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Original Article

Feasibility of rapid integrated radiation therapy planning with follow-up FDG PET/CT to improve overall treatment assessment in head and neck cancer

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Abstract: Inflammatory changes and residual disease are difficult to distinguish after high dose, definitive radiotherapy of head and neck malignancies. FDG uptake located within a high dose field may more likely represent inflammatory changes, and FDG uptake outside of the radiation field could represent unsuspected and under treated disease. In situ knowledge of the precise radiotherapy fields, therefore, may be useful in distinguishing these etiologies. This study aimed to evaluate the clinical feasibility of rapid integration of radiation treatment field images during follow-up FDG PET/CT imaging. Twenty head and neck cancer patients who underwent radiation therapy were identified. A MIM based workflow was created which fused the radiation treatment CT, including the planning volumes and isodose curves, into the follow-up imaging. Two board certified physicians, blinded to treatment outcome, reviewed the follow-up exams, half with the treatment information and half without. Each exam was scored for recurrent or residual disease, confidence of the read and a qualitative assessment to the overall usefulness of the treatment plan. Interpretation accuracy improved from 80 to 90% with integration of the treatment plan. Similarly, the sensitivity improved from 71% to 86%, while the specificity increased from 85% to 92%. Confidence also increased by 0.7 on a 5 point scale for both readers. Data demonstrate the clinical feasibility of rapidly incorporating radiation treatment dosimetry into follow-up FDG PET/CT exams in patients with head and neck cancer. Preliminary results demonstrated a simple, efficient method which improved accuracy of interpretation and overall reader confidence.

Keywords: Radiation treatment planning, FDG PET/CT, inflammation, tumor recurrence

Introduction

Squamous cell cancer is the most common malignant tumor of the head and neck and is particularly associated with a history of smoking and alcohol use, as well as HPV infections. While size and location of the primary tumor is crucial when evaluating treatment options, nodal disease also impacts survival [1]. Effective treatment necessitates accurate pre-therapy imaging, which is why ^{18}F-Fluorodeoxyglucose (FDG) PET/CT has become a well-established modality for both staging and therapeutic assessment of head and neck tumors [2-5]. Multiple prior studies have demonstrated the positive impact of fusing the pre-treatment PET/CT with the radiation planning CT [6-9].

Numerous studies have shown that FDG PET/CT at the completion of treatment is useful in identifying recurrent/residual disease [2, 4, 5, 10-12]. The results of the post-therapy PET scan can decrease the need for neck dissection, with a negative PET interpretation carrying a negative predictive value of 94% [13, 14]. While a negative study decreases the need for a neck dissection, the positive predictive value is low, due to the high number of false positive results related to post-radiation inflammation [11]. Prior studies have demonstrated that follow-up PET imaging 6 weeks after completion of chemoradiation therapy correctly identifies locoregional residual cancer with a sensitivity ranging from 67-91% and specificity of 53-93% [2, 4, 11, 12]. The broad range of results is an indication of the challenge in interpretation of these studies, with difficulty in correctly characterizing low level increased activity as residual/recurrent disease or inflammation from prior therapy. Given the three year survival for

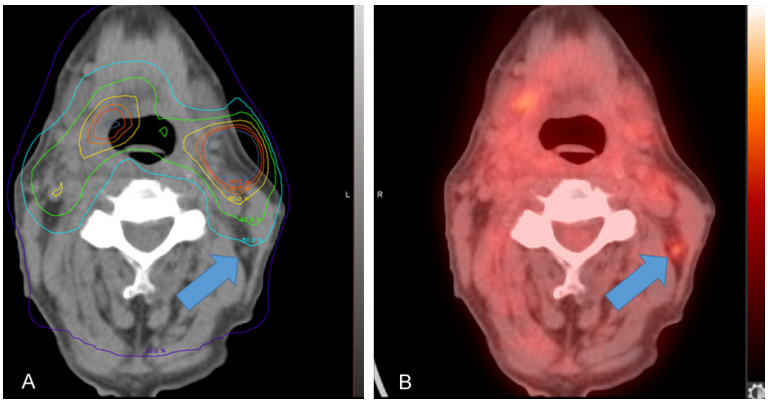

Figure 1. On the left (A) is the treatment planning CT which shows a small posterior left cervical lymph node just outside the 50% isodose curve. On the right (B) is the follow-up FDG PET/CT showing low level activity within this node.

patients with PET positive residual disease is much lower compared to those with a negative study (42.5% vs 70.5%, respectively), accurate assessment has significant prognostic implications [11].

While there are a variety of interpretative challenges when reading an FDG PET/CT on a patient with head and neck cancer who is status post radiation with or without chemotherapy, inflammation from the treatment can result in increased, non-specific, FDG uptake. There is considerable overlap between standardized uptake values of post-radiotherapy inflammation and residual tumor, particularly as it is related to mucositis, reactive nodes, soft tissue necrosis and radionecrosis of the bone [15-17]. The overlap leads to equivocal results which often necessitates short term follow-up imaging [17]. The challenge for imaging interpreters is lack of real-time knowledge regarding the location and dose levels of prior therapeutic radiation and whether activity identified is within or outside the treatment fields.

As an attempt to improve the current process we performed a pilot study to assess the feasibility and potential impact of integrating the radiation planning CT scan and associated dose contours with the post-therapy PET/CT images. By incorporating radiation treatment planning, which spatially define specific radiation doses, we may improve discrimination of inflammation from residual or recurrent disease. In order to maximize efficiency, we utilized a MIM workflow to integrate both studies into a single session.

Methods

This protocol was approved by the institutional IRB. We identified 20 patients with head and neck squamous cell carcinoma with both a pre-therapy and post- therapy FDG PET/CT scans separated by 2-6 months post radiation therapy, as recommended by the National Comprehensive Cancer Network practice guidelines [18]. Recurrent or residual disease at the site of FDG uptake was verified by biopsy or progression on imaging during follow-up within 1 year of completing therapy.

Our image visualization and analysis software package (MIM Encore™) allowed the authors to develop customizable workflows across imaging modalities and medical specialties. This software is also used at our institution by radiation oncology (MIM Maestro™) for contouring, fusion, and dose review as part of treatment planning. We developed an integrated workflow with the software (MIM Maestro™ and MIM Encore™ with MIM Assistant™) that automatically retrieved each patient's initial and follow-up FDG PET/CT, as well as radiation therapy planning CT and dose information. This information was then anonymized and transferred to a research server.

The software workflow (MIM Encore™) fused the radiation treatment plans to the follow-up FDG PET/CT, with the option to verify and correct the pre- and post-therapy registration to account for potential differences in head position. Two board certified readers reviewed each exam and recorded the following information: disease recurrence (yes/no), confidence in interpretation (Likert confidence scale 1-5), as well as whether they felt the treatment plan was useful in reviewing the study.

For patients 1-10, reader 1 utilized the prior FDG PET/CT and radiation treatment plan when interpreting the study, while reader 2 was not allowed to look at the treatment plan for the

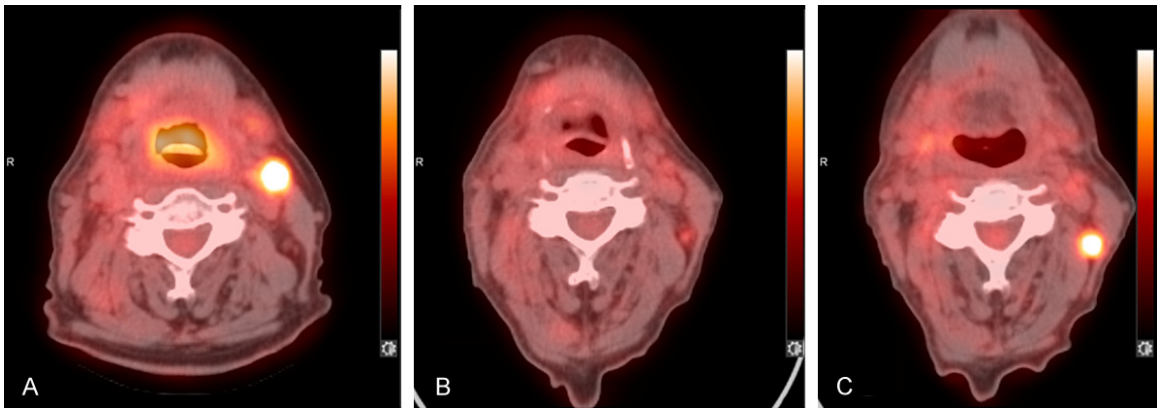

Figure 2. FDG PET/CT imaging of the same patient at diagnosis (A), following radiation therapy (B) and a short term follow-up (4 months later) (C) shows progression of metastatic disease.

first half of the patients. For patients 11-20 reader 1 was only allowed to use the prior FDG PET/CT in interpreting the exam, while reader 2 had access to the radiation treatment plans.

Results

Because all images and radiation fields were on the same vendor imaging platform (MIM Encore and MIM Maestro), all images were readily accessed without need for user intervention. All images were visually deemed as acceptable after fusion, and no images required manual adjustment of the co-registered fusion images. The time for the process to acquire, load and fuse the radiation therapy treatment planning images and the post-therapy FDG PET/CT was comparable to the time required for load pre- and post-therapy FDG PET/CT images in daily clinical practice.

Of the 20 patients with head and neck cancers, seven had recurrent disease while the remaining 13 were negative. There was a mixture of HPV positive and negative patients, 13 and 7 respectively.

Reader 1 correctly interpreted all but one of the first ten patients, when utilizing the treatment plans to assist the interpretation. When this information was not available for patients 11-20, the reader correctly interpreted the exam for eight of the ten patients. Of the three patients who were incorrectly categorized, one had recurrent disease on a follow-up FDG PET/CT five months later and the other two were miss categorized as having residual disease which on follow up was shown to be due to inflammation.

Reader 2 correctly identified 8 of 10 patients when utilizing the treatment plans to assist the interpretation. Of the two patients incorrectly categorized, one was the same patient reader 1 incorrectly categorized, who developed recurrence in a cervical lymph node on their five-month follow-up FDG PET/CT. The other contained FDG avid cervical lymph nodes that were felt to represent persistent nodal metastatic disease, but were actually inflammatory. Of the 10 patients reviewed with the treatment plan information, one patient was read as negative but had recurrent disease which was outside the treatment field.

The combined sensitivity of both readers improved from 71% to 86% and the specificity increased from 85% to 92%. Statistically the readers had a combined accuracy of 80% without the treatment plan information, which improved to 90% when this data was used.

Often with head and neck cancers areas of inflammation carry the caveat of not being able to exclude residual/recurrent disease. As seen in **Figure 1**, low level uptake in a posterior left cervical lymph may have been due to inflammation following radiation therapy, however after overlaying the radiation treatment contours, this focus was outside the 50% prescription isodose line and concerning for a new site of metastatic disease. **Figure 2**, is the same patient and demonstrates the initial exam, post-radiation treatment PET, where the low

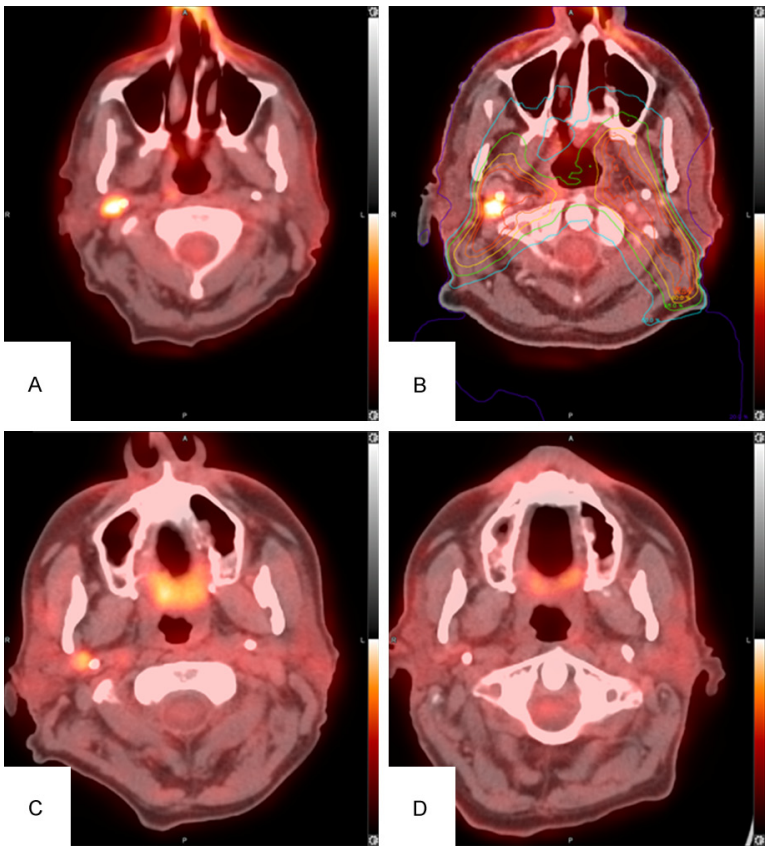

Figure 3. Top left image (A) demonstrate FDG avid nodal metastatic disease adjacent to the right styloid process. Top right image (B) shows this area was within the high dose treatment field. Bottom left image (C) is the patient's follow-up scan after therapy which showed improved but residual activity at this site of disease, which given prior treatment field is likely inflammation. Bottom right image (D) shows resolution of FDG avidity at this site on their next PET/CT.

level uptake was noted, and a follow-up PET/CT obtained 3 months later which demonstrates a now intensely FDG avid focus of nodal metastatic disease.

The reader confidence also improved with the treatment plan information. Reader 1 recorded a confidence of 3.5 without treatment information and 4.2 with this information, while Reader 2 had a confidence of 4.1 without and 4.8 with treatment information. This resulted in a statically significant increase in confidence (p-value = 0.025).

The one qualitative measure recorded during the study was whether the readers found the having the treatment information useful in the interpretation of the examination. Of the 20 FDG PET/CTs reviewed with treatment information the readers reported that for 15 of the 20 studies the additional information was helpful in reviewing the examination.

Discussion

Our study demonstrates integration of radiation treatment fields into the interpretation of follow-up PET examinations improves both our accuracy and confidence. A key aspect to this study was the clinical feasibility, and simplicity of integrating treatment fields and post-therapy PET/CT imaging. This process did not require a separate computer or significant time, but instead was as simple as choosing an alternate workflow.

While the sample size is small, the readers clearly demonstrated an increase in both confidence and accuracy following collaboration with our radiation oncology colleagues. The readers' sensitivity and specificity were in range of prior publications; however, it is worth noting that the incorporation of the treatment fields increased both values to the highest levels previously published, particularly for specificity. While the goal for interpreting physicians is to have high sensitivity and specificity, the impact of improving accuracy goes well beyond statistics. Correctly identifying inflammation versus recurrent disease means patients may avoid more aggressive and morbid therapies. It is our belief that the integration of the radiation treatment fields into follow-up imaging is not only helpful for challenging cases, but has the potential to truly impact patient outcomes.

Our study establishes a potential method for improving specificity, which may lead to decreased rate of repeat imaging, thus, reducing overall health care cost and patient radiation dose. The integration of the treatment fields allows the interpreter to clearly state that areas of increased activity are within or outside the isodose contours enhancing the clinical inter-

pretation for the treating physician. As **Figure 3** shows, areas of increased activity within the 100% treatment field improved on the follow-up study. Recurrent/residual disease does occur, however in this limited sample size, not a single patient has disease within their high dose field.

This study is limited by the retrospective nature and patient size. A larger, prospective study could further stratify HPV positive and negative patients, account for tumor stage, and incorporate long term follow up to assess the impact of imaging integration on outcome. Our study specifically examined the utility of integrating treatment fields into follow-up imaging of head and neck cancer, however, multiple other malignancies treated with external beam radiation therapy could also potentially benefit from this technique.

In summary, incorporating radiation treatment fields into follow-up PET exams is a clinically feasible, and efficient technique. Our preliminary results demonstrate higher overall accuracy, and overall higher reader confidence. This warrants further study in a larger trial to determine whether this technique can significantly improve treatment outcome.

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Disclosure of conflict of interest

None.

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