Target volumes were delineated using the MIM maestro version 6.1 software (MIM Software Inc., Cleveland, OH, USA). Two sets of target volumes were contoured for the pancreatic tumour of each patient. For the first target volume, the three-dimensional biological target volume (BTV3D) was contoured using 3D-PET. Next, the BTV3D was expanded by asymmetric margins to generate a series of internal target volume 3D (ITV3D) values. The ITV margins were expanded asymmetrically by 1.0, 0.7, and 0.6 cm along the respective superoinferior (SI), anteroposterior (AP), and medial-lateral (ML) directions, based on Goldstein's report [23]. For the second target volume, the ITV4D was contoured using 4D-PET. Each of the five phases of the 4D-PET was used for 4D contouring, and the ITV4D was constructed by summing the volumes defined on the five individual 4D-PET scans. Both the BTV3D and ITV4D were defined using the automatic definition technique. For each of the areas identified by a radiation oncologist in the first step, the volume was defined using an automatic threshold of 50% of the maximum standardized uptake value (SUV) of the lesion. This threshold has been suggested and also used in previous reports, as the 50% SUVmax showed the best agreement with the pathology [24,25].

1 Analysis

2 We measured the tumour motions and tumour volumes from the 3D and 4D-PET scans. Tumour motion
3 was calculated by the movement of the geometric centre of the FDG-avid tumour in all phases of 4D-PET.
4 The displacement along the SI, AP, and ML axes and total displacement vector were assessed. BTV3D
5 and ITV4D were used to compare the volumes of FDG-avid tumour, while ITV3D and ITV4D were used
6 to compare the ITVs. Non-parametric Wilcoxon matched-pair tests were used for comparison between
7 BTV3D and ITV4D and between ITV3D and ITV4D. A two-tailed p value less than 0.05 was used to
8 indicate statistical significance.

9 All of the statistical analyses were performed using EZR version 1.26 (Saitama Medical Center, Jichi
10 Medical University, Saitama, Japan), which is a graphical user interface for R version 3.1.1 (The R
11 Foundation for Statistical Computing, Vienna, Austria).

12

13 Results

14 Respiratory motion

15 FDG-avid tumours moved an average of 9.2, 2.7, and 3.1 mm, with ranges of 3.1–17.8, 0.7–9.4, and 0.4–
16 11.9 mm, in the SI, AP, and ML directions, respectively. The respiratory motions of the tumours were
17 greater than the above population-based margin in 6 of 14 (43%) tumours.

18 SUV

19 The SUV threshold was significantly higher using 4D-PET than 3D-PET ($p<0.001$). The median SUV
20 threshold values were 9.19 (range: 6.35–15.53) and 7.51 (range: 4.92–12.69), respectively.

21 Target volume delineation

22 The median BTV3D, ITV4D, and ITV3D values were 11.64, 14.15, and 24.33 mL, respectively (range:
23 2.16–15.66, 7.83–31.61, and 8.74–44.98 mL, respectively). FDG-avid tumours were, on average, $1.6 \pm$
24 0.7 fold greater in ITV4D than in BTV3D (Figure 3a; $p<0.001$). The ITV3D values were, on average, 2.0

± 0.6 fold larger than the corresponding ITV4D values (Figure 3b; $p < 0.001$). Nonetheless, ITV3D failed to adequately cover the ITV4D in 6 out of 14 (43%) tumours (Figure 2g–l).

Discussion

In this study, we evaluated the usefulness of 4D-PET in pancreatic cancer RT planning. The tumour volume was significantly larger when delineated using 4D-PET than 3D-PET. By contrast, the ITV defined using 4D-PET was significantly smaller than that using 3D-PET. To our knowledge, this is the first study comparing the target volume defined using 4D-PET and 3D-PET in pancreatic cancer RT planning.

The pancreatic tumour motion was readily visible in 4D-PET images in this study, and the degree of motion observed was consistent with that described in published reports [11–14]. Kim et al. analysed pancreas movement using 4D-CT in nine volunteers and found that the mean motions of the pancreatic head and tail were 12.8 and 13.0 mm, respectively [13]. To our knowledge, this is also the first report concerning the respiratory motion of pancreatic cancer analysed by 4D-PET.

The effect of 4D-PET in the diagnostic imaging of pancreatic tumours, including pancreatic cancer, was reported by a few authors [25,26]. Yukutake et al. evaluated 36 patients with pancreatic cancer and found that 4D-PET reduced respiratory motion artefacts and allowed a significantly higher SUVmax. They reported a median SUVmax of 8.1 ± 2.5 and 6.2 ± 2.1 in 4D-PET and 3D-PET respectively ($p < 0.01$) [25].

In our study, the median values were 9.19 (range: 6.35–15.53) and 7.51 (range: 4.92–12.69), respectively.

The results of our study agreed with those of previous studies.

Several authors have previously evaluated the usefulness of 4D-PET in RT treatment planning of tumour motion during respiration. For example, Lamb et al. generated the lung tumour ITV from 4D-PET in three patients with four tumours and found that PET-maximum intensity projection (MIP) images matched CT-MIP images better than 3D-PET images [16]. Aristophanous et al. examined the clinical usefulness of 4D-PET in RT planning in 10 patients with NSCLC and demonstrated that the target volume defined by 4D-PET was significantly larger than that by 3D-PET ($p < 0.01$) [17]. Our data also showed that ITV4Ds

1 were significantly larger than BTV3Ds. In fact, ITV4Ds were derived from respiratory-gated images and
2 included respiratory motion. The results of our study agreed with those of previous studies. However,
3 ITV4Ds were smaller than BTV3Ds in two patients (tumour 11, 13). There are two possible reasons. First,
4 the breathing patterns of patients might be changed between 3D- and 4D-PET [28]. Second, the SUVmax
5 of tumours in 4D-PET was much higher than that in 3D-PET. The target volume was defined using an
6 automatic threshold of 50% SUVmax of the tumour; therefore, when the SUVmax was high, the target
7 volume might have been small. Indeed, the SUVmax of tumours 13 and 11 in 4D-PET were 1.92 and 1.34
8 fold higher than those in 3D-PET, respectively, and these changes were the greatest and the third greatest
9 in 14 tumours (median: 1.18).

10 Moreover, 4D-PET could significantly decrease the ITV compared with 3D-PET, but ITV4D values still
11 exceeded ITV3D values in 6 of 14 (43%) tumours. Two reasons are possible. The first is that the
12 respiratory motions of the tumours were greater than the population-based margin used in the present
13 study; the second reason is the presence of a baseline drift of the tumours. First, Goldstein et al. contoured
14 pancreatic tumours in planning 4D-CT and found that an asymmetric expansion of 1.0, 0.7, and 0.6 cm
15 along the respective SI, AP, and ML directions is recommended if respiratory-correlated 4D-CT is not
16 available to evaluate tumour motion during treatment planning [23]. The latter finding could have resulted,
17 in part, from 4D-CT pancreatic tumour sample motion over a small time period. An additional benefit of
18 4D-PET over 4D-CT could be the tumour sample motion over the time of the entire PET bed imaging, 10
19 min in our study, which could help capture variations in tumour motion amplitude and baseline [20].
20 Indeed, the respiratory motions of the tumours were greater than the above population-based margin in
21 43% of tumours in this study, and Minn et al. reported that 4D-CT scans cannot accurately predict the
22 movement of pancreatic tumours during actual treatment [27]. Second, it is possible that the patients'
23 breathing pattern changed between the 3D and 4D-PET scan acquisitions [28].

24 Elective nodal irradiation is controversial for LAPC; therefore, involved-field RT (IFRT) is also used in
25 clinical practice. Although non-standard treatments, simultaneous integrated boost IMRT and SBRT are
26 also performed for LAPC. The identification of positive lymph nodes is more important in these
27 treatments. Aristophanous et al. evaluated 10 patients with NSCLC and showed that 4D-PET resulted in
28 the detection of additional suspicious positive lymph nodes that had been overlooked on 3D-PET in one

1 patient [17]. Yukutake et al. reported that 4D-PET allowed a significantly higher SUVmax, and the rate of
2 increase in SUVmax tended to be higher in lesions less than or equal to 2 cm in diameter in the study of
3 pancreatic cancer [25]. More accurate characterization of 4D-PET may be useful in these treatments.

4 The results of the present study indicate that 4D-PET is more accurate for ITV generation in the context
5 of FDG-avid pancreatic tumours. Moreover, Whitfield et al. reported that inter-patient variations were
6 greater than intra-patient variations, indicating a need for a patient-individualised approach to improve
7 targeting [29]. Where available, 4D-PET should be preferred for the generation of ITVs.

8 Murphy et al. showed that PTV volume correlated with significant gastrointestinal toxicity [30].
9 Shrinking the target volume becomes then more important. Apart from 4D-PET another strategy for
10 reducing the target volume is the management of respiratory motion. Although specialized RT
11 equipments can perform dynamic tracking of moving targets, respiratory motion management options
12 commonly used on a conventional RT machine are end-exhalation or deep inhalation breath-hold, and
13 respiratory gating. 4D-PET can also be used for target delineation in RT treatment planning for breath-
14 hold or respiratory gating. In our study, the median value of the ITV for respiratory gating RT,
15 constructed by summing the volumes defined on 2 exhale phases (40% and 60% of 4D-PET), was 11.16
16 mL (range: 4.17-18.47) and this contributed 21% reduction of ITV4D. Abdominal compression is also the
17 respiratory motion management technique and enables to shrink the target volume. However, there
18 remains concern about the reproducibility of the setup between simulation and each treatment [31].
19 Furthermore, abdominal compression system attenuates beams, so that dosimetric uncertainties or
20 constraints on gantry angle are increased. Therefore, reducing the target volume by 4D-PET might be
21 useful way than abdominal compression.

22 This study had several limitations. First, only one method was applied for the contouring of target
23 volumes. However, it has been commonly used in previous reports and commercially implemented in the
24 workstation used for contouring. Moreover, there is no standard reference for metabolic target lesion
25 contouring. Further studies combined with pathologic specimens are required to identify the optimal
26 threshold of automated segmentation algorithms to define the pancreatic tumour. Second, we did not
27 assess the interfractional positional variations. A single 4D-PET was acquired over a few minutes;

1 therefore, it cannot consider all of the random variations that could occur in the position of pancreatic
2 tumours resulting from nonrespiratory organ motion during daily treatment. Shiinoki et al. evaluated
3 interfractional reproducibility in the pancreatic position based on 4D-CT in 15 patients with pancreatic
4 cancer and found that the means of the interfractional positional variation were 0.9, 1.9, and 1.3 mm in
5 the LR, AP, and SI directions, respectively [32]. Third, we did not make the spatial and dosimetric
6 assessment of normal tissue irradiation, as the 4D-CT was not performed to avoid an additional radiation
7 exposure to patients. Further investigations of sparing normal tissue are warranted to evaluate the
8 contribution of 4D-PET combined with 4D-CT.

9 In conclusion, we demonstrated the usefulness of 4D-PET in pancreatic cancer RT planning. The use of
10 4D-PET in LAPC RT planning can reduce the ITV. ITV generated from 4D-PET can be used to improve
11 the accuracy or to reduce normal tissue irradiation compared with the ITV based on 3D-PET.

12 13 Acknowledgement

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- 2 on four-dimensional computed tomography. *Int J Radiat Oncol Biol Phys.* 2011;80:1567-72.

3

1 **Figure legends**

2 Figure 1. Comparison of the maximum standardized uptake value (SUVmax) in respiratory ungated
3 positron emission tomography (3D-PET) and respiratory-gated PET (4D-PET).

4 Figure 2. Sagittal slices of tumour 2. Biological target volume in the third dimension (BTV3D) (cyan) and
5 internal target volume in the fourth dimension (ITV4D) (magenta) were delineated on (a) respiratory
6 ungated positron emission tomography (3D-PET); (b) respiratory-gated PET (4D-PET) 0%; (c) 4D-PET
7 20%; (d) 4D-PET 40%; (e) 4D-PET 60%; (f) 4D-PET 80%. ITV3D (green) and ITV4D (magenta) were
8 delineated on (g) 3D-PET; (h) 4D-PET 0%; (i) 4D-PET 20%; (j) 4D-PET 40%; (k) 4D-PET 60%; and (l)
9 4D-PET 80%.

10 Figure 3a. Comparison of fluorooxyglucose (FDG)-avid tumours using respiratory ungated positron
11 emission tomography (3D-PET) and respiratory-gated PET (4D-PET).

12 Figure 3b. Comparison of the internal target volume using 3D-PET and 4D-PET.

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2 editors, both native speakers of English. For a certificate, please see:
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