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Variability in the Sequencing of Palliative Radiation with Targeted Therapy in the Treatment of Metastatic NSCLC: A Single Institutional Patterns of Care Analysis

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Purpose/Objective(s): The treatment of metastatic non-small cell lung cancer (NSCLC) varies on an individual basis but increasingly involves the use of palliative radiation in combination with molecularly targeted agents. There are currently no accepted guidelines for how to sequence or integrate palliative radiation with targeted therapies. Due to uncertainties regarding the timing and sequencing of these therapies, we sought to describe current patterns of care with respect to how these modalities are integrated in practice for patients with metastatic NSCLC.

Materials/Methods: The medical records of 96 consecutive patients who were treated with palliative radiation for metastatic NSCLC from June 2011 to December 2018 at a tertiary care-based comprehensive cancer center were reviewed. Subjects who received molecularly targeted therapies, including immuno-oncology agents, within thirty days of receiving palliative radiation comprised the primary population of the analysis. The timing of when radiation was delivered in relation to treatment with targeted therapy was documented, as well as clinical and treatment-related variables such as age, gender, performance status, and radiation dose. Only patients treated with external-beam techniques were included. Logistical regression was used to determine variables that influenced the likelihood of starting molecular targeted therapy in the pre-irradiation versus concurrent/post-irradiation setting.

Results: A total of 50 patients were identified that satisfied inclusion criteria with 59 courses of radiation treatments. The most commonly treated regions with palliative radiation were the brain (n=34), followed by the spine (n=11), and lung (n=11). The proportion of metastatic NSCLC patients treated by both palliative radiation and molecularly targeted agents have increased over time with 7 patients in 2011-2014 and 43 patients in 2015-2018. The most common targeted agents were tyrosine kinase inhibitors (n=31) followed by immunotherapy (n=25) and other biologic agents (n=3). The most commonly used radiation fractionation regimen was 30 Gy in 10 fractions (31%). Eighty-one percent (81%) of the patients started targeted therapy prior to initiation of radiation therapy, five percent (5%) during radiation therapy and fourteen percent (14%) post completion of radiation therapy. A significant proportion of patients (52%) experienced overlap of palliative radiation and molecularly targeted therapy.

Conclusion: While significant variability exists in the timing of palliative radiation with molecularly targeted therapies, the most common sequence identified was a sequential approach using the latter followed by the former. Additional data on how to optimally integrate palliative radiation with molecularly targeted therapies is needed.

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Impact of Patient's Age on Efficacy of Immune Checkpoint Inhibitors in Advanced Cancers: A Systematic Review and Meta-Analysis

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Purpose/Objective(s): The effects of immunosenescence on the efficacy of immune checkpoint inhibitors (ICI) in advanced cancers are unclear. We aimed to assess the difference in efficacy of ICI in advanced cancers between age groups ≥75 versus (vs) < 75 years old and ≥ 65 vs <65 years old.

Materials/Methods: We searched various biomedical databases for randomized trials (RCTs) comparing ICI with standard of care for treatment of advanced cancers that had available hazard ratios (HR) for overall survival (OS) according to the age groups (≥ 75 vs < 75 years old or ≥ 65 vs <65 years old). We calculated the pooled OS HR and its 95% confidence interval (CI) in the predefined age groups using a random-effects model and assessed the heterogeneity between the two estimates using an interaction test. Subgroup analyses include disease site, line of therapy, class of ICI and trial design.

Results: We found nine RCTs (5667 patients) for age groups ≥ 75 vs < 75 years old and 23 RCTs (13623 patients) for age groups ≥ 65 vs <65 years old. The difference in efficacy between ≥ 75 years old (HR 0.90 (95%CI 0.67-1.21)) and < 75 years old (HR 0.76 (95% CI 0.63-0.91)) was not significant (interaction p (IP) = 0.34). Subgroup analyses showed that there was a significant difference in efficacy between ≥75 years old (HR 1.19 (95%CI 0.85-1.68)) and < 75 years old (HR 0.73 (95% CI 0.63-0.84)) (IP = 0.01) in the second line setting. There was no difference in efficacy between age groups ≥ 65 (HR 0.77 (95% CI 0.70-0.86)) and <65 years old (HR 0.75 (95% CI 0.68-0.84)) (IP= 0.73). Subgroup analyses for age groups (≥65 vs <65 years old) recapitulated these findings.

Conclusion: The efficacy of ICI in patients ≥ 75 years old in the second line setting is significantly lower compared to patients < 75 years old. Future studies should focus on improving the efficacy of immunotherapies in elderly patients.

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Great Vessel Motion Mapping from 4D MRI to 3D CT - Implications for Oligo Metastatic Spinal SBRT Vessel Constraint

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Purpose/Objective(s): 4D-MRI imaging offers good soft tissue details & a real time motion assessment. We hypothesize that the actual volume of the aorta and the dose received by it would be more than what it seems on a static planning CT-image due to the dynamic pulsatile motion of the great vessel. In this study, we made an effort to quantify the volume and dose variations of the aorta with the volumes marked on planning CT-scan Vs 4D-MRI scan based PRV generation in cases of oligo metastatic spine SBRT.

Materials/Methods: Five patients of oligo metastatic spine SBRT (Lumbar-2; Dorsal-3) were chosen for this study. All patients underwent planning CT scan using deep inspiratory breath hold (DIBH) technique with RPM device. All patients underwent 4D-MRI scan sequences (FIESTA 4-chamber view, contrast LAVA, DEFFICO sequences) using pulse gated technique with breath holding in the treatment planning position on 1.5T MRI machine. Breathhold 4D MR Scan mitigates respiratory motion and allows us to capture true pulsatile motion. Aorta was delineated in 2 clinical contexts (1) Aorta MRI: Aorta delineated in one of the 4D-MRI bins (4 chamber view) was deformably propagated onto the rest of the bins using intensity based deformable registration algorithm software and the PRV for the aorta was generated. The PRV Aorta MR volume was registered with BH CT Scan and contours were mapped. (2) Aorta CT: On static BH planning CT scan. The target volume and all other OARs were contoured on the Planning CT scan and transferred to TPS for planning. The target coverage parameters and OAR constraints were achieved as per RTOG protocol. The PRV Aorta volumes on MRI and CT along with the D max and Threshold dose received by the respective PRV Aorta (Aorta MRI & Aorta CT) where assessed. These parameters were analyzed using Paired sample t test in SPSS software.

Results: The median motion of aorta due to its pulsations was 2mm (Range 1-2.5mm). The PRV Aorta Volumes in MR were significantly more compared to CT (p value-0.008). Similarly, the D max and threshold dose received by the PRV Aorta MR as compared to CT were more and were statistically significant (p Value-0.05 and p Value-0.008 respectively).

Conclusion: We noticed statistically significant change in the volumes and doses (max and threshold) of aorta contoured on 4D-MRI vs Planning CT scan. As the tolerance limit of great vessel (aorta) for single fraction spine

SBRT is higher than the maximum doses delivered to the target, these results may not hold any significance but this study may form a basis for future studies of SBRT in abdominal malignancies close to great vessels in terms of dose fluctuations due to their pulsations. This is the first study reported in literature and proof-of-concept to map the 4D MR motion on the 3D CT datasets & analyze the dose deformations.

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Intra-Fraction Motion of Non-Spine Bone SBRT Patients

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Purpose/Objective(s): SBRT has become increasingly applied to non-spine bone oligometastases or in the setting of re-irradiation; however, treatment guidelines are not well-defined. The purpose of this study was to determine the planning target volume expansion necessary to adequately compensate for intra-fraction patient motion of non-spine bone SBRT targets in the femur and iliac.

Materials/Methods: Twenty-five non-spine, bone SBRT patients (7 femur, 18 iliac), treated between August 2017 and December 2018, were retrospectively evaluated for this study under IRB approval. GTV targets were defined based on MRI and CT imaging with an additional 1-2 cm CTV expansion into bone. Initial patient positioning was performed using calculated shifts to isocenter from markers on the immobilization device. Intra-treatment imaging was performed between treatment arcs with stereotactic x-rays and orthogonal kV images, with additional verification using cone beam CT (CBCT) images if detected shifts were out of a prespecified tolerance of 1-2 mm and 1-2 degrees. All intra-treatment images were carefully aligned to planning images over 6 degrees of freedom using a 2D-3D match for planar images or a 3D-3D match for CBCT. The standard deviations of the intra-treatment imaging shifts were then used to model patient movement during treatment. Ellipsoids were fit to target volumes by assessing the lengths of the 3 principle axes of each target. Each ellipsoid was then rotated by the observed patient shifts and rotations. A Monte Carlo method was used to numerically solve for the volume of target missed due to a given set of shifts and rotations. The isotropic expansion required for each target volume to achieve 99% target coverage was found to account for 99% (3*sigma) of the observed treatment shifts and rotations.

Results: A total of 98 intra-treatment images were evaluated (39 femur, 59 iliac). For femur cases, intra-fraction patient shift standard deviations were 0.6, 0.6, and 0.4 mm in the lateral, longitudinal and vertical directions and 0.21, 0.52, and 0.23 degrees in pitch, roll and rotation axes respectively. For iliac cases, intra-fraction shift standard deviations were 0.4, 0.5, and 0.4 mm in the lateral, longitudinal and vertical directions and 0.32, 0.41, and 0.23 degrees in pitch, roll and rotation respectively. An isotropic 2 mm target margin was adequate to achieve 99% target coverage for 99% of all observed shifts during treatment for femur cases and a 1.5 mm isotropic margin was required to achieve similar metrics for iliac cases.

Conclusion: The goal of this study was to determine the target margins necessary to account for patient motion observed during non-spine bone SBRT treatments of the femur and iliac using modern immobilization devices. The results imply that intra-fraction treatment imaging is unnecessary if at least 2mm and 1.5mm target margins are added for femur and iliac SBRT treatment planning respectively.

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Stereotactic Ablative Radiotherapy (SABR) May Reduce the Need for Long-Term Androgen Deprivation Therapy (ADT) in Patients with Oligometastatic Prostate Cancer

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Purpose/Objective(s): We hypothesized that using SABR to treat men with 1-5 prostate adenocarcinoma metastases may reduce the need for long-term ADT.

Materials/Methods: Men with 1-5 nodal, skeletal, or visceral prostate adenocarcinoma metastases were treated with SABR on a prospective clinical trial (NCT01859221) or registry. Active prostate disease was treated with standard radiotherapy. ADT was recommended but not required. Follow-up imaging was not required without PSA progression. Biochemical progression-free survival (bPFS) was defined as a PSA rise $\geq$2 ng/mL after SABR, clinical-PFS (cPFS) as new metastases on radiographic/clinical assessment, castrate-resistant-PFS (CRPC-PFS) as PSA/clinical progression despite continuous ADT, and widespread progression-PFS as $\geq$6 new metastases. Outcomes were assessed using the Kaplan Meier method from the start of the first course of SABR. Additional courses of SABR were considered at the time of oligoprogression. Metastasis site control was calculated from the start date of each course of SABR and censored at time of last imaging/biochemical assessment or widespread progression. Univariate analysis was performed using log-rank test.

Results: 37 men (29 clinical trial and 8 prospective registry) received SABR to 102 metastases (62 non-spine bone, 22 spine, 17 lymph node, and 1 lung). 95% had hormone sensitive disease. Doses ranged from 18-50 Gy in 1-10 fractions (50 Gy/10, 64% and 50Gy/5, 30%). 6 patients had synchronous primary disease. 32% had 1 metastasis, 32% had 2 metastases, and 34% had 3-5 metastases. 9 patients (24%) declined ADT, 15 (41%) stopped ADT after 6-12 months, and 13 (35%) remained on long-term continuous or intermittent ADT ($\geq$24 months). Median follow-up was 3.6 years (1.7-5.2 years). 3-year metastasis site control was 97%. There was a trend towards improved 3-year bPFS survival in men who received upfront long-term ADT compared with no/short-term ADT (51% versus 14%, $p = 0.08$). However, long-term ADT did not appear to improve OS (80% versus 86%, $p = 0.33$), CRPC-PFS (61% versus 78%, $p = 0.5$), widespread-PFS (51% versus 61%, $p = 0.74$), or cPFS (38% versus 41%, $p = 0.86$). Of the 24 patients who initially declined or received short-term ADT, the median time to next therapy was 1.8 years (0.6-5.2), and 63% remain alive without clinical or 46% without biochemical progression and 21% remain off therapy. Only 1 grade 3+ toxicity (lumbar radiculopathy) was attributed to SABR.

Conclusion: Oligometastatic prostate cancer caries a favorable long-term prognosis and SABR resulted in excellent metastasis site control with low morbidity. The majority of men declined upfront long-term ADT with no apparent impact on clinical disease control, progression to CRPC, or survival. These results warrant further validation including assessment on the impact on quality of life.

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Outcomes from Stereotactic Body Radiation Therapy (SBRT) for Oligometastatic Colorectal Cancer (CRC)

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Purpose/Objective(s): Recent studies have demonstrated a potential survival advantage in using ablative radiation to treat oligometastatic disease traditionally treated with systemic therapy alone. We aim to better understand outcomes in CRC patients with oligometastases after ablative treatment using a single institution prospectively collected SBRT database.