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The Expanding Role of Physiologic Imaging in Radiation Oncology

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Functional imaging of tumor and normal tissue physiology provides novel opportunities to further optimize radiation therapy (RT) treatments by identifying refined critical structures and biological target volumes (BTVs) within the tumor for preferential targeting. Advances in functional imaging and adaptive RT techniques have the potential to lead to the development of improved dose−response relationships for normal tissues and RT treatments that are tailored to individual patients. In this "Oncology Scan" for the special issue on Imaging in Radiation Oncology, members of the physics editorial team discuss 3 thought-provoking articles that reflect recent and noteworthy advances in the combined use of functional imaging and adaptive RT to exploit heterogeneity in tumor and normal tissue biology. First, Welz et al (1) present early results of a phase 2 clinical trial aimed at prospectively determining the prognostic value of tumor hypoxia defined by [^{18}F]fluoromisonidazole (FMISO)−positron emission tomography (PET)/computed tomography (CT) and targeting hypoxic tumor volumes with dose escalation in patients with locally advanced squamous cell carcinomas of the head and neck (LASCCHN). Second, Lapointe et al (2) present a novel method for obtaining functional information about normal lung tissue using dual-energy CT (DECT). Third, Lee et al (3) present preliminary results of a study combining functional lung avoidance and dose escalation to BTVs for non−small cell lung cancer (NSCLC) patients. Treatment planning objectives are expanded to include reduction in dose to ^{99m}Tc-labeled macro aggregated albumin ([^{99m}Tc]MAA)−single photon emission computed tomography (SPECT)/CT perfused lung and redistribution of an escalated boost dose within a [^{18}F]fluorodeoxyglucose (FDG)-PET/CT−defined volume. The innovations presented in these 3 articles consist of using established physiologic imaging techniques in a novel way to enhance treatment planning in radiation oncology.

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Welz et al. Prognostic value of dynamic hypoxia PET in head and neck cancer: Results from a planned interim analysis of a randomized phase II hypoxia-image guided dose escalation trial. *Radiother Oncol* 2017. (1)

Summary: Molecular imaging offers unique opportunities to visualize relevant tumor physiology and adapt RT treatment plans to exploit biological heterogeneity between patients. In this work, Welz et al (1) report the preliminary results of a randomized phase 2 trial aimed at establishing a relationship between locoregional control (LRC) and baseline tumor hypoxia determined by dynamic [^{18}F]FMISO-PET imaging and assessing feasibility and toxicity of dose escalation to hypoxic tumors in patients with LASCCHN. The authors present an interim analysis of data from 25 patients. A baseline dynamic [^{18}F]FMISO-PET scan was acquired for all patients before RT and used to derive hypoxic volumes. Patients with baseline hypoxia were randomized either to conventional RT (70 Gy in 35 fractions) or dose escalation, in which the hypoxic volume was boosted to 2.2 Gy per fraction using a simultaneously integrated boost technique. The authors report that LRC in hypoxic patients receiving conventional RT (n = 10) was 44.4% and significantly worse compared with a 2-year LRC of 100% in the nonhypoxic group (n = 5) (median follow-up of 27 months). In hypoxic patients randomized to dose escalation (n = 10), 2-year LRC increased to 70.0%. No significant differences in acute and late toxicity were observed between dose escalation and conventional RT. In summary, these preliminary results demonstrate that tumor hypoxia identified on baseline FMISO-PET imaging is associated with increased local failure in LASCCHN patients. Although patient numbers are not yet adequate to determine whether improvements in outcome are

statistically significant, the authors have demonstrated that dose escalation to hypoxic volumes of LASCCHN tumors is feasible, well tolerated, and may result in increased tumor control.

Comments: Tumor hypoxia has been recognized as a major clinical risk factor in cancer therapy for many decades. Patients with hypoxic tumors not only have an increased risk of metastasis but are also more resistant to conventional treatments, such as RT and chemotherapy. Higher levels of hypoxia have been shown to result in poorer RT outcomes for a variety of tumor types (4, 5). These clinical results have generated much interest in developing functional imaging techniques that can be used to noninvasively and reliably quantify hypoxia in human tumors. In particular, molecular imaging with PET has been studied extensively (6) and provides a promising and practical method to identify patients who may respond poorly to conventional treatments.

Despite level 1a clinical evidence that hypoxia modification therapy can improve locoregional control in SCCHN patients (7), decades of negative or statistically insignificant clinical results have hampered widespread implementation of therapies aimed at overcoming the radioprotective effect of hypoxia. Poor patient selection may be a contributing factor to past failures of hypoxia-targeted therapies. In this work, Welz et al (1) use functional imaging to overcome this challenge of patient selection and provide new and encouraging preliminary results that further support the clinical use of hypoxia modification therapy for SCCHN. This is the first phase 2 randomized clinical trial investigating feasibility, toxicity, and efficacy of dose escalation to hypoxic volumes based on pretreatment dynamic FMISO-PET imaging. The authors demonstrate that LRC is significantly worse in hypoxic patients and that dose escalation to hypoxic tumors may result in enhanced LRC (2-year LC 70% compared with 44.4% in nonboosted patients). More patients and longer follow-up times are needed to determine whether durable LRC is significantly improved for patients with hypoxic tumors receiving dose escalation.

One of the main challenges with therapies targeting tumor hypoxia is pre-selection of the appropriate patient population. Clinical trials of treatment strategies aimed at overcoming hypoxic radioresistance must select hypoxic patients before randomization (5). Accurate methods to quantify the spatial and temporal distributions of hypoxia are therefore needed to identify patients who will actually benefit from a therapy aimed at targeting hypoxic radioresistance. The most common strategy, as used by Welz et al (1), consists of identifying a hypoxic tumor subvolume that will receive dose escalation (8). One potential barrier to this approach is that the spatial distribution of tumor hypoxia may change even over a period of several days for some patients (9). Practical strategies may therefore require periodic imaging of patients throughout their treatments, combined with adaptive planning, to fully exploit dose escalation for some patients.

Lapointe et al. Assessing lung function using contrast-enhanced dual-energy computed tomography for potential applications in radiation therapy. *Med Phys* 2017. (2)

Summary: In this work, Lapointe et al (2) present a technique utilizing contrast-enhanced DECT to determine the functional lung volume. They compute differential lung function for each lobe and compare with standard methods based on SPECT/CT and single-energy CT (SECT) in 5 patients. All patients presented in this study underwent perfusion SPECT/CT at free-breathing and contrast-enhanced DECT using a dual-source CT scanner (100 kVp, 140 kVp) at voluntary exhale breath-hold. A weighted average of the 2 image sets, referred to as a mixed CT, was also generated and used for analysis of the SECT. Two patients received an additional 4-dimensional CT scan, which was used in treatment planning to generate a functional dose−volume histogram, as proof of concept. Each segment of the lung was manually contoured by a radiation oncologist and used to calculate the differential function of the segments. The SPECT/CT perfusion studies in the lung assess the blood flow in a region according to an integrated number of counts. The DECT scans are used to calculate an iodine concentration map, which is used to determine the volume of perfused blood throughout the lungs. The contrast agent is distributed through the lung's entire vascular system, therefore a threshold on the CT numbers was determined visually, to limit the analysis of function to the lung parenchyma, removing the tumor and great vessels from the evaluation. In the SECT method the function is determined on the basis of CT numbers, which are assumed to be proportional to the functional level of each voxel. For the 5 patients evaluated in this study, the authors demonstrated a good correlation in the differential function per lobe between SPECT/CT and DECT (Pearson's coefficient $r = 0.91$). Single-energy CT showed a weaker correlation with SPECT/CT ($r = 0.46$), with mean differences in left lung differential function of 17%, compared with 7% observed for DECT. The authors also reported on the impact of the threshold values used in separating lung parenchyma from the great vessels and tumor and showed less than 1% difference for both DECT and SECT. The authors conclude that functional information from DECT scans shows a strong correlation with SPECT/CT data, making it feasible to utilize this information in optimizing the treatment plan on the basis of regions of higher and lower function, to help reduce toxicity.

Comments: One of the main limiting factors in the treatment of thoracic targets is the potential risk of radiation-induced lung damage. This can have a larger impact in lung cancer patients with compromised lung function and

other comorbidities (10). Although functional maps of the lung have been used for functional avoidance in treatment planning, clinical use has been limited by the availability and efficacy of imaging techniques. Implementation of functional imaging techniques, such as SPECT and SPECT/CT, provides a volumetric view of lung function, allowing us to identify the regions within the lung that are higher functioning compared with those that are less functioning and adapt the beam geometry and dose distribution accordingly (10).

Although SPECT/CT is the most commonly used technique for functional imaging in the lung, there is increasing interest in finding alternative imaging techniques that provide more accurate, higher-resolution imaging information or techniques that improve the overall workflow and accessibility by utilizing imaging techniques that are already part of the treatment process, such as PET, magnetic resonance imaging, or 4-dimensional CT (11, 12). Although much research has focused on magnetic resonance with various types of hyperpolarized gas, implementation of this technique is still limited to few specialized centers (13, 14). Computed tomographic imaging, on the other hand, is widely available across all RT departments, making it suitable for this application (15, 16).

In this work, Lapointe et al (2) provide a new CT-based methodology, using a DECT scanner for determination of functional regions in the lung. They also demonstrate the use of the resulting images for planning purposes and evaluation of a functional dose−volume histogram. Despite the limited number of patients studied here, the preliminary results seem to be promising and an improvement over the standard CT-based single-energy imaging techniques currently available.

Lee et al. Functional lung avoidance and response-adaptive escalation (FLARE) RT: Multimodality plan dosimetry of a precision radiation oncology strategy. *Med Phys* 2017. (3)

Summary: The work by Lee et al (3) reports a preliminary study evaluating the technical and dosimetric feasibility of a novel precision medicine approach for functional lung avoidance and target dose escalation in RT of locally advanced and unresectable NSCLC. The study investigators introduce a combination approach, whereby multimodality pretreatment imaging is used to simultaneously account for spatial heterogeneity in both pulmonary functional capacity and tumor metabolic uptake in plan optimization. The study serves as a precursor to an investigator-initiated phase 2 clinical trial (NCT02773238) to test the efficacy of functional lung avoidance and response-adaptive escalation radiation therapy (FLARE-RT).

Eight patients undergoing definitive RT for locally advanced NSCLC received standard of care treatment planning 4-dimensional CT, in addition to pretreatment lung perfusion [^{99m}Tc]-MAA-SPECT/CT and [^{18}F]-FDG PET/CT. The CT components from the functional scans facilitated rigid spatial registration with the planning geometry. Lung avoidance structures were automatically generated from the perfusion SPECT by partitioning lung voxels into 7 equally spaced bins between the minimum and maximum lung uptake values. For functional avoidance planning, 20 Gy mean lung dose was redistributed among bins inversely according to relative mean bin uptake. A threshold 70% of the maximum lung uptake was used to delineate highly functional lung for dosimetric evaluation. A BTV was identified as the union of the manually contoured gross tumor volume on CT and region of interest on FDG-PET determined by an automated gradient search. The BTV was similarly partitioned into 7 equally spaced bins between the minimum and maximum PET uptake values. Adaptive escalation planning linearly redistributed mean 14 Gy BTV concomitant boost according to relative mean bin uptake. A 1-cm-diameter sphere centered on the maximum BTV uptake voxel was used to delineate peak standardized uptake value (SUV_{peak}) for dosimetric evaluation.

The FLARE-RT plans were separately generated for both photon−volumetric modulated arc therapy (VMAT) and proton pencil beam scanning (PBS) for comparison against a conventionally optimized VMAT reference. A hybrid modality consisted of PBS beams used for functional avoidance in combination with VMAT arcs used explicitly for adaptive BTV escalation. Compared with the reference, FLARE-VMAT plans resulted in higher mean dose to BTV (73.7-61.3 Gy), higher mean dose to peak SUV_{peak} (89.7-60.8 Gy), and lower mean dose to highly perfused lung (7.3-14.9 Gy), at the expense of higher mean dose to heart (9.4-5.8 Gy) and higher maximum dose to cord (50.1-44.6 Gy). Compared with FLARE-PBS, FLARE-VMAT plans resulted in higher mean dose to SUV_{peak} (89.7-79.2 Gy), higher mean dose to normal lung (15.6-11.9 Gy), V_5 (62%-35%), V_{10} (46%-29%), and higher maximum dose to cord (50.1-15.6 Gy). The slope of voxel-wise linear dose redistribution between BTV dose and FDG uptake was significantly ($P = .002$) higher in magnitude for the combination FLARE-PBS plus VMAT (0.36 Gy per%SUV_{max}) compared with either FLARE-VMAT (0.27 Gy per%SUV_{max}) or FLARE-PBS (0.17 Gy per%SUV_{max}) alone. The linear regression slopes serve as an indication for the relative effectiveness by which BTV dose is linearly redistributed according to the FLARE-RT planning objectives.

Comments: This preliminary study is an innovative and promising step toward a precision framework for personalized RT of locally advanced NSCLC. The authors acted in response to converging lines of clinical evidence suggesting potential for improved local control (17) and mitigation of radiation toxicity (18) by utilization of multimodality pretreatment functional imaging in plan optimization. They

have demonstrated respective strengths and relative drawbacks of both VMAT and PBS implementations to affect voxel-level dose redistribution according to the spatial heterogeneities of lung perfusion and tumor metabolic uptake, while maintaining standard dosimetric constraints. They have further introduced the potential synergy associated with a broader approach leveraging the relative attributes of complementary delivery modalities.

Some potential limitations are evident that warrant further characterization as data are accrued in the ongoing trial. Notably, appropriate utilization of spatial registration methodology and associated implications cannot be understated. Voxel-level precision in redistribution dose painting must be considered within a spatial uncertainty framework, wherein local registration mismatch on the order of several millimeters in target or normal lung is possible. It is likely that at least an affine-level transform will be necessary for registration of the multiple image sets, particularly if not all acquisitions are obtained using treatment immobilization or if mid-treatment image-based adaptation in functional avoidance or BTV escalation is to be a possibility. Similar sensitivity considerations are applicable with respect to the choice of image resampling algorithm, as well as spatial dimension of any applied reconstruction smoothing kernels. The optimal scheme for designating the preferential functional avoidance hierarchy is also subject to ongoing debate. Various strategies, including, for example, percentile normalization, point-based threshold normalization, and automated clustering algorithms, have been previously proposed. The clinical implications with respect to functional delineation approach must be characterized. Likewise, as pointed out by the authors, it remains to be determined whether ventilation or perfusion imaging metrics optimally inform a functional avoidance framework for predicting or reducing radiation-induced toxicity. Finally, dosimetric gains in pulmonary dose redistribution should be considered in light of any potential escalation in cardiac dose, regardless of whether standard dosimetric constraints are met.

References

1. Welz S, Mönnich D, Pfannenberg C, et al. Prognostic value of dynamic hypoxia PET in head and neck cancer: Results from a planned interim analysis of a randomized phase II hypoxia-image guided dose escalation trial. *Radiother Oncol* 2017;124:526-532.
2. Lapointe A, Bahig H, Blais D, et al. Assessing lung function using contrast-enhanced dual-energy computed tomography for potential applications in radiation therapy. *Med Phys* 2017;44:5260-5269.
3. Lee E, Zeng J, Miyaoka RS, et al. Functional lung avoidance and response-adaptive escalation (FLARE) RT: Multimodality plan dosimetry of a precision radiation oncology strategy. *Med Phys* 2017;44:3418-3429.
4. Movsas B, Chapman JD, Hanlon AL, et al. Hypoxic prostate/muscle pO2 ratio predicts for biochemical failure in patients with prostate cancer: Preliminary findings. *Urology* 2002;60:634-639.
5. Rischin D, Hicks RJ, Fisher R, et al. Prognostic significance of [^{18}F]-misonidazole positron emission tomography-detected tumor hypoxia in patients with advanced head and neck cancer. *J Clin Oncol* 2006;24:2098-2104.
6. Kelada OJ, Carlson DJ. Molecular imaging of tumor hypoxia with positron emission tomography. *Radiat Res* 2014;181:335-349.
7. Overgaard J. Hypoxic modification of radiotherapy in squamous cell carcinoma of the head and neck—a systematic review and meta-analysis. *Radiother Oncol* 2011;100:22-32.
8. Bentzen SM, Gregoire V. Molecular imaging-based dose painting: A novel paradigm for radiation therapy prescription. *Semin Radiat Oncol* 2011;21:101-110.
9. Lin Z, Mechalakos J, Nehmeh S, et al. The influence of changes in tumor hypoxia on dose-painting treatment plans based on 18F-FMISO positron emission tomography. *Int J Radiat Oncol Biol Phys* 2008;70:1219-1228.
10. Marks LB, Spencer DP, Sherouse GW, et al. The role of three dimensional functional lung imaging in radiation treatment planning: The functional dose-volume histogram. *Int J Radiat Oncol Biol Phys* 1995;33:65-75.
11. Ireland RH, Bragg CM, McJury M, et al. Feasibility of image registration and intensity-modulated radiotherapy planning with hyperpolarized helium-3 magnetic resonance imaging for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2007;68:273-281.
12. Siva S, Thomas R, Callahan J, et al. High-resolution pulmonary ventilation and perfusion PET/CT allows for functionally adapted intensity modulated radiotherapy in lung cancer. *Radiother Oncol* 2015;115:157-162.
13. Bauman G, Scholz A, Rivoire J, et al. Lung ventilation- and perfusion-weighted Fourier decomposition magnetic resonance imaging: In vivo validation with hyperpolarized (3)He and dynamic contrast-enhanced MRI. *Magn Reson Med* 2013;69:229-237.
14. Couch MJ, Ball IK, Li T, et al. Inert fluorinated gas MRI: A new pulmonary imaging modality. *NMR Biomed* 2014;27:1525-1534.
15. Guerrero T, Sanders K, Noyola-Martinez J, et al. Quantification of regional ventilation from treatment planning CT. *Int J Radiat Oncol Biol Phys* 2005;62:630-634.
16. Guerrero T, Sanders K, Castillo E, et al. Dynamic ventilation imaging from four-dimensional computed tomography. *Phys Med Biol* 2006;51:777-791.
17. van Elmpt W, De Ruysscher D, van der Salm A, et al. The PET-boost randomised phase II dose-escalation trial in non-small cell lung cancer. *Radiother Oncol* 2012;104:67-71.
18. Faught AM, Miyasaka Y, Kadoya N, et al. Evaluating the toxicity reduction with computed tomography ventilation functional avoidance radiation therapy. *Int J Radiat Oncol Biol Phys* 2017;99:325-333.