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Predictive value of interim and post-treatment PET/CT for clinical evaluation in pediatric and adolescent Hodgkin lymphoma: A comparison of the Deauville Criteria and the International Harmonization Project Criteria

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Abstract

Background. The criteria for response evaluation in pediatric and adolescent Hodgkin lymphoma (HL) are controversial. We compared different criteria for the interpretation of interim and post-treatment PET/CT to predict the outcome of pediatric and adolescent HL. Procedure. Baseline, interim, and post-treatment 18F-FDG-PET/CT scans of 147 pediatric and adolescent HL patients were interpreted according to the International Harmonization Project Criteria (IHPC) and Deauville Criteria (DC). Two thresholds of positivity were used for the DC: DC-3, scores of 3–5; and DC-4, scores of 4–5. Diagnostic performance of interim and post-treatment PET in outcome prediction was evaluated. Progression-free survival (PFS) was analyzed by the Kaplan-Meier method and Cox proportional hazards model. Results. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of interim FDG-PET/CT were 82%, 33%, 15%, 93%, and 39%, respectively, for IHPC, 82%, 51%, 19%, 95%, and 55%, respectively, for DC-3, and 27%, 78%, 15%, 88%, and 72%, respectively, for DC-4. The corresponding values for post-treatment PET/CT were 73%, 74%, 23%, 96%, and 74% for IHPC, 67%, 80%, 27%, 96%, and 79% for DC-3, and 47%, 90%, 33%, 94%, and 86% for DC-4. PFS significantly differed between patients with positive and negative post-treatment PET/CT according to IHPC, DC-3, and DC-4 ($P < 0.01$ for all), but only DC-4 was an independent prognostic factor for PFS (hazard ratio: 7.82). Conclusion. Compared to interim PET/CT, post-treatment PET/CT better predicted the outcomes of pediatric and adolescent HL. DC-4 had superior diagnostic performance over IHPC and DC-3.

INTRODUCTION

Hodgkin lymphoma (HL) accounts for 6%˜8% of all childhood malignancies and 15%–20% of all childhood lymphomas[1]. ^{18}F-Fluorodeoxyglucose positron-emission tomography-computed tomography (^{18}F-FDG-PET/CT) is widely used for staging, response evaluation, and surveillance in lymphoma[2]. The outcomes of pediatric and adolescent patients with HL have improved since the application of PET/CT-based, response-adapted therapy[3-5]. In a study by the Children's Oncology Group, the cumulative incidence of relapse in pediatric and adolescent HL patients was 17%, and the 5-year progression-free survival (PFS) rate was 83%[6]. Interim PET/CT has been used to identify patients with an inadequate response, and has been demonstrated to be an accurate predictor of prognosis in adult lymphoma. Post-treatment PET/CT is also highly useful for outcome prediction, with high negative predictive values (NPVs) of 94%–100% and positive predictive values (PPVs) of 91%–92% for a PFS [?] 2 years in adult HL patients treated with the ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) regimen[7-10]. However, similar studies concerning interim

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and post-treatment PET/CT in pediatric and adolescent HL patients are limited. A few retrospective studies with small sample sizes have reported NPVs of 90%–100% but PPVs of only 20%–40%[11, 12].

In 2007, the Imaging Subcommittee of the International Harmonization Project in Lymphoma recommended the International Harmonization Project Criteria (IHPC) for post-treatment assessment; however, the IHPC do not relate specifically to interim treatment, and their inter-observer variability has not been assessed[13,14]. In 2009, the Deauville Criteria (DC) were proposed for the visual evaluation of interim PET scans based on the application of a 5-point scale; these criteria showed good diagnostic accuracy and inter-observer concordance in patients with HL and non-Hodgkin lymphoma[15, 16]. However, the use of the DC relies on consistency in scanning conditions over serial scans, scan acquisition, and quality control of imaging equipment[17]. Moreover, it is unclear whether a DC score of 3 should be considered as positive, and the threshold of FDG uptake chosen to define response is controversial. Although PET/CT has demonstrated similar diagnostic performance and clinical utility in pediatric and adolescent HL, experience with this technique is still limited[15,18]. Therefore, the true effectiveness of the IHPC and DC remains unclear, and the optimal criteria for defining treatment response in pediatric and adolescent HL patients remain to be determined. Hence, this study reviewed the baseline, interim, and post-treatment PET/CT scan data of pediatric and adolescent patients with HL. The aims of this study (1) to determine the diagnostic performance of interim and post-treatment PET/CT when applying the IHPC and DC for the prediction of clinical outcomes in pediatric and adolescent HL patients, and (2) to identify which criteria better predict the risk of progression in this patient population.

MATERIALS AND METHODS

Patients

The institutional review board of Sun Yet-Sun University Cancer Center approved this retrospective study. We reviewed the clinical data of eligible patients with HL who were treated at the Department of Pediatric Oncology in Sun Yet-Sun University Cancer Center between January 2008 and May 2019. Patients were eligible for analysis when they fulfilled all of the following criteria: (1) Patients were aged < 21 years and had biopsy-proven, classic HL diagnosed according to the 2008 World Health Organization classification[19]. (2) Staging was performed according to the baseline FDG PET/CT scan results and the Ann Arbor staging system. (3) Interim PET/CT was performed after 2 cycles of chemotherapy (4) Post-treatment PET/CT was performed at least 3 weeks after the end of chemotherapy or 6 weeks following radiotherapy. (5) Complete remission (CR) was achieved at the end of the first-line treatment based on the PET/CT scan results. (6) Complete clinical data were available, including the date of diagnosis, details of anticancer treatment, and findings of outpatient follow-up.

Exclusion criteria: (1) Patients who were adults or diagnosed with other types of lymphoma, patients without baseline or post-treatment PET/CT scans, (2)Patients with refractory HL defined as progression or new lesions on PET/CT within three months of first-line treatment[20]. Patients without interim PET/CT, for example, whose PET/CT was performed after 4–6 cycles of chemotherapy, were also excluded. (3) Patients without interim PET/CT, for example, whose PET/CT was performed after 4–6 cycles of chemotherapy.

Teatment

Based on the findings of studies conducted by the Children' Oncology Group, the patients were administered the ABVD(doxorubicin, bleomycin, vincristine, dacarbazine)[21], BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[22], or ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide) regimen[5], depending on the disease stage and risk stratification (low, middle, or high risk). Interim PET/CT-based, response-adapted chemotherapy was administered according to the doctors' experience. Involved-field radiotherapy was performed for areas of bulky disease or FDG-avid areas.

^{18}F-FDG PET/CT imaging

Between January 2008 and January 2014, PET/CT scans were acquired using the dedicated PET/CT

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system Discovery ST-16 (GE Medical Systems, Milwaukee, WI, USA). Between February 2014 and May 2019, scans were acquired using Biograph mCT.X (Siemens Healthineers, Henkestrasse,Erlangen, Germany), another dedicated PET/CT system. All patients were instructed to fast for at least 6 h before^{18}F-FDG administration. Image acquisition was performed 45–60 min after the intravenous injection of 3.7 MBq/kg^{18} F-FDG. CT (100 mA, 100 kV, 0.8 s per tube rotation) was used to generate a PET attenuation correction map. The patients were scanned from the skull to the middle of the femur while lying in a supine position.

^{18} F-FDG PET/CT analysis

All ^{18}F-FDG PET/CT analyses and reviews were performed by two experienced nuclear medicine physicians who had access to the results of previous imaging and clinical information, but were unaware of the follow-up results. Interim and post-treatment PET/CT scans were analyzed using the IHPC and DC. According to the IHPC, a PET/CT scan was considered positive if a residual mass had a greatest transverse diameter of >2 cm and showed more intense residual uptake than the mediastinal blood pool activity. A smaller residual lesion or a normal-sized lymph node was also considered positive if its activity was above that of the surrounding background. Other criteria for defining PET positivity in the spleen, liver, lungs, and bone marrow were consistent with the established IHPC. According to the DC, PET/CT scans were assigned scores on a 5-point scale as follows: no residual uptake, 1 point; residual uptake less than or equal to the mediastinum, 2 points; residual uptake greater than the mediastinum but less than the liver, 3 points; residual uptake moderately higher than the liver, 4 points; and residual uptake markedly higher than the liver or the presence of new sites of uptake, 5 points. Two separate cutoffs were used for the DC scores. With a cutoff of 3 points (the DC-3 model), DC scores of 3–5 were considered positive, whereas scores of 1–2 were considered negative. With a cutoff of 4 points (DC-4), DC scores of 4–5 were considered positive, whereas scores of 1–3 were considered negative.

Statistical analysis

The statistical software packages SPSS version 22.0 (Chicago, IL, USA) and GraphPad Prism version 5.00 for Windows (San Diego California USA) were used to analyze the data. To determine the value of interim and post-treatment PET/CT in the prediction of the outcomes of pediatric and adolescent HL patients, we calculated the sensitivity, specificity, positive likelihood (+LH), negative likelihood (-LH), area under the curve (AUC), positive predictive value (PPV), negative predictive value (NPV) and accuracy for the IHPC, DC-3, and DC-4 models. Survival curves were estimated using the Kaplan-Meier method with Rothman's 95% confidence intervals (CIs) and log-rank tests. PFS was defined as the interval from the diagnosis to the first clinical or radiological progression or the date of the last follow-up visit for those without events. Factors with A P value of less than 0.05 were introduced into multivariate analysis, performed by the Cox proportional hazard model using the forward procedure. A P value of less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 147 patients completed the post-treatment PET/CT scan, including 104 (70.7%) boys and 43 (29.3%) girls. Their median age was 14 years (range, 2–21 years). There were 3.4% (5/147) stageIpatients, 57.1% (84/147) stageIIpatients, 21.1% (31/147) stage III patients, 18.4% (27/147) stage IV patients, respectively. Risk stratification placed 44.2% (65/147) of the patients in the low-risk group, 10.9% (16/147) in the middle-risk group, and 44.9% (66/147) in the high-risk group. All patients achieved CR after first-line chemotherapy with a median course of 6 cycles (range, 4–14 cycles). Radiotherapy was performed in 66.7% (98/147) of the patients. The median follow-up duration was 48 months (range, 8–117 months), during which time, 15 patients experienced relapse, and 1 patient died of relapse. 89/147 patients completed interim PET/CT after 2 cycles of chemotherapy. The characteristics of the patients with only post-treatment PET/CT scans and those with both interim and post-treatment PET/CT scans are summarized in Table 1.

Diagnostic performance of interim and post-treatment PET

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Of the 89 patients who completed the interim PET/CT scans (Table 2), 61 (68.5%) patients had a positive PET/CT scan according to the IHPC. The sensitivity, specificity, PPV, NPV, and accuracy of the IHPC were 81.8%, 33.3%, 14.8%, 92.9%, and 39.3%, respectively. Likelihood ratio analysis yielded a +LH value of 1.2 and -LH value of 0.6. The AUC was 0.6 (95% CI: 0.47–0.68). When using the DC-3 cutoff, 52.8% (47/89) of patients had a positive PET/CT. The sensitivity, specificity, PPV, NPV, and accuracy of DC-3 were 81.8%, 51.3%, 19.1%, 95.2%, and 55.1%, respectively. The +LH was 1.7, and the -LH was 0.4. The AUC was 0.7 (95% CI: 0.56–0.76). With the DC-4 cutoff, 22.5% (20/89) of patients had a positive PET/CT. The sensitivity, specificity, PPV, NPV, and accuracy of DC-4 were 27.3%, 78.2%, 15.0%, 88.4%, and 71.9%, respectively. The +LH, -LH, and AUC were 1.3, 0.9, and 0.5 (95% CI: 0.42–0.63), respectively.

Of the 147 patients who completed the post-treatment PET/CT scans (Table 2), 46 (31.3%) had a positive PET/CT scan according to the IHPC. The sensitivity, specificity, PPV, NPV, and accuracy of IHPC were 73.3%, 73.5%, 23.4%, 96.0%, and 73.5%, respectively. In the likelihood ratio analysis, the +LH was 2.8, and -LH was 0.4. The AUC was 0.7 (95% CI: 0.66–0.80). When using the DC-3 cutoff, 24.5% (36/147) of patients had positive PET/CT scans. The sensitivity, specificity, PPV, NPV, and accuracy of DC-3 were 66.7%, 80.3%, 27.0%, 95.5%, and 78.9%, respectively. The +LH, -LH, and AUC were 3.4, 0.4, and 0.7 (95% CI: 0.66–0.80), respectively. According to the DC-4 cutoff, 13.6% (20/147) of patients had positive PET/CT scans. The sensitivity, specificity, PPV, NPV, and accuracy of DC-4 were 46.7%, 90.2%, 33.3%, 93.7%, and 85.7%, respectively. The +LH, -LH, and AUC were 4.7, 0.6, and 0.7 (95% CI: 0.60–0.76), respectively.

Kaplan-Meier analysis and Cox regression analysis results

The results of Kaplan-Meier analysis and multivariate analyses performed to identified the prognostic factors for PFS are shown in **Table 3.** Kaplan-Meier analysis indicated that histopathological subtype (P = 0.01), a positive result of interim PET/CT when using DC-3 ((P = 0.02, Fig. 1A), a positive result of post-treatment PET/CT when using IHPC ((P<0.01, Fig 1B), DC-3 (P<0.01, Fig 1C) and DC-4 (P<0.01, Fig 1D) were associated with worse PFS. Variables with P<0.05 in univariate analysis were incorporated into multivariate Cox regression analysis and the results showed that only DC-4 was an independent prognostic factor for PFS (P < 0.01, hazard ratio: 7.82, 95% CI: 2.65–23.05).

DISCUSSION

^{18}F-FDG-PET/CT has been formally incorporated into the standard initial staging, interim response evaluation, and residual disease evaluation at the end of treatment for both adult and pediatric patients with HL[23-25]. PET/CT-based, response-adapted treatment has been proven to improve survival and reduce the risk of long-term toxicity in pediatric HL patients[5]. It is critical that the response assessment is reliable and reproducible, but the interpretation of interim and post-treatment PET/CT scans can be difficult due to false-positive results[8,26, 27]. The IHPC and DC are the main criteria for the clinical evaluation of both interim and post-treatment PET/CT[13-16]. In the present study, we used the IHPC and DC to analyze a homogeneous cohort of pediatric and adolescent HL patients who underwent regular interim PET/CT after 2 cycles of chemotherapy and underwent post-treatment PET/CT. Our study found that post-treatment PET/CT showed a better diagnostic performance than interim PET/CT in the prediction of the outcomes of pediatric and adolescent HL patients. Moreover, the DC-4 cutoff could further improve diagnostic accuracy when compared with the IHPC and DC-3 (Table2).

In our patient cohort, 89 patients underwent interim PET/CT after 2 cycles of chemotherapy, and their PET/CT scan results were analyzed. Given that the index reflecting reduced metabolism is expected to be more discriminating after 2 cycles of chemotherapy than after 4 or 6 cycles[28], we excluded the results of irregular PET/CT scans. Our study indicated that interim PET/CT had a relatively low PPV (15%, 19%, and 15% when using the IHPC, DC-3, and DC-4, respectively), but a high NPV (93%, 95%, and 88%, respectively). A retrospective study of 34 children with HL indicated that interim PET/CT had a good PPV of 75% and a high NPV of 96%[29]. Similar results have been reported for adult patients with HL and NHL, with PPVs of 57%–85% and NPVs of 80%–100%[9,30, 31]. However, some studies concerning the interim PET/CT visual assessment in pediatric HL patients have showed poor and variable PPVs (ranging

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between 11% and 30%) and high NPVs (ranging between 80% and 100%)[32]. The poor PPVs observed in the present study and in previous studies might be explained by high false-positive rates. Like adult lymphomas, cervical lymph node hyperplasia and inflammation show high FDG uptake on PET/CT scans, but are benign processes and cause false-positive results in pediatric and adolescent patients with lymphoma[33]. The residual ^{18}F-FDG uptake observed on interim PET/CT scans might be related to inflammatory cells. Although the diagnostic accuracy was improved by using DC-4 (75%) rather than IHPC (39%) or DC-3 (55%) in the present study, the diagnostic performance of interim PET/CT was still poor. Moreover, no significant differences in PFS were observed between patients with positive and negative interim PET/CT scans according to the IHPC, DC-3, and DC-4. It should be noted however that both the present study and previous studies concerning interim PET/CT in pediatric and adolescent HL were retrospective in nature and limited by small sample sizes.

Given the results of interim PET/CT in our study, interim PET/CT could not circumvent the need for post-treatment PET/CT evaluation. Thus, we further analyzed the 147 post-treatment PET/CT scans. Improved PPVs were observed using the post-treatment PET/CT scans as compared with the interim PET/CT scans (IHPC: 23% vs. 15%, DC-3: 27% vs. 19%, and DC-4: 33% vs. 15%), indicating that the use of post-treatment PET/CT might reduce false-positive rates. Furthermore, the AUC and accuracy of post-treatment PET/CT were both higher than those of interim PET/CT (Tables 2). Consistent with our findings, a prospective study of 57 pediatric HL patients reported that the predictive value of interim PET/CT was low, and that post-treatment PET/CT evaluated using the DC had better specificity (96% vs. 76%) and PPV (33% vs. 8%) than conventional imaging[34]. The above finding is probably a consequence of response-adapted treatment in our study: Patients with DC scores of 4 and 5 in the interim PET/CT evaluation received chemotherapy-dose escalation and radiotherapy; hence, the post-treatment PET/CT was more valuable in predicting progression.

In our study, among the three models of PET/CT evaluation, DC-4 showed the highest specificity, AUC, and accuracy, indicating that DC-4 might have a superior diagnostic performance than IHPC and DC-3. Furthermore, Cox regression and Kaplan-Meier analyses revealed that a positive post-treatment PET/CT according to DC-4 was strongly associated with a high risk of progression (hazard ratio: 7.82). A similar conclusion was drawn in a retrospective study of 101 adult patients with lymphoma: the specificity, accuracy, and hazard ratio of positive post-treatment PET/CT were all higher when using the DC-4 rather than the DC-3 and IHPC (specificity: 87% vs.76% vs. 67%, accuracy: 86% vs. 84% vs. 76%, and hazard ratio: 3.2 vs. 0.7 vs. 1.57, respectively)[9]. However, another retrospective study of 72 pediatric HL patients reported that the IHPC showed a higher specificity (95% vs. 70%), accuracy (89% vs. 46%), and PPV (40% vs. 25%) than the DC in the evaluation of post-treatment PET/CT[11]. The application of the IHPC depends on the evaluator's experience and is limited by the quality of image reconstruction[35, 36]. In contrast, concordance among observers when using the DC has been demonstrated, and discordant interpretations among reviewers occur in only a few challenging cases[37]. Furthermore, the threshold selected for PET/CT positivity may vary depending on the histological subtype and the treatment. Thus, on the basis of our results, we tentatively regard that the DC-4 had a superior diagnostic performance than the IHPC and DC-3 in the evaluation of post-treatment PET/CT among pediatric and adolescent patients with HL.

Our study has several limitations. First, there was variability in image and data acquisition due to the retrospective nature of our study. Second, some patients received interim PET/CT-based, response-adapted treatment, but the definition of the threshold of positivity varied among doctors. Treatment bias might potentially influence survival. Furthermore, we excluded patients with primary refractory HL, with a consequent impact on overall survival. Further large prospective studies are required to define the best strategy for the use of the DC in specific clinical situations.

CONCLUSION

This retrospective study found that in pediatric and adolescent HL patients treated with first-line chemotherapy, the predictive value of ^{18}F-FDG-PET/CT for clinical evaluation was influenced by the interpretation criteria adopted. DC-4 showed superior diagnostic performance compared with the IHPC and DC-3. The

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diagnostic performance of post-treatment PET/CT was higher than that of interim PET/CT. Due to the limitations of a small sample size and a retrospective study design, the above results need to be verified in randomized prospective trials.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

COMPLIANCE WITH ETHICAL STANDARDS

Ethical approval: All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments. The institutional review board of Sun Yet-Sun University Cancer Center approved this retrospective study (approval number: B2020-132-01).

Informed consent: This is a retrospective study based on hospital database. Study associated medical examination or treatment won't harm patients' health, so informed consent has been exempted.

Availability of data and materials: The key raw data have been deposited into the Research Data Deposit (http://www.researchdata.org.cn; approval number: RDDA2020001520).

Author contributions: All authors contributed to the final analysis and writing of the manuscript.

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FIGURE LEGENDS

FIGURE 1. Kaplan-Meier analysis of progression-free survival in relation to interim PET/CT results using the DC-3(A), post-treatment PET/CT results using the IHPC(B), DC-3(C) and DC-4(D) criteria respectively.

Figure 2 and figure 3 are typical examples of baseline, interim and post-treatment PET/CT scans of pediatric and adolescent patients with HL, which have not been cited in the text.

FIGURE 2 A 13-year-old boy with stage II Hodgkin lymphoma. (A) Coronal PET/CT images before treatment show disseminated metabolically active lesions in the cervical and mediastinal areas. (B) Interim coronal PET/CT images after 2 cycles of chemotherapy show that the residual uptake is markedly higher than the liver. This result corresponded to a Deauville Criteria (DC) score of 5 and a positive International Harmonization Project Criteria (IHPC) score. (C) Post-treatment coronal PET/CT images show that at the end of therapy, a few cervical lymph nodes have a slightly high FDG uptake (yellow arrow). (D) Post-treatment merged axial PET/CT images show a residual cervical lymph node (10 mm) with an activity above that of the surrounding background. This result corresponded to a DC score of 3 and a positive IHPC score. This patient showed continuous complete remission after a follow-up of 17 months.

FIGURE 3 A 19-year-old girl with stage IV Hodgkin lymphoma. (A) Coronal PET/CT images before treatment show intense tracer uptake in the bilateral cervical lymph nodes, mediastinum, left armpit, left pulmonary hilum, and bone marrow. (B) Interim coronal PET/CT images show that after 2 cycles of

chemotherapy, the residual uptake in the bilateral cervical lymph nodes, mediastinum, and left armpit is markedly higher than the uptake in the liver. This result corresponds to a Deauville Criteria (DC) score of 5 and a positive International Harmonization Project Criteria (IHPC) score. (C) Post-treatment coronal PET/CT images show that at the end of therapy, the uptake of a residual left supraclavicular lymph node and a residual left axillary lymph node is moderately higher than that of the liver (yellow arrow). (D) Post-treatment axial fused PET/CT images show a residual left supraclavicular lymph node smaller than 2 cm. (E) A residual left axillary lymph node greater than 2 cm on CT images. This result corresponds to a DC score of 4 and a positive IHPC score, and may be a false positive caused by inflammation. This patient showed continuous complete remission after a follow-up of 22 months.

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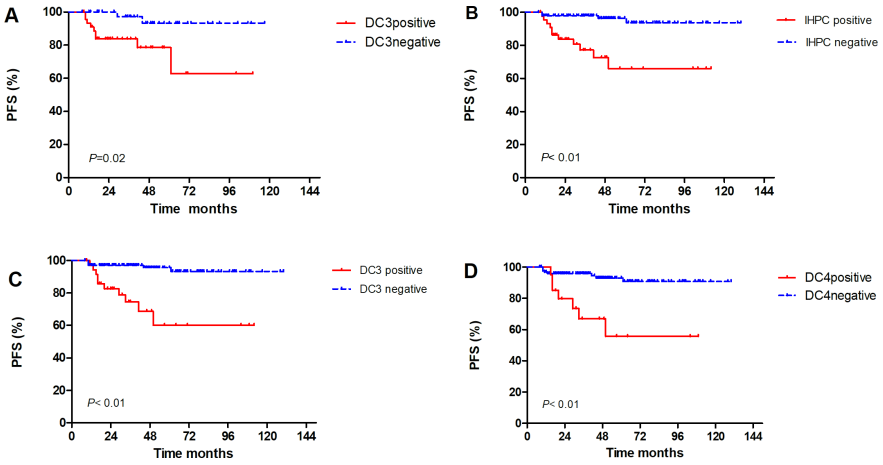

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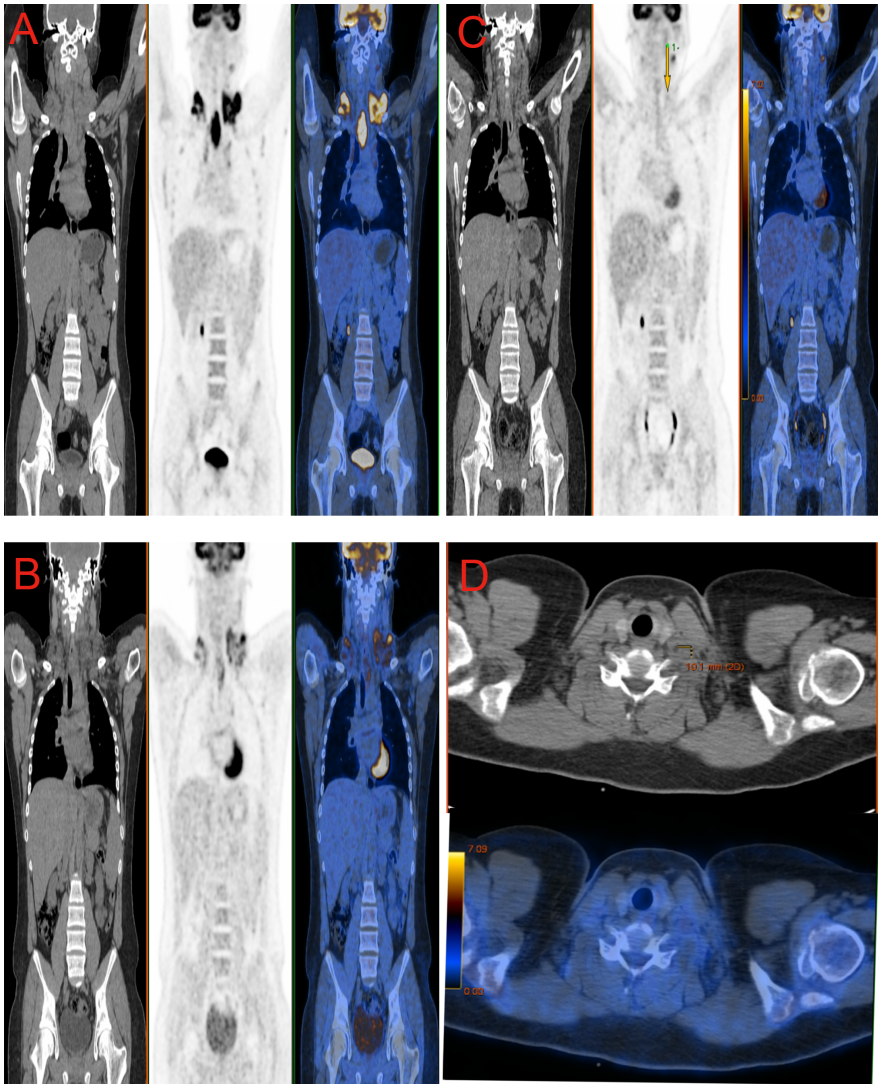

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