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Purpose or Objective

To determine the change over time in circulating cell free DNA (cfDNA) in patients with locally advanced non-small cell lung cancer (NSCLC) during chemo-radiotherapy. Furthermore, the possibility for detection of circulating cell free tumor DNA (ctDNA) was assessed using shallow whole genome sequencing (sWGS) and size selection.

Material and Methods

Ten patients were included in a two-phase trial. The first four patients had blood samples taken prior to treatment and at 30 minutes, 1 hour and 2 hours after treatment to estimate the short-term dynamics of cfDNA after a therapy session. The remaining six patients had one blood sample taken on six treatment days 30 minutes post radiotherapy to measure the changes in cfDNA. Presence of ctDNA as indicated by chromosomal aberrations was investigated using sWGS. The sensitivity of the method was further enhanced using *in silico* size selection.

Results

The cfDNA concentration from baseline to 120 min after therapy was stable within 95% tolerance limits of +/- 2 ng/ml cfDNA. Changes in cfDNA were observed during therapy with an apparent qualitative difference between adenocarcinoma (average increase of 0.69 ng/ml) and squamous cell carcinoma (average increase of 4.0 ng/ml), see Figure 1. Silent chromosomal profiles were observed in 18 out of 23 samples across the two cancer types using sWGS. Size selection enhanced the detection rate from 22% to 74%. Tumor shrinkage on daily cone beam computer tomography scans during radiotherapy did not correlate with changes in concentration of cfDNA.

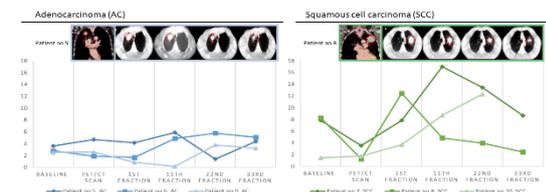


Figure 1. Representative PET/CT and CBCT scans and fluctuation in cfDNA concentration during radiation therapy in adenocarcinoma patients (AC) and patients with squamous cell carcinoma (SCC). Representative scans on corresponding time points are shown for AC (Patient 9) and for SCC (Patient 8).

Conclusion

cfDNA remain stable during the first 2 hours after a treatment fraction. However, based on the sWGS profiles, ctDNA represented only a minor fraction of cfDNA in this group of patients. The detection sensitivity of genomic alterations in ctDNA strongly increases by applying size selection.

EP-1369 Heart delineations based on 3DCT, AVG and MIP scans: are they representative of the total motion?
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Purpose or Objective

Evidence is emerging that the heart is more radiosensitive than previously assumed [1-2]. However, only delineations on the average projection or 3D CT scans are used for treatment planning. Therefore the motion of this organ due to respiration and contraction is not accounted for. In this pilot study, we assessed how representative the delineations based on the 3D CT scan, average (AVG) and maximum intensity projections (MIP) are.

Material and Methods

Both 3D and 4D CT scans for 10 lung cancer patients treated by SABR were used in this study. Median delineations, derived from 3 independent observers following a previously agreed protocol, were calculated on the 3D CT, AVG, MIP and 25% exhale scans. Delineations on each 4D phase scan (n=8) were created by propagating the median 25% exhale contours using RayStation v5.99. The volume representing the maximum extent of motion was estimated as the union of all 4D phase delineations (U4D), see figure 1 for an example. Surface distances from the U4D to 3D, AVG, MIP volumes were calculated. Distances in the most extreme surface points (1cm most superior/inferior, 10% most right/left/anterior/posterior) are reported.

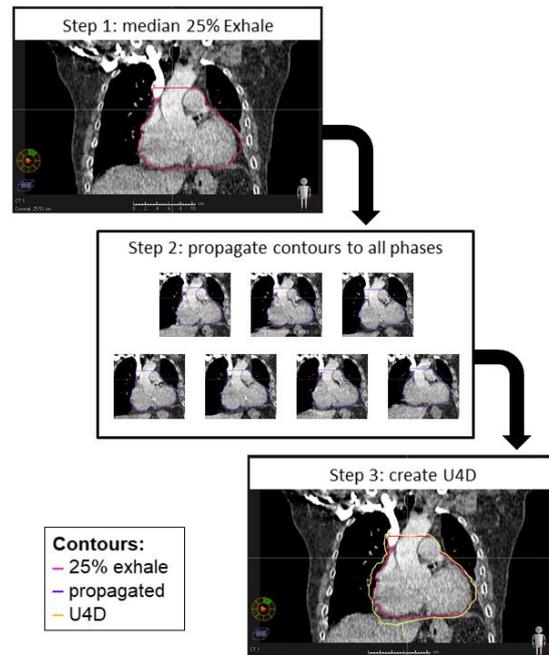


Fig 1: Creating the maximum extent of motion as the union of all 4D phase delineations (U4D).

Results

Figure 2 shows the distances for the most extreme surface points, for each delineation and direction (left-right, anterior-posterior and superior-inferior) summarized for

all patients. From the three delineations, MIP is the 'closest' to the maximum extent of motion, followed by AVG and 3D (smaller boxes and closer to zero).

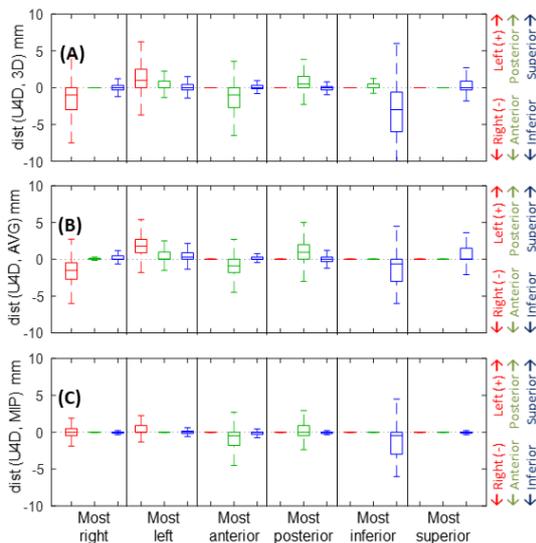


Fig 2: Box plot reporting distances of the most extreme points from the maximum extent of motion volume (U4D) to the (A) 3D, (B) AVG and (C) MIP volumes, discriminated by direction. The lines inside the boxes represent the medians, the boxes extend between the 25 and 75 percentiles and the whiskers represent Tukey fences (1.5 x inter-quartile range).

Conclusion

None of the delineations represented the heart's maximum extent of motion; the MIP was the 'most representative' volume. Current work includes determining the margin required for any of the delineations to better represent the maximum extent of motion. Research including dosimetric measurements and inter-observer variability is needed to determine the relevance of creating a planning organ at risk volume (PRV) of the heart.

[1] Johnson-Hart et al. *IJROBP*. 2018 Oct 1;102(2):434-442.

[2] Wang et al. *J Clin Oncol*. 2017. 35(13):1387-94.

EP-1370 The impact of fractionation on lymphocyte counts in stage III NSCLC received chemoradiotherapy

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Purpose or Objective

Radiation-related lymphopenia (RIL) is associated with inferior clinical outcomes in lung cancer patients treated with radiation (RT) and immune checkpoint inhibitors (ICIs) following RT. This study was performed to investigate whether fractionation regime affects the peripheral total lymphocyte counts (TLCs) in definitive concurrent chemoradiotherapy (CCRT) for unresectable stage III non-small lung cancer (NSCLC).

Material and Methods

We retrospectively reviewed 118 patients undergoing definitive CCRT for stage III NSCLC. Dose given to tumor and fractionation received determined by doctor and the intention from patients. The baseline of TLCs was defined as the value measured within one week before RT and a lymphocyte nadir was calculated as the minimum value measured during period of definitive RT. Patients were categorized into three groups. Group A received 2.0-2.2 Gy per fraction (ConRT), while group B received 2.3-2.8

Gy per fraction (moderately HypoRT, mHypoRT), and group C received 3 Gy per fraction Gy (HypoRT).

Results

There were 52 (44.1%) patients in the ConRT group, 34 in mHypoRT (28.8%) and 32 (27.1%) in HypoRT. Median planning target volume was larger in ConRT (283.89 cm³) than in mHypoRT (154.35 cm³, P = 0.005) and in HypoRT (118.76 cm³, P = 0.001) while there were no difference in gross tumor volume between groups (P = 0.395). Three groups had similar median baseline of TLCs (P = 0.959). During radiation, 70.59% of mHypoRT patients had severe lymphopenia (ie, TLC <500 cells/μl) vs 48.08% of ConRT patients, and 37.50% of HypoRT patients (P < 0.021). Multivariate linear analyses demonstrated that lower baseline TLCs (P < 0.001), higher mean lung dose (P = 0.004) and mHypoRT (P = 0.014) were significantly risk factors of RIL. Higher post-RT TLCs was associated with improved progression-free survival (hazard ratio [HR]: 0.585; 95% confidence interval: 0.369-0.926; P = 0.022) regardless of fractionation regime.

Conclusion

HypoRT may be more appropriate fractionation regime in definitive concurrent chemoradiotherapy for unresectable stage III non-small lung cancer (NSCLC) as it brings less severe RIL compared with mHypoRT and higher radiation dose compared with ConRT. Further large-scale studies are needed to confirm our findings.

EP-1371 Impact of target volume delineation on weekly simulation CT during conformal radiotherapy in NSCLC

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Purpose or Objective

Anatomical changes during radiotherapy in lung cancer might contribute to target missing and discrepancies between planned and delivered doses. Modern radiotherapy techniques manage the geometrical uncertainties of treatment planning and treatment delivery and thereby improve target coverage with a much steeper dose gradient and less irradiated normal tissue. The aim is to evaluate the shrinkage of target volume in patients with locally advanced NSCLC treated with concurrent radiochemotherapy (RCT) with an adaptive approach

Material and Methods

Patients with locally advanced NSCLC treated with RCT were investigated. All patients had stage IIIA/IIIB or intrathoracic relapse after surgery. Treatment was performed with a linear accelerator (Varian Medical System) in a photon regimen, with a 6/15-MV nominal energy and three-dimensional conformal technique with multiple planar and nonplanar beams. Concurrent chemotherapy regimens were platinum-based doublets or monotherapy. All patients received a weekly CT simulation. On each weekly CT the CTV was delineated and in case of tumor's shrinkage, a new CTV was created and a new treatment plan outlined ("replanning")

Results

From 2012 to 2014 replanning was outlined in 50 patients of 217 patients with locally advanced NSCLC treated with RCT and subjected to weekly simulation CT. Patients' characteristics were: mean age 69.6 years (range 38-92), squamous histology 56%, 32% adenocarcinoma, other 12%, stage IIIA 58% and IIIB 42%. The median total dose delivered was 66.6Gy (range 45-75.6) with standard fractionation. Median CTV at CT simulation was 125.2 cc. Contouring CTV on the weekly CT, we observed a progressive shrinkage of the target volume, in particular at the median dose of 19.8, 27, 36 Gy and 45 Gy we registered a reduction of 13%, 20%, 16%, and 43 %