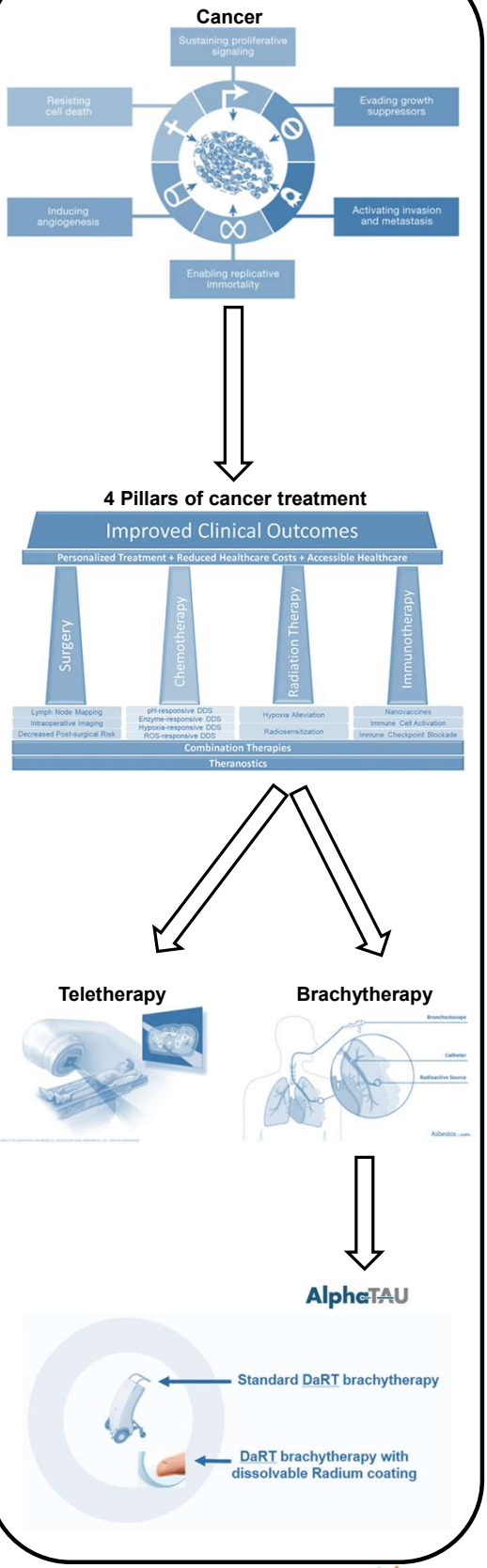
Diffusing Alpha-Emitters Radiation Therapy: Enhanced Understanding of Daughter Migration, Improved Safety Estimates, and the Potential of Deliberate 224Ra Release

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Introduction and Research aim

Abstract

Diffusing Alpha emitters Radiation Therapy (Alpha DaRT) utilizes intratumoral 224Ra-labeled sources that release short lived, alpha emitting daughters to provide ultra localized treatment. This technique has been applied to over 100 patients worldwide, showing significant promise with high clinical efficacy in challenging tumor sites where conventional radiotherapy often lacks suitable solutions, such as the pancreas and Glioblastoma Multiforme (GBM). This study evaluates the safety of the treatment and the radiation dose to limiting Organs at Risk (OAR) using a refined ICRP biokinetic model, calibrated with data derived from patients, mice, and pigs.

Innovation and Impact of DART in Cancer Treatment

Pancreatic cancer remains one of the most aggressive malignancies, with limited
treatment options and poor prognosis. Unlike External Beam Radiation Therapy (EBRT), which often causes damage to surrounding organs at risk (OARs), DART offers a highly localized and targeted approach. This technique involves implanting metallic sources loaded with 224Ra into tumors, where its short-lived alpha-emitting progeny destroy cancerous cells without affecting nearby healthy tissues.

DaRT technology is investigated both in Israel and worldwide. Recent clinical results demonstrate the promise of this approach: 41 patients, primarily treated at Hadassah Medical Center, exhibited an average of overall life extension of 11 months post-treatment. Among the patient were 2 partial responses and one complete response (no evidence of disease). Such outcomes underscore the potential of DART as a game-changing modality for cancers located in areas difficult to reach or in radiation sensitive environment.

My research seeks to better model the administered dose to OARs and target structures while expanding the treatment options and modalities by developing:
1. Biokinetic Model for Accurate Dosimetry and refining existing models to provide more accurate estimates of the doses
delivered to patients.
2. Evaluating the actual doses received by OARs, improving treatment planning and safety assessments to allow for larger tumors volumes to be treated.

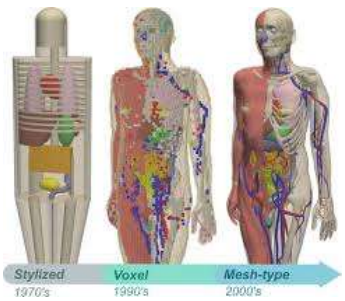
Results and Discussion

Results

Clinical analysis revealed a 212Bi/212Pb blood activity ratio of 0.77 ± 0.16 which was significantly lower than standard ICRP predictions and necessitated a model modification adding a direct 212Bi release pathway from red blood cells. The murine study established a renal alpha particle tolerance dose between 2 and 6 Gy, supported by a strong linear correlation (R2 = 0.987) between blood and renal specific activities. Pig experiments showed that intracerebral sources exhibited ~3 times lower 212Pb systemic leakage than subcutaneous sources. Integration of these data established a conservative clinical safety limit of 4 mCi for maximal administered 224Ra activity in humans.

Conclusions

This study establishes a validated biokinetic framework that integrates multi-species data to provide precise, patient-specific dosimetry for Alpha DaRT model. By using correlated blood and renal activity, we were able to estimate the nephrotoxicity in alpha particles in mice. The refined biokinetic model demonstrates that the radiation dose to the kidneys is lower than previously estimated, supporting a significant increase in the number of administered 224Ra sources potential.



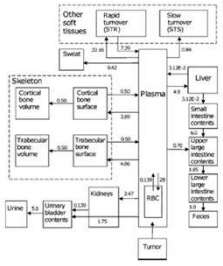


Figure 3: Block diagram of the biokinetic lead model, transfer rates (in d^{-1})