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OncoFlash - Research Updates in a Flash!

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Is Stereotactic Body Radiotherapy a Safe Treatment for Ultra-central Non-Small Cell Lung Cancers?

Stereotactic Radiation for Ultra-Central Non-Small Cell Lung Cancer: A Safety and Efficacy Trial (SUNSET) Meredith EG et al. Int J Radiat Oncol Biol Phys 2024 [1].

- Thirty patients with early stage (T1-3N0M0) non–small cell lung cancer (NSCLC) were enrolled in one of 5 Canadian centres to assess the maximum tolerated dose of stereotactic body radiotherapy (SBRT) for ultra-central (UC) lesions. A time-to-event continual reassessment method was employed in this phase 1 study.
- UC tumours were defined by a planning target volume (PTV) that abuts or overlaps with the central bronchial tree, oesophagus or pulmonary vessels. Inclusion criteria required tumours to be located within the lung parenchyma and the patient to have an Eastern Cooperative Oncology Group (ECOG) score of 0–2. Patients with hilar nodes or endobronchial invasion were excluded from the study.
- The primary outcome was to determine the maximum tolerated dose of SBRT, defined as: the highest dose associated with less than 30% of participants undergoing grade 3–5 treatment-related toxicity within 2 years post-treatment. The starting dose was 60Gy in 8 fractions, with options to escalate to 60 Gy in 6 or 60 Gy in 5 fractions. These options were removed from the trial protocol after recruitment began. Multiple recruiting centres acknowledged that these escalated doses are higher than those on their protocols for central tumours, and opted against giving higher doses to even more centrally located tumours. All recruited patients received 60 Gy in 8 fractions.
- Secondary outcomes included time to progression, progression free survival (PFS), overall survival (OS) and quality of life measures. The median follow-up was 3 years (range: 0.74–4.2 years). Two patients (6.7%) experienced grade 3 to 5 dose-limiting toxicities; one had grade 3 dyspnoea and another had grade 5 pneumonia on a background of undiagnosed interstitial lung disease. Actuarial outcomes at 3 years included local control in 89.6%. Three-year OS was 72.5% (95% CI 52.3–85.3%) and 3-year PFS was 66.1% (95% CI 46.1–80.2%). Quality of life scores decreased over time, with a significant decrease in the FACT-G score at 2 years from baseline (-11.5 ± 17 (SD) $p = 0.0007$). At 3 years, the difference from baseline was no longer significant (-2.3 ± 12.2 (SD) $p = 0.56$).
- SBRT of 60 Gy over 8 fractions to UC NSCLC in a carefully selected cohort limited to those with lung parenchymal and excluding nodal lesions was associated with a low adverse event rate. The authors will update the patient outcomes with a publication following the 5-year timepoint.

Can Radiotherapy Dose be Safely De-escalated in Human Papillomavirus (HPV)-related Oropharyngeal Carcinoma Based on Assessment of Individual Tumour Hypoxia?

Hypoxia-Directed Treatment of Human Papillomavirus Oropharyngeal Carcinoma. Lee N et al. J Clin Oncol 2024 [2].

- One hundred and fifty-two participants with HPV-related tonsil, base of tongue or unknown primary oropharyngeal cancer suitable for treatment with radiotherapy and concurrent high-dose cisplatin or carboplatin were enrolled to this phase 2 trial at 7 US

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centres. All patients were staged T0-2/N1-2c/M0 and underwent surgical resection of their primary disease, with technique left at the surgeon's discretion.

- ^{18}F-fluoromisonidazole (FMISO) positron emission tomography (PET) was performed around 3 weeks post-operatively to assess baseline disease hypoxia status. Hypoxia was determined by a hybrid quantitative-qualitative technique. 30 Gy intensity modulated radiotherapy (IMRT) at 2 Gy/fraction/day targeting the resected primary site (entire oropharyngeal axis for unknown primary site), gross neck nodes and areas at risk of microscopic spread was planned for all patients. Those with baseline hypoxia (n = 110) underwent a further FMISO PET 1–2 weeks into treatment. Those without resolution of hypoxia on repeat scan (n = 24) also received a 40 Gy boost in 2 Gy/fraction to a total of 70 Gy. One hundred and twenty-four patients received the 30 Gy regimen.
- The primary endpoint was 2 year loco-regional control (LRC). Secondary endpoints included distant metastasis, PFS, OS and patient-reported quality of life outcomes.
- LRC was 94.7% (CI 89.8–97.7), comparing favourably with the author's historical standard of care control rate of 95% and other series. 2-year PFS was 94% and 96% for the 30 Gy and 70 Gy cohorts, respectively. Two-year OS was 100% and 96%.
- Acute toxicities were more prevalent in the 70 Gy cohort. 96% vs 57% ($p < 0.001$) experienced acute dysphagia in the 70 Gy and 30 Gy cohorts. Other acute toxicities were experienced less in the 30 Gy cohort: dermatitis (47.6% vs 95.8%, $p < 0.001$), oral mucositis (78.9% vs 95.8%, $p < 0.001$) and dysgeusia (93.8% vs 100%, $p < 0.001$). Hypothyroidism was less common in the long term in the 30Gy cohort (12.5% vs 31.8%, p 0.05).
- This is a novel, biomarker-guided radiation dose de-escalation study. Access to FMISO PET is not universal, and its use as a biomarker is not yet fully validated. Follow-up was short and therefore did not allow for a long-term clinical outcome comparison.

Is Actinium-225-PSMA Radioligand Therapy a Safe and Effective Treatment for Metastatic Castrate Resistant Prostate Cancer (mCRPC)?

Actinium-225-PSMA radioligand therapy of metastatic castration-resistant prostate cancer (WARMTH Act): a multicentre, retrospective study. Sathekge M et al. Lancet Oncol 2024 [3].

- Prostate specific membrane antigen (PSMA), expressed by mCRPC cells, is an attractive target for therapies. ^{225}Ac emits high-energy alpha particles, in contrast to the beta particles emitted by ^{177}Lu, already used in PSMA-targeted radioligand therapy.
- Retrospective study of 488 men with mCRPC who received at least one cycle of ^{225}Ac-PSMA-RLT in 7 centres across four countries/continents was performed to assess primarily OS and PFS, and secondarily prostate specific antigen (PSA) response and salivary gland, haematological and renal toxicities.
- The median number of cycles received was 2 (IQR 2–4). 38% of participants had received at least 4 lines of treatment for mCRPC prior to commencing ^{225}Ac-PSMA-RLT. 91% of participants received ^{225}Ac-PSMA-RLT as a last-line therapy due to ineligibility for other options.
- The median follow-up period was 9 months (IQR 5–17.5 months). Multivariate predictors of OS included PSA decline of 50% or over (HR 0.348, $p < 0.0001$), liver metastasis (HR 1.895, $p = 0.0025$), peritoneal metastasis (HR 5.025, $p = 0.0002$) and anaemia at baseline (HR 1.615, $P = 0.0016$). The baseline ECOG was not predictive of OS in univariate analysis (HR 1.223, $p = 0.19$), but was predictive of PFS in univariate analysis (HR 1.452, $p = 0.002$); however, it was not predictive of PFS in multivariate analysis (HR 1.031, $p = 0.82$).
- Xerostomia was common and reported in 68% of participants after 1 cycle of ^{225}Ac-PSMA-RLT and increasing with subsequent cycles. Prevalence of anaemia increased from 67% at baseline to 80% after ^{225}Ac-PSMA-RLT. Leukopaenia and thrombocytopaenia were also more prevalent after ^{225}Ac-PSMA-RLT as was renal function impairment, which increased from 50% to 55%.
- ^{225}Ac-PSMA-RLT is an effective therapy in this group of patients that provides an alternative PSMA-directed therapy in mCRPC. Cost-effectiveness was not considered in this study.

Do Immune Checkpoint Inhibitors in Neoadjuvant or Adjuvant Treatment Regimens Result in More Treatment-related Deaths and High-grade Toxicities?

Treatment-related adverse events, including fatal toxicities, in patients with solid tumours receiving neoadjuvant and adjuvant checkpoint blockade: a systematic review and meta-analysis of randomised controlled trials. Fujiwara Y et al. Lancet Oncol 2024 [4].

- Twenty-eight phase 2 (n = 9) and 3 (n = 19) RCTs incorporating 16,976 patients were included in this systematic review and meta-analysis of adjuvant and neoadjuvant immune checkpoint inhibitors are used for solid tumours. Included trials were required to report treatment-related deaths. Included studies compared immune checkpoint inhibitor use in combination with the treatment used in the control group.
- The addition of immune checkpoint inhibitors to either a neoadjuvant or adjuvant treatment regimens

did not result in a significant increase of treatment-related deaths (OR 1.76, p = 0.073). Forty treatment-related deaths were identified in 9864 patients treated with immune checkpoint inhibition. This compares with 13 treatment-related deaths occurred in the 7112 patients not treated with checkpoint blockade.

- The most common immune checkpoint inhibitor-related fatal toxicities were pneumonitis (15%), myocarditis (12.5%) and colitis (7.5%).
- Subgroup analyses of the trials of the addition of neoadjuvant or adjuvant cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) blockade (n = 7), programmed death 1 (PD-1) blockade (n = 10) and PD-L1 blockade (n = 11) to routine regimens found no increased risk of death.
- Neoadjuvant and adjuvant use of immune checkpoint inhibitors was associated with greater incidence of grade 3-4 adverse events (OR 2.73, p <0.0001) as well as those of all grades (OR 2.6, p <0.0001), with types of reactions not specific to immune checkpoint inhibitor class. On subgroup analysis, significantly increased grades 3-4 adverse effects were limited to immune checkpoint inhibitor use in the adjuvant and not the neoadjuvant setting.
- This study utilises large numbers of patients and provides important insights into the use of immune check point inhibitors, constituting a useful tool for clinical practice.

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