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Functional Adaptation in Radiation Therapy

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The promise of adaptive therapy to improve outcomes in radiation oncology has been an area of interest and research in the community for many years. One of the sources of data that can be used to drive adaptive therapy is functional information about the tumor or normal tissues. This avenue of adaptation includes many potential sources of data including global markers and functional imaging. Global markers can be assessments derived from blood measurements, patient functional testing, and circulating tumor material and functional imaging data comprises spatial physiological information from various imaging studies such as positron emission tomography, magnetic resonance imaging, and single photon emission computed tomography. The goal of functional adaptation is to use these functional data to adapt radiation therapy to improve patient outcomes. While functional adaptation holds a lot of promise, there are challenges such as quantifying and minimizing uncertainties, streamlining clinical implementation, determining the ideal way to incorporate information within treatment plan optimization, and proving the clinical benefit through trials. This paper will discuss the types of functional information currently being used for adaptation, highlight several areas where functional adaptation has been studied, and introduce some of the barriers to more widespread clinical implementation.

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Functional adaptation in radiation oncology utilizes physiological information about targets or normal tissue from imaging or other tests in order to facilitate adaptive radiotherapy. Previously in this issue, adaptive radiotherapy (ART), has been defined as *radiotherapy where the delivered dose is monitored for clinical acceptability during the course of treatment and modified as needed with the goal of improving clinical outcomes*. Functional adaptive radiotherapy allows modification of the treatment plan to account for changes in target or normal organ function with the goal of accurately delivering dose to maximize normal tissue function and minimize tumor-preserving functions of the target. In most cases, functional adaptation would be applied on an offline timescale due to the required incorporation of functional tests or imaging into the treatment planning process. However, newer technologies could also support both online and real-time functional adaptation.

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Uses of Functional Information for Adaptation in Radiation Therapy

There are myriad types of functional information that are being used to inform radiation therapy plan design. Some data and images have long been used for baseline decision-making or planning, such as positron emission tomography (PET) imaging for staging and target delineation, or pulmonary function tests to ensure a patient has sufficient respiratory capacity to safely undergo therapy. Fewer functional data are being utilized to guide adaptation at present. In order to be useful for functional adaptation, one must be able to detect a change in function of the tumor or normal tissue, either globally or locally, that can be acted upon by changing the treatment plan. Here, we highlight several of the major categories as they may apply to functional adaptation.

Global Assessment of Patient Risk of Recurrence or Toxicity

Global assessments represent holistic measurements from blood measurements or other assessments that can provide

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information regarding organ or tumor function. These measures do not provide spatial resolution on the function of the patient, an organ, or tumor. Some of these measures have meaningful changes during the course of therapy which can be monitored and used as a basis of adaptation to improve outcomes. One such example is the use of indocyanine green (ICG) to measure liver function. Feng et al have used ICG level during radiation therapy for individualized adaptive therapy of dose in liver stereotactic body radiation therapy.[2] Cytokine levels present another opportunity for global functional adaptation. Bossi et al. demonstrated the potential for using cytokine levels to identify head and neck cancer patients at risk for mucositis.[3]

A wide array of pulmonary function tests, including forced spirometry, body plethysmography, impulse oscillometry, carbon monoxide diffusing capacity, fraction of exhaled nitric oxide, arterial blood gases, and a 6-minute walk test, were longitudinally evaluated by Torre-Bouscoulet et al and found to demonstrate functional change ahead of clinical imaging assessment, suggesting they could be targets for global functional adaptation.[4]

Additionally, functional indicators for tumors, such as circulating tumor cells, may be used to gauge treatment efficacy and adapt when appropriate. Currently, the use of circulating tumor cells and DNA for guiding baseline decision making is an area of study in a variety of different tumor types including breast, pancreas, lung, head and neck, and others.[5-8] Using CTCs or ctDNA for adaptation, while promising, is likely still several years into the future.

Functional Imaging in Radiotherapy

Functional imaging lends itself regularly to radiotherapy functional adaption. Barriers to the utilization of functional imaging include technical uncertainties such as those from the imaging itself, image processing and image registration. A recent paper by Verma et al highlighted functional imaging use for target delineation and includes a number of useful references from a variety of body sites.[9] Below, various functional imaging and other methods for functional adaptation in targets and normal tissues are highlighted.

Functional Adaptation to Maximize Tumor Control

Undeniably, functional imaging modalities, such as PET, single photon emission computed tomography (SPECT) and magnetic resonance (MR) imaging can be and have been utilized for defining target volumes in radiation therapy and for assigning relative risk levels and prescription dose for procedures such as intensity modulated dose painting.[10-16] For those modalities which demonstrate changes during radiotherapy that can be tied to outcomes, there becomes the potential to use this information for functional adaptive therapy. Functional adaptation for targets has a longer history than functional adaptation for normal tissues. Perhaps the most observed example would be adjustment or boosting of the tumor target based on midtreatment imaging capable of identifying a high-risk tumor subvolume. Functional features that have been targeted for subvolume boosting are hypoxia, low perfusion, and high metabolism.[11,13,17]

Hypoxia has been studied across multiple tumor types and is one example of a potentially functionally changing phenomenon which can be targeted by adaptive therapy and adaptive boosting. A recent study by Epel et al demonstrated an advantage in therapeutic ratio when delivering a boost to hypoxic tumor regions.[18] Another clinical trial in lung and other tumors demonstrated the ability to perform longitudinal hypoxia imaging using 18F-EF5-PET and found that it was a predictor of local recurrence.[19] Trials in PET-based adaptation for lung cancer, for example, have demonstrated a potential local control benefit of using midtreatment adaptation and boosting to targets defined by FDG-PET.[17] In high-risk head and neck cancer, persistent low blood volume[20] or high apparent diffusion coefficient (ADC)[21] tumor subvolumes have been identified as potential targets and an ongoing randomized trial is underway to evaluate the effect of subvolume boosting to 86Gy EQD2 (NCT02031250). Figure 1 shows an initial and adaptive treatment plan for a patient being treated on this randomized trial, boosting areas of poor perfusion or restricted diffusion on multi-parametric MRI.

However, functional boosting must be done with both expertise and caution. Teng et al showed the potential difficulty in identifying such subvolumes both initially and in the adaptive scenario.[22] When looking at head/neck patients with FDG-PET, DCE-MRI, and DW-MRI, the overlap of so-called “high risk” regions was fairly small between modalities. The lack of persistent overlap after several weeks of treatment was even more concerning. It is clear that functional adaptation, especially for targets, may have multiple target regions that could be boosted. However, a recent report by Berwouts et al suggested that boosting subvolumes may come at an increased risk of toxicity and there is uncertainty as to whether or not the benefit outweighs this risk.[23] Work and trials are ongoing to test this hypothesis. More randomized trials testing hypotheses of improved outcomes when using functionally adaptive targets are needed to bring these techniques to the mainstream.

In favorable prognosis HPV-related oropharynx cancer, pretreatment low metabolic tumor volume (MTV) has been associated with favorable outcomes.[24] Additionally, decreases in GTV volume, FDG-uptake and hypoxia as assessed by 18F-PET have been noted midtreatment to be associated with favorable response.[25-27] Ongoing functional imaging adaptive clinical trials include: (1)The Mi-ADAPT trial to prospectively de-escalate RT dose based on pre- and midtreatment FDG-PET response assessment (NCT03416153), (2)The MR-ADAPTOR trial is ongoing to de-escalate RT based on weekly MRI assessment where GTV volume will be decreased weekly as seen on MRI with areas of tumor that completely resolve during RT to receive a minimum of 50 Gy(NCT03224000),[28] (3) ARTFORCE trial to redistribute RT dose to 64-84 Gy based on pre- and midtreatment PET (NCT01504815).

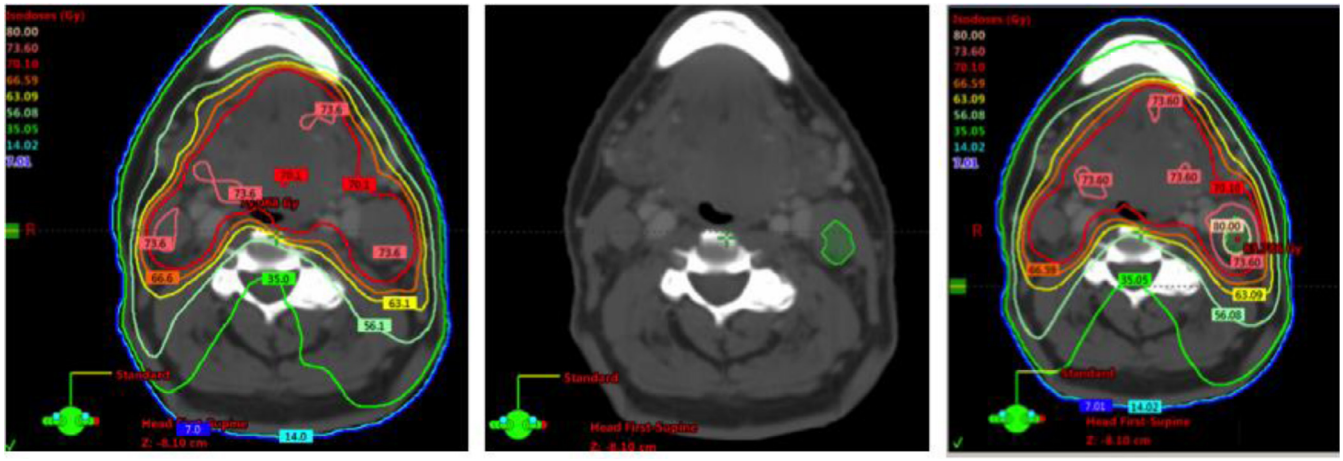

Figure 1 Patient with a cT4N2 HPV+ squamous cell carcinoma of base of tongue was treated with definitive chemoRT on an institutional prospective clinical trial randomizing patients to receive RT boost to areas of poor perfusion or restricted diffusion in multiparametric MRI. (A) Initial RT plan (B) Low BV (poor perfusion) area of tumor spatially identified on pre- and mid-treatment DCE-MRI (C) Adaptive replan to treat the low blood volume tumor subvolume in to left neck to 80Gy (86Gy EQD2).

In cervical cancer, Mayr et al. established functional risk volumes from DCE-MRI that could predict outcomes as early as 2-5 weeks into treatment, suggesting the potential for adaptation.[29] A follow-up study from the same group studied 21 cervical cancer patients with longitudinal multiparametric functional images and found that radiomic assessment of tumor heterogeneity over the course of treatment had the potential to personalize radiotherapy. Figure 2 shows pretreatment and 2- and 5-week midtreatment multiparametric images from the same patient. Notable changes in image intensity between modalities and time-points can be observed.

Imaging, such as PET, for adaptive therapy has been studied in various body sites including abdominal sites. A recent review by Bulens et al suggests that PET-based adaptation for GI tumors could be very advantageous due to the heterogeneity observed in these tumors.[30] Despite this, the reports on the use of functional adaptation in GI tumors are limited. One potential challenge, but also an opportunity for adaptation, is

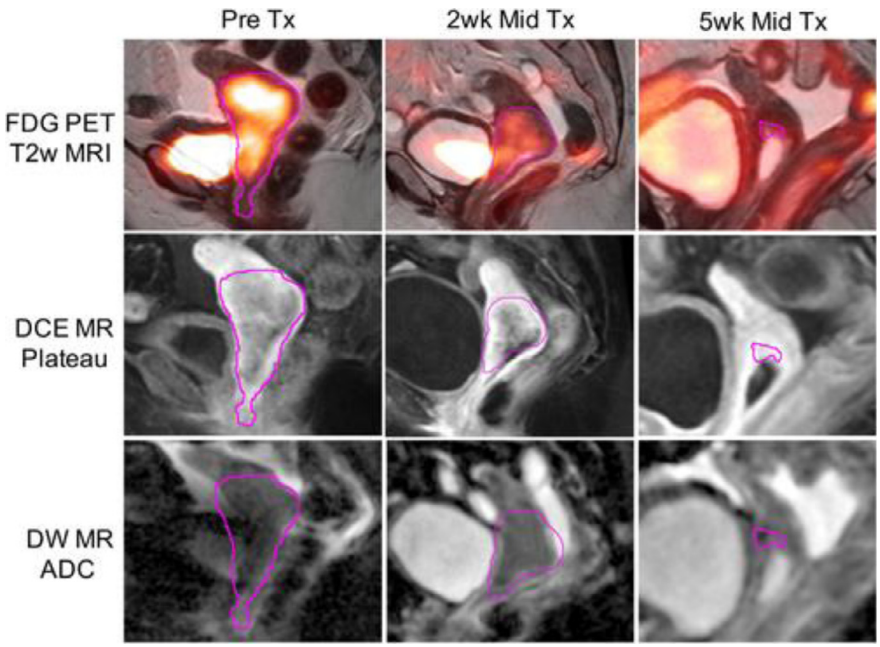

Figure 2 MRI–PET fusion, DCE MR plateau (postcontrast), and DW MR ADC images for a representative cervical cancer patient at three different timepoints: prior to radiation therapy, early during RT (2 weeks), and midway during RT (5 weeks). Gross tumor was delineated at each timepoint (magenta contour), from which voxel distribution histogram features were extracted. Tumor voxels suffering from bladder artifact on FDG PET or distortion artifacts on DW MRI were excluded by threshold from calculation of SUV and ADC histogram features, respectively. Note the variable heterogeneity in image intensity between modalities (FDG PET, DCE MRI, DW MRI) and variable changes during therapy. *Reproduced with permission from John Wiley and Sons. Original Figure 1 and caption from Bowen et al.*[1]

the extensive anatomical change often observed during treatment of both tumor and surrounding organs. As in many other body sites, the combination of anatomic and functional adaption is essential, but it may be difficult to both realize and differentiate the benefits. In esophageal cancer, Ma et al showed significantly improved local response and overall survival with an FDG-PET defined boost approximately 75% of the way through treatment although details of the PET adaptive strategy were not given.[31] In pancreatic cancer, Wilson et al investigated the potential of defining an FDG-PET boost volume in 17 patients and found that the pretreatment PET could predict areas of residual disease for boosting.[32] It is interesting to note the extensive manual segmentation, image registration, and image transfer procedures highlighted in this study, further demonstrating the need for efficiency and automation if functional adaptation is going to become more widely applied. The authors also point out that a more robust strategy for adaptation in pancreas may involve biological markers as well as multimodal imaging including, for example ^{18}F-fluormisonidazole-PET/CT, ^{18}F-fluorthymidine-PET/CT, and diffusion-weighted MRI.

Outside of the abdomen, functional changes can be easier to isolate and act upon. In the brain, for example, there are a number of PET tracers of interest which can identify hypoxia, metabolism, proliferation, inflammation, and cellular membrane synthesis. A recent review by Troost et al highlighted many potential modalities for defining functional tumor subvolumes.[33] In a study of 26 patients, the proliferative volumes from 18F-FLT-PET/CT were associated with overall survival.[34]

MRI-guided adaptation for targets is attractive due to the recent advances to combine MR and radiotherapy delivery (Co-60 or Linac).[35] This reduces some of the uncertainty in offline adaptive registration since the on-board MR is used for imaging guidance and potential adaptation simultaneously. Additionally, on-board MR imaging can improve access to repeat functional imaging throughout the course of treatment, providing longitudinal functional imaging information without additional burden to the patient or the clinical workflow. Several groups have begun to show the potential for real-time functional imaging on this type of platform for both brain and liver, indicating that functional adaptation would be a possibility in the future.[36] Bringing online functional adaptation into the clinic comes with many challenges. A recent review by Datta et al describes some of the innovations for onboard functional imaging while bringing to light the many challenges, including imaging time, internal physiological motion, and the availability of specialized imaging sequences required for functional imaging.[37]

In general, anatomical MR images required for patient setup can be acquired in a fraction of the time it takes to acquire and process functional MR images, regardless of the specific implementation in various MR-linac systems. This increases the time that the patient is on the table and can potentially compromise delivery accuracy because of patient discomfort. Therefore, all implementations of on-board functional MR imaging on the MR-linac should be optimized to minimize interference with the treatment delivery.

Direct Treatment Planning Objectives

While functional images can be used for defining subvolumes that can be used in inverse planning cost functions for intensity modulated delivery techniques, other sophisticated methods of plan optimization can take functional imaging information as direct input into the objective function to potentially further maximize the therapeutic ratio. Wu et al have demonstrated the potential to maximize the probability of post-treatment global liver function by taking into account the dose-dependent response of perfusion or function loss during liver SBRT.[38] Similarly, in lung, Matuszak et al have demonstrated the ability to use lung perfusion maps as input to minimize functional generalized equivalent uniform dose (gEUfD) in conventionally fractionated lung treatment.[39] In addition to direct optimization of objectives that minimize normal tissue risk, one could also define a tumor control probability objective based on functional imaging input, such as was defined based on the hypoxic subvolume in recently published work by Chvetsov et al.[40] In head and neck, a voxel-based objective to maximize TCP was implemented into the research version of a commercial planning system, showing promising translation moving closer to clinical use.[15]

Functional Adaptation to Minimize Normal Tissue Risk

One form of utilizing functional information to affect outcomes is to adapt a treatment plan in order to minimize or reduce the risk of damaging normal tissue or causing toxicity. This type of adaptation could be done in response to a perceived injury in order to prevent further damage, such as in the case of an inflamed esophagus noted on PET imaging during treatment for lung cancer or based on predicted damage due to modeled or observed changes between two functional scans, such as baseline vs midtreatment lung ventilation imaging or liver functional maps with agents such as gadoxetic acid. In this scenario, many investigators are still struggling to show impactful differences in treatment plans and outcomes based on functional avoidance treatment plans vs standard plans. In most cases that have looked at function adaptation, the change from baseline standard planning to baseline functional planning is noticeably more than from baseline functional to adaptive functional planning. While there may be changes in the functional images from initial to midtreatment, the main changes observed were tumor regression, which resulted in functional improvement, but not necessarily due to redistribution of the function.[41] The interim analysis of a multi-institution functional avoidance clinical trial included patients who were resimulated and updated functional avoidance structures were created from resimulation 4DCT.[42] While it was not reported to what extent the plan may have changed based on functional versus anatomic changes, it is promising to observe that an adaptation including functional changes is achievable in a clinical time frame. Figure 3 shows an initial and adaptive

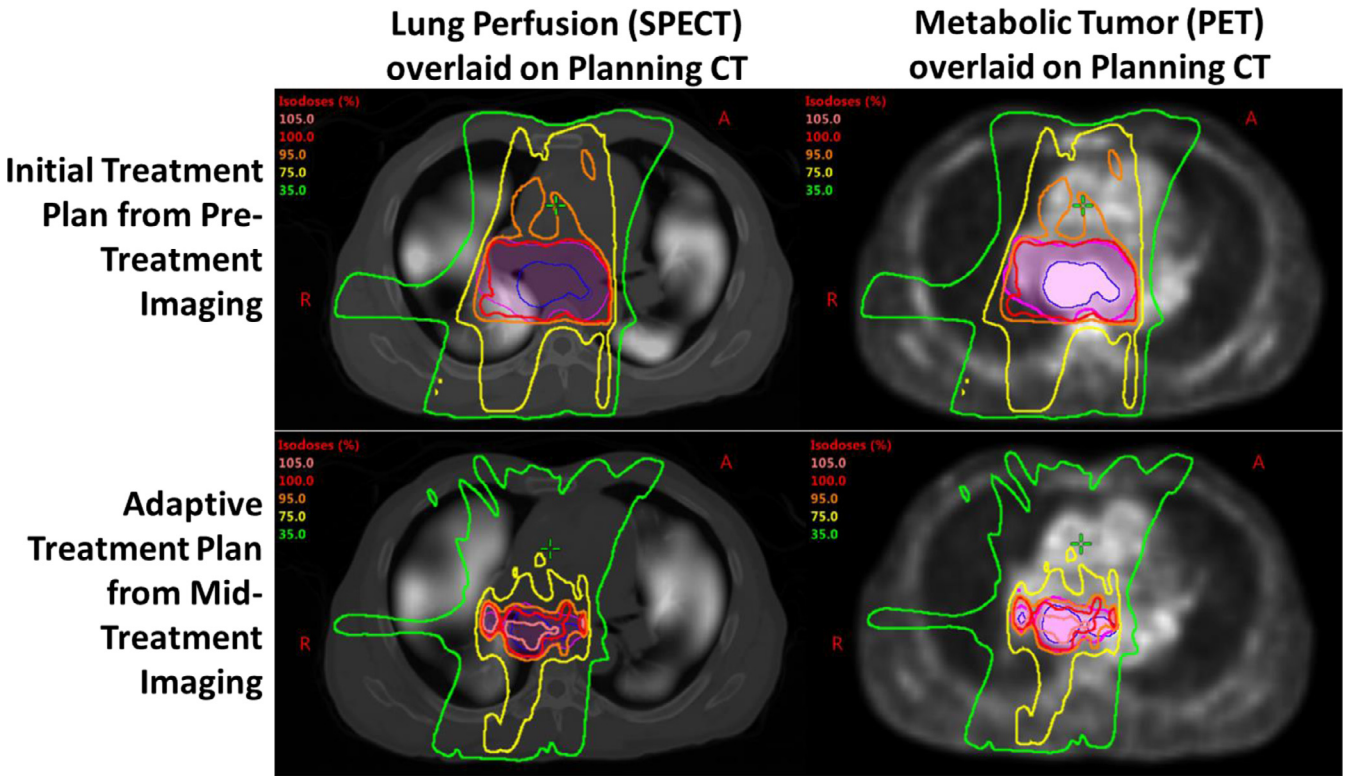

Figure 3 Initial (top row) and adaptive treatment plans for a patient on personalized adaptive trial for advanced stage nonsmall cell lung cancer. Functional target information (FDG-PET, 2nd column) and normal lung function (perfusion SPECT, first column) is used to guide plan optimization for both baseline and adaptive planning.

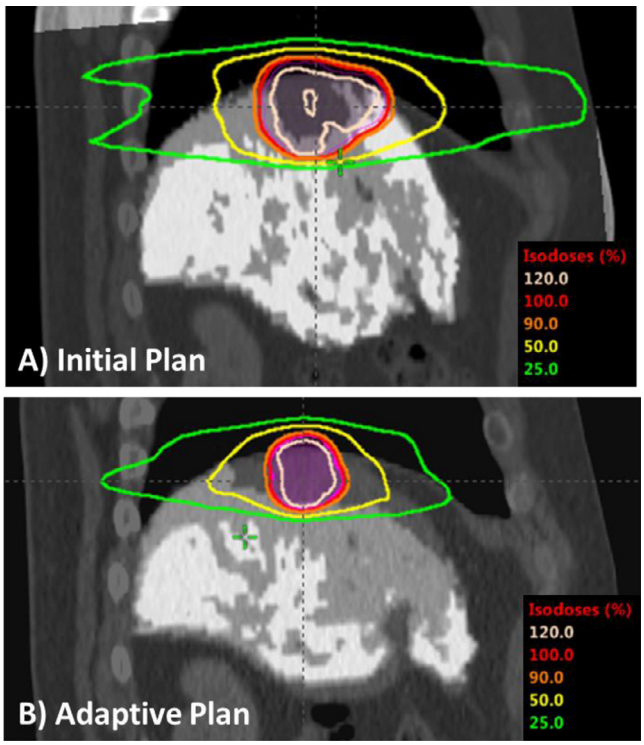

Figure 4 (A) Initial and (B) adaptive treatment plans for a patient on personalized adaptive trial for hepatocellular carcinoma. Functional liver information (thresholded functional maps from gadoxetic acid DCE-MRI) is used to guide plan optimization for both baseline and adaptive planning. Note that the target volume is also adapted.

treatment plan based on both tumor and normal tissue response from PET and SPECT images. Similar to determining the clinical benefits from anatomic vs functional adaptation, it may be difficult to completely separate the benefits to normal tissue from functional avoidance planning vs reduced tumor volumes.

The use of imaging to evaluate neurocognitive function in the brain and potentially minimize any radiation-induced functional changes is an area of great potential. The advances in both online and offline MR imaging show promise in this area. Recent work by Ajithkumar et al evaluated the role of imaging to prevent neurocognitive dysfunction in survivors of pediatric brain tumors treated by radiotherapy.[43]

In head and neck cancer, late xerostomia has been correlated with pre-RT parotid features on FDG-PET and MRI as well as midtreatment CBCT volumetric changes most prominent on FDG-PET.[44-46] Midtreatment CT perfusion changes in pharyngeal constrictors are correlated with physician-graded late dysphagia and DCE-MRI changes in swallowing structures correlate with RT dose.[47,48] These studies identify potentially actionable functional imaging changes for prospective study.

Immune Response

Immunotherapy is emerging as an additional modality for the treatment of cancer[49] and there is significant interest in understanding how to incorporate it with traditional

treatment modalities. Immunotherapies rely on activation of the adaptive and innate immune system to limit tumor growth and spread. The emergence of this treatment modality has led to focusing on the immune tumor microenvironment as a determinant of efficacy and toxicity of treatment. It is now appreciated that tumors are multicellular organs with variable immune infiltrates which may both assist with oncogenesis and promote immune clearance. Functional imaging and global assessments may allow functional adaptation to maximize immune stimulation in the future.

Functional imaging assessments of the immune system are a potential way to adapt treatment. Immunotherapy relies on CD8+ T effector cells. Recently, a radiomic signature to identify tumors with increased T-cell infiltration has been developed, and this could be utilized to escalate therapy to those patients who are not developing antitumoral immunity.[50] Further, tracers including PD-L1 ^{89}Zr may allow functional adaptation through measuring engagement of immune checkpoints in tumors.[51]

Global assessments of antitumoral immunity provide another possible methodology to adapt treatment. Recent work by Formenti et al suggested that cytokine levels and immune cell changes could predict response to combined immunotherapy and radiation.[52] Further analysis in a responding patient supported the hypothesis that radiation-induced exposure of immunogenic mutations to the immune system may contribute to the infrequently observed abscopal responses. Thus flow cytometric measurement of the number and function of T cells could inform treatment plans. Quantification of mid-treatment cytokines could help provide insight into the immune status of the tumor and dictate differential treatment.[53] These new developments are exciting from the standpoint of functional adaptation.

Challenges in Functional Adaptation

It is clear that there is potential for identifying actionable functional changes in patient status through functional imaging and myriad other functional evaluations of the patient, tumor, and normal tissues and organs. However, there remain many challenges to see prospective functional adaptation in clinical use both in and eventually out of clinical trials.

Proving Clinical Benefit

As is the case in many clinical endeavors, one must prove the clinical benefit of functional adaptation is worth the resources required to maintain a functional adaptation program. Clinical benefit in the functional adaptation scenario requires that researchers have identified a proper time point for adaptation, be able to adapt in a safe and meaningful way, and then observe a benefit in patient outcomes. This process can be extremely lengthy depending on the type of adaptation being evaluated. It can also require difficult-to-obtain resources such as time and imaging. In most cases, functional information used for adaptation is not gathered during treatment as part of the standard of care. Therefore, patients must undergo additional tests to obtain the functional status. These additional tests can be burdensome on patients and make it more difficult to complete clinical trials. With the ever-growing costs of health-care, we must remain diligent in our efforts to prove true patient benefit to functional imaging incorporation and adaptation within radiation oncology.[54]

Timeline for Adaptive Therapy

A challenge in any adaptive scenario is obtaining the information needed for a safe adaptation in a timeframe that is necessary for that intervention to be of benefit to the patient. With functional adaptation, there is a higher likelihood of required image processing and evaluation before making a plan change. For functional adaptation in the tumor, it is becoming clear that multiparametric imaging may be required to identify targets for adaptation and dose painting. Therefore, work must be done to register, segment, and run various analyses to determine which areas to adapt dose to. While progress has been made to automate these steps, there is still manual review and editing that can be required. In a thoracic functional avoidance trial utilizing 4DCT, investigators estimated that an additional 1.5 hours per patient was required by physics and dosimetry for functional avoidance treatment planning and oversight. The use of 4DCT for functional adaptation is attractive because it is typically available within the radiation oncology clinic and easily taken and processed as part of the general standard of care. Other modalities used for functional avoidance such as PET and SPECT imaging have the disadvantage of requiring potentially more coordination between departments, extra patient appointments, and additional transfer and processing. Therefore, the clinical benefit of utilizing these clinical resources must be compelling.

Another challenge in the adaptive timeline is uncertainty and standardization of when to adapt to maximize benefit to the patient. This requires extensive imaging and other data to create models to predict the optimal adaptation time. There is also uncertainty on whether or not to adapt based on pre or midtreatment data or the change in mid and pretreatment data. Given all of these challenges, there is likely a threshold for choosing adaptive patients in order to derive a noticeable benefit.

Adaptive Optimization Strategies

Depending on the type of functional information being employed for adaptation, the requirements on the treatment plan optimization algorithm will differ. For example, devising a new treatment plan based on a new segmented target region may be much less complex that optimizing an objective function that maximizes patient survival based on voxelized input from functional imaging. For those adaptations which require more complex optimization strategies, it may be necessary to support a noncommercial treatment plan optimization system and thus difficult to deploy the strategy outside of an in-house clinical trial. Gago-Arias et al recently studied multiple adaptive optimization strategies meant to treat tumors with heterogeneous biological characteristics.[55]

In their dose painting scheme, they optimized objective functions which minimized tumor cell survival or maximized the homogeneity of the density of the surviving cells. They also studied the difference between daily and weekly adaptive optimizations.

Wu et al employed an interior point optimization scheme to optimize the probability of post-treatment liver function using pretreatment functional imaging data from dynamic contrast-enhanced MRI.[38] Similar schemes would be necessary depending the objective function form if one needs to take into account voxel-based imaging data to calculation organ function. On the other hand, if similar gains can be achieved with simpler contour-based optimization schemes, it may be easier to deploy on a wider scale and implement within clinical trials. Figure 4 shows an initial and adaptive plan from an adaptive liver trial at the University of Michigan where liver function maps generated from gadoxetic acid DCE-MRI[56] are discretized into 3 levels and used in treatment planning to minimize dose to the high and mid-functional levels within the cost function. The changes during treatment in the functional maps are apparent in the blended images.

Isolating the Signal

In adaptive therapy based on functional change, it can be easy for the predicted improvement based on the functional intervention to be masked by improvements based on more geometric or anatomic adaptations. There is not always a clear line between an anatomic versus functional change. For example, in adaptively boosting residual tumor based on midtreatment imaging, one may be targeting some specific biology or functions of the tumor. Therefore, complementary imaging and tests that can help determine underlying function of tissue may help us to uncover the differences. Incorporating functional information into tumor shrinkage predictions may be able to separate outliers and further improve therapeutic gains from adaptive therapy.[57] However, it still remains a challenge due to the multiple potential sources of uncertainty that can contribute to masking the true effects. Imaging, image processing, image registration, and modeling uncertainties can all contribute to this challenge. As mentioned previously, a functional avoidance radiotherapy trial in lung included adaptive resimulation for some patients, but it is unknown the true benefit of the functional adaptation vs anatomic adaptation.[41]

Discussion

The role of radiation therapy in cancer treatment has evolved over the past several decades from a primary treatment modality giving a uniform dose to an area of both tumor and normal tissues to an extremely precise and targetable treatment where dose can be modulated within the tumor and normal tissue and combined with a number of other therapeutic approaches. Increasing sources of functional data relating to tumor subvolumes and normal tissue function and response have begun to further alter the role that radiation therapy can play in the treatment of cancer by allowing improved targeting, better regional functional avoidance, and triggering of immune responses. This functional data can be obtained and used for decision making and treatment planning not only prior to treatment, but also during and after treatment to guide adaptive therapy as well as build predictive models for normal tissue and tumor response. While extremely promising, the utilization of functional adaptation in radiation therapy is only beginning. Implementation of functional adaptation is challenging due to uncertainties associated with the incoming data and modeling, as well as challenges in obtaining outcomes information. Furthermore, determining the benefit of functional adaptation will require implementation of well-designed clinical trials that would allow us to separate the impact of anatomic adaptation from that of functional adaptation. As a field, we must prioritize determining the benefits of functional adaptation to improve patient outcomes.

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