Can pre-chemoradiotherapy FDG PET/CT identify residual metabolically active areas within individual esophageal tumors?

Innovation/Impact:
Presence of residual metabolically active areas in patients after chemoradiotherapy (CRT) correlates with worse local control and survival. If the residual areas can be identified by areas of high metabolic or FDG uptake on the pre-CRT FDG PET/CT scans, selective dose escalation to these areas at the highest risk for residual tumor may improve outcomes. To our knowledge, this is the first such study in esophageal tumors.

Methods:
This study included twenty patients with locally advanced esophageal cancer, treated with tri-modality therapy (CRT plus surgery), and had both FDG-PET/CT scans pre-CRT and post-CRT. A rigid registration in Insight Segmentation and Registration Toolkit was used to align the post-CRT CT with the pre-CRT CT, by maximizing their normalized correlation. The registration results were visually examined and adjusted if deemed necessary by a diagnostic radiologist. The resulting transform was directly applied to register the post-CRT PET to the pre-CRT PET. All images were now aligned spatially.

A rough volumetric rectangle enclosing a tumor was defined by a nuclear medicine physician on the pre-CRT scans. Within the rectangle, the primary tumor and residual metabolically active areas were delineated using a region-growing algorithm with a threshold of standard uptake value (SUV) ≥ 2.5 on the pre-CRT and post-CRT images, respectively. Seven areas of high FDG uptake pre-CRT were defined using thresholds SUV 2.5 (primary tumor), SUV 5.0, 34%, 40%, 50%, 60%, and 70% of the maximal SUV (SUVmax), respectively. The overlap fraction (OF), between the areas of high FDG uptake pre-CRT and the residual areas, was defined as the volume of overlap divided by the volume of the residual areas. The OF and the centroid distance were computed to quantify the similarity and proximity of these two areas.

Results:
All primary tumors showed increased metabolic activity (SUVmax ≥ 2.5). Of all 20 patients, six had residual metabolically active areas (SUV ≥ 2.5) within or in close proximity of the primary tumor on the post-CRT scans. Among the other 14 patients, five showed none residual metabolic activity (SUVmax < 2.5), three showed minimal residual metabolic activity (SUVmax of 2.5, 3.0, 2.5, and residual areas of 0.1, 0.4, and 1.4 cm³, respectively) that was considered resolved (metabolically), while six showed new metabolic activity located away from the primary tumor (1 in liver, 1 in stomach, and 4 in other parts of esophagus).

Figure 1 shows representative images of four of the six patients with residual metabolically active areas. Patient 1 represented three patients who showed residual metabolic activity with decreased SUV and located within or in close proximity of the primary tumor. They had high overlap fractions (100%, 74% and 91%). Patient 2 showed residual metabolic activity with decreased SUV but extended into the neighborhood of the primary tumor. It had a low overlap fraction of 43%. Patient 3 showed residual metabolic activity with unchanged SUV and extended beyond the primary tumor. It had a low overlap fraction of 37%. Patient 4 showed residual metabolic activity with decreased SUV. Though the residual areas resided at similar levels in the esophagus as the primary tumor, it had the lowest overlap fraction of 14% with the primary tumor. On pre-CRT images the tumor infiltration was eccentric leading to focal dilation of the esophageal lumen (red arrow) in the opposite direction, while on post-CRT image this dilated lumen was almost completely resolved. Because of this large change in non-FDG-avid tissue near the tumor, the overlap was low.
Patient 1, OF = 100%
Patient 2, OF = 43%
Patient 3, OF = 37%
Patient 4, OF = 14%

Fig. 1. FDG PET/CT images of four patients pre-CRT (left) and post-CRT (right). The blue contours indicate the primary tumors on pre-CRT image and residual metabolically active areas on post-CRT image, respectively. For Patient 4, the red arrow indicates a dilated and not-FDG-avid esophageal lumen that was almost completely resolved on post-CRT images.

As depicted in Fig. 2, the average overlap fractions between the seven areas of high FDG uptake pre-CRT and the residual metabolically active areas were all less than 60%, with large variations among the six patients. The average centroid distances were all greater than 8.6 mm, and increased as the threshold increased. Fig. 2 indicated that areas of higher FDG uptake pre-CRT had lower overlap fraction and larger centroid distance to the residual areas post-CRT.

Fig. 2. The average overlap fractions (a), and centroid distances (b) between the seven areas of high FDG uptake pre-CRT and the residual metabolically active areas. Error bar indicate 1 SD.

In conclusion, the results suggested that pre-CRT PET/CT can not reliably identify the residual metabolically active areas in esophageal cancer. Selective dose escalation to areas of high FDG uptake may not be benefit for many patients.