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Is there any impact of PET/CT on radiotherapy planning in rectal cancer patients undergoing preoperative IMRT?

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Background/aim: To investigate the effect of positron emission tomography-computed tomography (PET/CT)-based contouring on dosimetric parameters in rectal cancer patients undergoing preoperative intensity-modulated radiation therapy (IMRT).

Materials and methods: Preoperative radiation therapy plans with conformal radiotherapy (CRT) or IMRT were created and examined according to the CT- and PET/CT-based contouring of 20 rectal cancer patients, retrospectively.

Results: The target volumes delineated with PET/CT were significantly larger than the volumes created by CT (P = 0.043). Dose delivered to 98% of the planning target volume was high in IMRT planning contouring with CT and PET/CT compared with CRT planning, but the difference was not statistically significant (P = 0.056). Percent volumes receiving 105% of dose and 110% of dose were low in IMRT planning when compared with CRT (P < 0.0001 and P = 0.044, respectively). The volumes receiving 45 Gy for the small intestine, femur heads, and bladder and the maximum dose received by the bladder were significantly lower in IMRT.

Conclusion: We showed that the target volumes created with PET/CT are significantly larger than the target volumes created with CT and that IMRT provides lower radiation exposure to the tumor-free tissues compared to the CRT planning. The dosimetric results primarily favor IMRT planning in rectal cancer patients and consequently present the significant alteration in target volumes.

Key words: Intensity-modulated radiation therapy, PET/CT, rectal cancer, conformal radiotherapy, computed tomography

1. Introduction

Colorectal cancer is the third most common malignancy after breast and lung cancers. Although surgery is accepted as the main treatment strategy in colon cancer, a multidisciplinary approach including surgery, radiotherapy, and chemotherapy is usually necessary in rectal cancer (1). Long-course chemoradiotherapy or short-course radiotherapy followed by surgery is the standard protocol in the management of locally advanced rectal cancer (LARC) (2,3). After the German trial CAO/ARO/AIO-94, preoperative radiotherapy combined with chemotherapy followed by surgery and adjuvant chemotherapy is now widely accepted as the standard of care for patients with stage II–III rectal cancer (4). The results of the CAO/ARO/AIO-94 study emphasized low toxicity, downstaging, sphincter preservation, and high local control rates through an accurate delineation of tumor extent with preoperative chemoradiotherapy (5).

Although conventional computerized tomography (CT) is the standard imaging technique in radiation planning for rectal cancer, it has considerably low sensitivity and specificity toward the primary tumor and the lymph nodes (6). The target volume created with CT frequently does not fit to the true tumor volume in clinical practice (7). Therefore, more precise assessment tools are necessary to show local and distant tumor extensions in rectal cancer.

Recently, new imaging techniques for tumor visualization, such as positron emission tomography-computed tomography (PET/CT), have begun to have a major impact on radiation therapy planning (8), although PET/CT is still gaining acceptance for its use in many tumor types. Nevertheless, in rectal cancer, a PET/CT-based tumor volume definition may provide higher local control rates given the accurate tumor delineation, defined as 'biologic target volume', obtained through metabolic information (9). Furthermore, PET-directed irradiation, which has been shown to facilitate dose escalation in the tumor and reduce toxicity to normal tissue in various tumors, can be used in LARC (10).

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Dose escalation can improve local tumor control in rectal cancer. However, the toxicity to surrounding normal tissue is an important dose-limiting factor. Therefore, intensity-modulated radiation therapy (IMRT) might be effective in minimizing this problem. IMRT also allows better dose conformity and improved possibility of closely tailoring the dose distribution around the target compared to 3-dimensional conformal radiotherapy (CRT) techniques (11,12). Moreover, using PET/CT in conjunction with IMRT may have additional advantages in rectal cancer radiation therapy. Despite the existence of cumulative data on the use of PET/CT in CRT planning, to our best knowledge, there is no published study observing the potential benefits of PET/CT in IMRT planning for rectal cancer.

The aim of the present dosimetric study is to elucidate the effect of PET/CT-based contouring on the target volumes and critical structures in LARC patients undergoing preoperative radiation therapy with either CRT or IMRT planning.

2. Materials and methods

This study was conducted in Gazi University Hospital, Department of Radiation Oncology, Turkey. The study design was approved by the local ethics committee. The data of rectal cancer patients who received preoperative chemoradiotherapy with the diagnosis of LARC between March 2008 and July 2011 were retrospectively evaluated. Twenty patients who had PET/CT on their initial evaluation were enrolled.

The radiation treatment planning data and PET/CT and CT images of the patients were reloaded into our radiation treatment planning system. The target volumes were contoured by a radiation oncologist with experience in colorectal cancer treatment according to the guidelines of the International Commission on Radiation Units and Measurements Report 62 (13). First, all radiologically visible tumors were contoured as the gross tumor volume according to the CT findings (GTV_{tm-CT}). Secondly, $GTV_{tm-PET/CT}$ was delineated on PET/CT fused images using axial images and the window and level settings found most appropriate for each patient. Autocontouring for tumor delineation on PET/CT fused images was not used. Since all of the target volumes were greater than 4 cm^3, a fixed threshold value of 40% of the maximum uptake in the lesion to define $GTV_{tm-PET/CT}$ was chosen (14). The tumor clinical target volume (CTV_{tm}) was contoured for microscopic disease with a 1.5 cm additional margin peripherally and 2.5 cm craniocaudally over the GTV_{tm-CT}/$GTV_{tm-PET/CT}$. The lymph node clinical target volume (CTV_{node}) was delineated according to the Radiation Therapy Oncology Group (RTOG) guidelines of colorectal cancer treatment planning. The planning target volume (PTV_{CT}/$PTV_{PET/CT}$) was created with an additional 0.5 cm margin over the CTV_{CT}/$CTV_{PET/CT}$ (15). The small intestines were contoured as the complete peritoneal cavity and were defined as organs at risk (OAR) together with the bladder and femoral heads.

Radiation fields were designed as 2 lateral wedged fields and 1 posterior field for CRT planning and the 5-field technique was applied for IMRT planning. The radiation dose was defined as 1.8 Gy/fx up to a total dose of 45 Gy, for both CRT and IMRT planning. For each patient, 2 different CRT plans were developed: a CT-guided plan and a PET/CT-guided plan. Similarly, 2 IMRT plans were developed for the same patient. Thus, 4 different plans were created for each patient, namely 3D CRT-CT, 3D CRT-PET/CT, IMRT-CT, and IMRT-PET/CT.

Dose limits in IMRT plans for the small intestine (small intestine ≤180 cm^3, dose limit >35 Gy; small intestine ≤100 cm^3, dose limit >40 Gy; small intestine ≤65 cm^3, dose limit >45 Gy; no small intestine, dose limit >50 Gy.), femoral heads (femoral heads ≤40%, dose limit >40 Gy; femoral heads ≤25%, dose limit >45 Gy; no femoral head, dose limit >50 Gy), and bladder (bladder ≤40%, dose limit >40 Gy; bladder ≤15%, dose limit >45 Gy; no bladder, dose limit >50 Gy) were applied according to the RTOG 0822 protocol (15). The percent dose delivered to 98% of the planning target volume (PTV D98), percent volumes that received 105% of the dose (V105), percent volumes that received 110% of the dose (V110), and percent volumes that received 115% of dose (V115) were generated on dose-volume histograms. Doses received by OAR were also evaluated; the small intestine received percent volumes of 35 Gy, 40 Gy, and 45 Gy (V35, V40, V45) and the femoral heads and bladder received percent volumes of 40 Gy and 45 Gy (V40, V45).

All the data were collected in a database and were verified by a second independent physician. Descriptive statistics were generated for all study variables, including mean and standard deviation (SD) or median and range for continuous variables and relative frequencies and percentages for categorical variables.

The PET-GTV and PET-CTV were compared with CT-GTV and CT-CTV by Wilcoxon rank test for paired data. All data were reported as mean ± SD and 95% confidence interval (CI) for continuous variables, or as a percentage with 95% CI calculated using binomial distribution. Statistical analysis was performed using SPSS 16 for Windows, (SPSS Inc., Chicago, IL, USA).

The results of the planning data (3D CRT-CT, 3D CRT-PET/CT, IMRT-CT, and IMRT-PET/CT) were compared by Kruskal–Wallis test and 2 independent groups were evaluated by Mann–Whitney U-test. Consistency with RTOG 0822 protocol was compared by chi-square test. $P < 0.05$ was considered statistically significant.

3. Results

The volumes delineated by PET ($CTV_{PET/CT}$) were significantly larger than the volumes defined according to the CT findings (CTV_{CT}) (P = 0.043) (Table 1). The median $CTV_{PET/CT}$ was 559.73 mm^3 (minimum 226.32 mm^3; maximum 857.62 mm^3), and the median CTV_{CT} was 468.43 mm^3 (minimum 226.32 mm^3; maximum 750.15 mm^3). The conformity index was approximately 1 in IMRT planning with PET/CT contouring. There was no statistically significant difference among all 4 groups with regards to conformity indexes. Homogeneity indexes in IMRT planning were statistically better than in CRT planning. D98 PTV was higher in IMRT planning, but the difference did not reach a statistically significant level (P = 0.056). V_{105} and V_{110} were lower in IMRT planning than in CRT planning (P < 0.0001 and P = 0.044, respectively). V_{105} median values were 15.71% in CT-CRT, 16.28% in PET/CT-CRT, 1.25% in CT-IMRT, and 1.26% in PET/CT-IMRT.

V_{45} values of the small intestine, femoral heads, and bladder were statistically lower in IMRT planning (Table 2). The maximum dose received by the bladder was lower in IMRT planning than in CRT planning and this was statistically significant (P < 0.0001).

Therefore, it is demonstrated that the isodose distribution correlates more precisely to the tumor volume in IMRT planning than in CRT planning (Figures 1A–1D).

4. Discussion

To our knowledge, this is the first dosimetric study demonstrating the value of PET/CT in target delineation for preoperative IMRT planning in rectal cancer. According to our results, CRT or IMRT plans created with the guidance of PET/CT were not superior to the CRT and IMRT plans created with the guidance of CT. However, we showed that CTV as delineated with the guidance of PET/CT was significantly larger than the CTV delineated with the guidance of CT.

Table 1. Clinical target volumes of 20 LARC patients created by CT and PET/CT. CTV = Clinical target volume; CT = computed tomography; PET = positron emission tomography.

Patient no.	CTV by CT (mm^3)	CTV by PET/CT (mm^3)	Altered CTV by PET/CT(mm^3)
1	324.72	390.94	+66.22
2	750.15	857.67	+107.52
3	499.64	523.93	+24.29
4	349.07	418.26	+69.19
5	448.10	463.90	+15.8
6	572.01	618.57	+46.56
7	492.54	593.13	+100.59
8	456.78	509.40	+52.62
9	370.01	367.42	–2.59
10	494.72	666.37	+171.65
11	350.99	457.30	+106.31
12	654.80	638.37	–16.43
13	483.85	576.17	+92.32
14	480.07	560.06	+79.99
15	287.28	322.05	+34.77
16	226.32	226.32	0
17	417.49	500.82	+83.33
18	577.11	590.10	+12.99
19	403.57	440.16	+36.59
20	612.75	626.14	+13.39

Table 2. The output of planning (CT-CRT, PET/CT-CRT, CT-IMRT, PET/CT-IMRT) in terms of critical structures. CT = Computed tomography; CRT = conformal radiation therapy; IMRT = intensity-modulated radiation therapy; PET = positron emission tomography.

Volume receiving 45 Gy	CT-CRT (median, cm^3)	PET/CT-CRT (median, cm^3)	CT-IMRT (median, cm^3)	PET/CT-IMRT (median, cm^3)	P-values
Small intestine	116.50	122.30	61.50	67.75	0.026
Femoral heads	4.75	6.00	2.91	1.70	0.008
Bladder	87.55	86.85	55.00	55.00	<0.0001

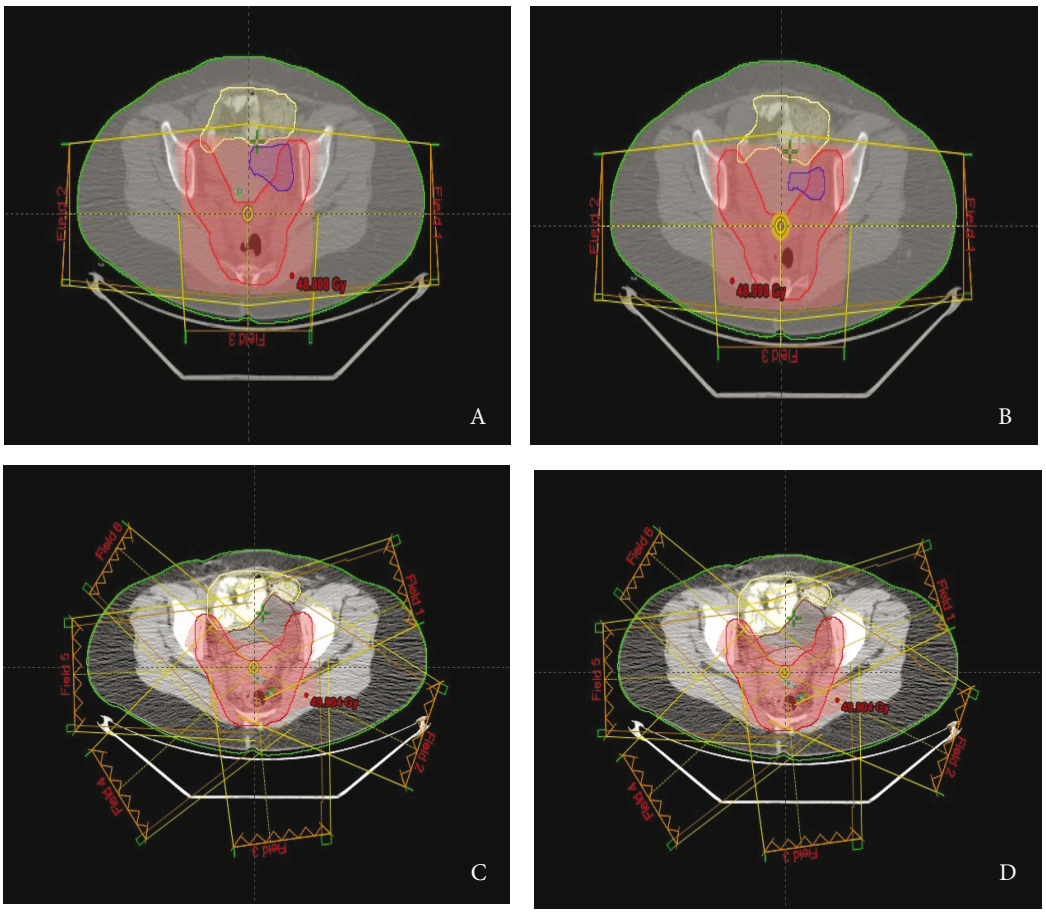

Figure 1. The conformal radiation therapy (CRT) plans with CT contouring **(A)** and with PET-CT contouring **(B)**. The intensity-modulated radiation therapy (IMRT) plans with CT contouring **(C)** and with PET-CT contouring **(D)**.

Similarly, Anderson et al. reported the data of 25 patients with rectal cancer and showed that integration of PET data altered the PTV in 17% of patients and the radiation treatment-planning process was changed in 26% of patients (16). In contrast to our study, this study evaluated PET/CT in conventional CRT planning.

Ciernik et al. evaluated the application of PET/CT in radiation planning of patients with rectal cancer (17). An increase in GTV was observed in approximately half of the patients (56%), with a mean GTV increase of 50% and a PTV increase of 20%. The results of our study also showed that target volumes contoured with PET/CT were larger than volumes contoured with CT and this was statistically significant (P = 0.043).

PET is a functional and valuable method that was used as a research tool for over 25 years before it was recognized for its clinical benefits 15 years ago; it has since had a role in the clinical setting. PET is currently most widely used in the diagnostic evaluation of oncological patients and it has been extensively applied in the planning of radiotherapy (18).

The introduction of the concept of 'biologic target volume' in radiotherapy amplifies the importance of PET in radiation oncology. This concept aims to clearly define the target volume through true biologic information in order to create more accurate radiation treatment volumes. The biologic target volume contoured according to the PET images potentially reduces the risk of geographic misses, allowing maximal sparing of surrounding healthy tissues. Although CT-guided target volume is still the most widely accepted standard procedure for CRT of rectal cancer, PET-guided radiation therapy is rapidly gaining acceptance (19). Moreover, through the understanding of the potential benefits of the PET/CT combination in the clinical settings, and given its importance in assessing tumor biologic activity and improving staging accuracy with spatial localization, PET/CT is becoming an accepted and routine clinical tool for radiation delivery (20).

The value of anatomic-biologic tumor targeting achieved with PET/CT in the radiotherapy planning process has been clearly defined in lung, head, and neck malignancies as well as lymphoid neoplasms (8–10). Published data also suggest improvements in the imaging of esophageal, cervical, and rectal cancers (21,22). For colorectal cancers, PET/CT is frequently used in the initial staging of tumors, evaluation of treatment response, and detection of tumor recurrence. The accuracy of PET/CT for rectal cancer initial staging is between 83% and 93%, and it has been shown to have a sensitivity and specificity of 96% and 97%, respectively, on local recurrence and of 95% and 98%, respectively, in the detection of distant metastases (16). Although these results are considerably high and comparable with other cancer sites, some studies on the inflammatory processes in and around the tumor in rectal cancer emphasize a low specificity (43%–79%) as shown by PET/CT (23). Some studies therefore suggest the use of contrast-enhanced FDG-PET/CT, which has been shown to be more accurate in the preoperative staging of rectal cancer (3).

Currently, PET/CT-targeted radiation treatment delivery is not a standard procedure in rectal cancer; nevertheless, the clear benefits of adapting PET/CT in multimodality imaging technology of radiation planning has developed a great interest in this area. The precise delineation of the primary tumor and accurate detection of local nodal disease is the state-of-the-art in preoperative radiation management of rectal cancer (24). With the impact of PET/CT on showing the biological target volume, applying irradiation to the whole tumor without missing any sections might be possible. Another important issue is interobserver variability in tumor contouring among radiation oncologists, which may adversely affect the radiation planning. Functional PET imaging in radiation simulation in lung cancer has been shown to significantly decrease the inter- and intraobserver variation in tumor contouring (25). The functional imaging and anatomical confirmation achieved by PET/CT radiotherapy in rectal cancer simulation may provide these opportunities.

We showed that IMRT planning was superior to CRT in terms of dosimetric factors when contouring with both CT and PET/CT. We could only demonstrate the impact of PET/CT on target volumes in preoperative rectal cancer patients. Interestingly, even if larger volumes were contoured according to the PET/CT findings on radiotherapy planning, IMRT planning had better dosimetric outcomes. IMRT was superior regarding both conformity index and tolerance doses of OAR and was compatible with RTOG dose limits in our dosimetric analysis.

Additionally, compared with CRT, IMRT has the advantage of adapting the dose distribution to the shape of the target while sparing critical normal structures. With regards to altering local control while maximizing the dose to the tumor without increasing toxicity to critical structures, IMRT emerges as the prominent treatment modality in radiotherapy for rectal cancer (26,27).

The volumes contoured with PET/CT were larger in our experience; however, the conformity index of IMRT planning was better than that of CRT planning. This was the same with IMRT plans created with CT volumes. Therefore, the present dosimetric study primarily favors IMRT planning in rectal cancer patients and consequently presents the significant alteration in target volumes with PET/CT contouring.

However, the following study limitations should be addressed. First, we examined radiation treatment planning retrospectively; nevertheless, the high accuracy of our patient records minimizes the negative impact of this aspect. Additionally, given that this is a dosimetric study, we believe that the retrospective study pattern does not have a considerable effect. Secondly, the low number of included patients may be seen as a limitation. This is inevitable, given that PET/CT is not yet a standard procedure in rectal cancer management and therefore not all rectal cancer patients are routinely scanned with PET/CT. In addition, the number of patients is statistically acceptable for a dosimetric study.

In conclusion, the results of our study showed that both CT-guided and PET/CT-guided IMRT provide a lower radiation exposure to the tumorless tissues than CRT. With the propensity to use PET/CT in radiation treatment planning, IMRT appears to be an essential radiotherapy technique for preoperative rectal cancer patients. This is only a dosimetric study, but we argue that the clinical reflection of our study will be better as can be estimated easily. Further clinical studies including a larger

number of rectal cancer patients may show the impact of PET/CT-guided CRT and PET/CT-guided IMRT. A prospective randomized clinical study has been planned following the promising results of the present study. In addition, long-term follow-up of the patients will clarify the gain of survival and toxicity profile. We propose that the results of this dosimetric study should be considered when designing clinical studies in this field.

References

1. Paskeviciute B, Bölling T, Brinkmann M, Rudykina G, Ernst I, Stegger L, Schober O, Willich N, Weckesser M, Könemann S. Impact of (18)F-FDG-PET/CT on staging and irradiation of patients with locally advanced rectal cancer. Strahlenther Onkol 2009; 185: 260–265.
2. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997; 336: 980–987.
3. Brush J, Boyd K, Chappell F, Crawford F, Dozier M, Fenwick E, Glanville J, McIntosh H, Renehan A, Weller D et al. The value of FDG positron emission tomography/computerised tomography (PET/CT) in pre-operative staging of colorectal cancer: a systematic review and economic evaluation. Health Technol Assess 2011; 15: 1–192.
4. Rödel C, Liersch T, Becker H, Fietkau R, Hohenberger W, Hothorn T, Graeven U, Arnold D, Lang-Welzenbach M, Raab HR et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol 2012; 13: 679–687.
5. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, Becker H, Raab HR, Villanueva MT, Witzigmann H et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012; 30: 1926–1933.
6. van Baardwijk A, Baumert BG, Bosmans G, van Kroonenburgh M, Stroobants S, Gregoire V, Lambin P, De Ruysscher D. The current status of FDG-PET in tumour volume definition in radiotherapy treatment planning. Cancer Treat Rev 2006; 32: 245–260.
7. Yavuz MN, Topkan E, Yavuz AA, Aydin M, Onal C, Reyhan M, Kotek A, Pehlivan B, Yapar AF. FDG-PET/CT imaging-based target volume delineation for preoperative conformal radiotherapy of rectal carcinoma. Int J Hematol Oncol 2010; 20: 67–74.
8. Grosu AL, Piert M, Weber WA, Jeremic B, Picchio M, Schratzenstaller U, Zimmermann FB, Schwaiger M, Molls M. Positron emission tomography for radiation treatment planning. Strahlenther Onkol 2005; 181: 483–499.
9. Bassi MC, Turri L, Sacchetti G, Loi G, Cannillo B, La Mattina P, Brambilla M, Inglese E, Krengli M. FDG-PET/CT imaging for staging and target volume delineation in preoperative conformal radiotherapy of rectal cancer. Int J Radiat Oncol Biol Phys 2008; 70: 1423–1426.
10. Bundschuh RA, Andratschke N, Dinges J, Duma MN, Astner ST, Brügel M, Ziegler SI, Molls M, Schwaiger M, Essler M. Respiratory gated (18F)FDG PET/CT for target volume delineation in stereotactic radiation treatment of liver metastases. Strahlenther Onkol 2012; 188: 592–598.
11. Fodor A, Fiorino C, Dell'Oca I, Broggi S, Pasetti M, Cattaneo GM, Gianolli L, Calandrino R, Di Muzio NG. PET-calation tomotherapy in malignant pleural mesothelioma. Strahlenther Onkol 2011; 187: 736–743.
12. Pinkawa M, Holy R, Piroth MD, Klotz J, Nussen S, Krohn T, Mottaghy FM, Weibrecht M, Eble MJ. Intensity-implementing molecular imaging with 18F-choline PET-CT to define a simultaneous integrated boost. Strahlenther Onkol 2010; 186: 600–606.
13. International Commission on Radiation Units and Measurements. ICRU Report 62. Prescribing, Recording, and Reporting Photon Beam Therapy (Supplement to ICRU Report 50). Bethesda, MD, USA: ICRU; 1999.
14. Erdi YE, Mawlawi O, Larson SM, Imbriaco M, Yeung H, Finn R, Humm JL. Segmentation of lung lesion volume by adaptive positron emission tomography image thresholding. Cancer 1997; 80: 2505–2509.
15. Myerson RJ, Garofalo MC, El Naqa I, Abrams RA, Apte A, Bosch WR, Das P, Gunderson LL, Hong TS, Kim JJ et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring atlas. Int J Radiat Oncol Biol Phys 2009; 74: 824–830.
16. Paulino AC, Johnstone PA. FDG-PET in radiotherapy treatment planning: Pandora's box? Int J Radiat Oncol Biol Phys 2004; 59: 4–5.
17. Ling CC, Humm J, Larson S, Amols H, Fuks Z, Leibel S, Koutcher JA. Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality. Int J Radiat Oncol Biol Phys 2000; 47: 551–560.
18. Sachelarie I, Kerr K, Ghesani M, Blum RH. Integrated PET-CT: evidence-based review of oncology indications. Oncology 2005; 19: 481–490.
19. Lin LL, Mutic S, Low DA, LaForest R, Vicic M, Zoberi I, Miller TR, Grigsby PW. Adaptive brachytherapy treatment planning for cervical cancer using FDG-PET. Int J Radiat Oncol Biol Phys 2007; 67: 91–96.
20. Leong T, Everitt C, Yuen K, Condron S, Hui A, Ngan SY, Pitman A, Lau EW, MacManus M, Binns D et al. A prospective study to evaluate the impact of FDG-PET on CT-based radiotherapy treatment planning for oesophageal cancer. Radiother Oncol 2006; 78: 254–261.

21. Anderson C, Koshy M, Staley C, Esiashvili N, Ghavidel S, Fowler Z, Fox T, Esteves F, Landry J, Godette K. PET-CT fusion in radiation management of patients with anorectal tumors. Int J Radiat Oncol Biol Phys 2007; 69: 155–162.

22. Capirci C, Rampin L, Erba PA, Galeotti F, Crepaldi G, Banti E, Gava M, Fanti S, Mariani G, Muzzio PC et al. Sequential FDG-PET/CT reliably predicts response of locally advanced rectal cancer to neo-adjuvant chemo-radiation therapy. Eur J Nucl Med Mol Imaging 2007; 34: 1583–1593.

23. Brunetti J, Caggiano A, Rosenbluth B, Vialotti C. Technical aspects of positron emission tomography/computed tomography fusion planning. Semin Nucl Med 2008; 38: 129–136.

24. Steenbakkers RJ, Duppen JC, Fitton I, Deurloo KE, Zijp LJ, Comans EF, Uitterhoeve AL, Rodrigus PT, Kramer GW, Bussink J et al. Reduction of observer variation using matched CT-PET for lung cancer delineation: a three-dimensional analysis. Int J Radiat Oncol Biol Phys 2006; 64: 435–448.

25. Ciernik IF, Dizendorf E, Baumert BG, Reiner B, Burger C, Davis JB, Lütolf UM, Steinert HC, Von Schulthess GK. Radiation treatment planning with an integrated positron emission and computer tomography (PET/CT): a feasibility study. Int J Radiat Oncol Biol Phys 2003; 57: 853–863.

26. Ciernik IF, Huser M, Burger C, Davis JB, Szekely G. Automated functional image-guided radiation treatment planning for rectal cancer. Int J Radiat Oncol Biol Phys 2005; 62: 893–900.

27. Pinkawa M, Piroth MD, Holy R, Escobar-Corral N, Caffaro M, Djukic V, Klotz J, Eble MJ. Quality of life after intensity-modulated radiotherapy for prostate cancer with a hydrogel spacer. Matched-pair analysis. Strahlenther Onkol 2012; 188: 917–925.