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The International Cancer Expert Corps (ICEC): Implementing a global force to address the catastrophic rise in cancer in the developing world.

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Purpose: The growing burden of cancer and non-communicable diseases in the developing world is well recognized by the WHO and IAEA culminating in a declaration of the need to address them by the UN General Assembly in 2011. It is projected that ~75% of cancer cases will be in Low & Lower-Middle Income Countries (LMIC) by 2025. Effective solutions require technological and logistical approaches and sufficient expertise to establish sustainable capacity and capability in country.
Materials/methods: Recognizing that the essential component for any solution requires expertise, the ICEC (1,2) was established in 2013 as a not-for-profit non-government organization to address the human resources shortage. An extensive analysis by the Global Task Force for Radiation for Cancer Control under the auspices of the Union for International Cancer Control indicates that a solution is both possible and economically feasible (3).
Results: There is a confluence of forces and opportunities that makes the solution to what appears to be an overwhelming problem one that can and must be addressed. This includes:
a) the necessity for collaboration among existing programs, allowing for individual recognition and approaches while minimizing competition that can dissuade investment
b) a cohort of early stage career cancer experts committed to global health
c) participation of the private sector in global cancer education and training
d) success in addressing health disparities in indigenous populations in resource-rich countries that is part of global cancer care
e) an influx of retirees seeking opportunities to use their skills
f) interest in eliminating dangerous nuclear material especially in unstable countries
The ICEC mentorship model is in active organizational and funding development. Essential features and challenges are:
a) establishing a career path with metrics for academic advancement so that time, effort and contributions become an integral component of a medical career and not an extracurricular activity
b) supporting time and effort in both resource-rich and –poor countries
c) conducting guideline/protocol-based multi-modality cancer care at international standards so that LMICs can participate fully in research and training
d) being multi-national from the outset, capitalizing on existing twinning programs
e) creating an essential role for radiation therapy.
f) incorporating innovations in physics, information technology and telecommunications
Conclusions: The need, opportunity and a path forward for reducing the global burden of cancer are in hand. A concerted effort and sustainable investment by a broad range of partners are essential. The ICEC addresses the sustainable human resources problem with catalytic and disruptive innovation in cancer care delivery including a career path, economics, technology, public-private partnerships as well as visionary leaders and investors.

Key words: Global health, health disparities, disruptive innovation

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Comparison of Arterial Input Functions by Magnitude and Phase Signal Measurement in DCE MRI of brain cancer patients

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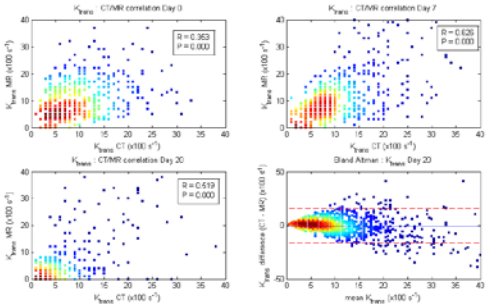
Purpose: The aim of this work is to (1) investigate the accuracy and robustness of magnitude and phase-derived arterial input functions (AIF) as compared to “gold standard” volumetric DCE-CT; and (2) evaluate the impact of individualized magnitude and phase signal AIF measurements on resulting perfusion parameter maps using a common 4D temporal dynamic analysis (TDA) method in metastatic brain cancer patients treated with stereotactic radiosurgery.
Methods: We evaluated 14 brain metastases imaged with volumetric DCE-CT (Toshiba, Aquilion ONE) and DCE-MRI (IMRIS 3T Verio) at baseline then 7 and 21 days post-radiosurgery. Both variable-flip-angle (VFA) T1 measurements and dynamic imaging used 3D-FLASH with matched TE/TR of 1.8/4.8ms, with 1x1x5 mm voxels. Voxel-based whole brain TDA was performed on all data using in-house software to: (1) compare the AIF curve from DCE-CT using the internal carotid artery (AIF) and sagittal sinus (VIF) curve from the DCE-CT against DCE-MRI [magnitude (VIFmag) and phase-based (VIFph)] (2) compare kinetic parameters area under the curve (AUC) and K_{trans}, assuming the Modified Tofts model when using individual CT AIF, MRI Magnitude and Phase-based VIF (Sagittal Sinus) and population-based AIF as well as individual voxel-based T_{10} maps versus assumed T_{10}= 2400 msec.
Results: The AUC of individual AIF and VIF on DCE-CT were similar and resulting median K_{trans} (0.048 +/- 0.03 s^{-1}) was also similar. For DCE-MRI, using measured voxel-based T_{10} maps, the resulting K_{trans} was higher than for CT using individual VIFmag (0.181 +/- 0.11 s^{-1}) or VIFph (0.121 +/- 0.099 s^{-1}). This is likely resulting from the smaller AIF peak since the population AIF (which more closely resembles CT) correlates better to DCE-CT metrics. The measured median T_{10} value was 1572 +/- 594 (n=41) and using the assuming T_{10}=2400 ms resulted in significantly higher K_{trans} (0.3 +/- 0.14 s^{-1}) and AUC ($p<0.0006$). Voxel-wise correlation between K_{trans} values than from CT and $MRI_{popAIF,T10}$ resulted in high R^2 values (~0.5, $p<0.05$) for all imaging days and showed good interchangeability (see Bland-Altman plot in Figure 1).
Conclusion: This preliminary data highlights the stability of DCE-CT calculations as well as susceptibility of DCE-MRI K_{trans} measurements to various imaging factors, including AIF selection and T_{10} values used in the model. Using the same voxel-based analysis platform for both DCE-CT and MR significantly improved correlation values confirming the need to take into account tumor heterogeneity when assessing functional data.

Keywords: Brain metastases, biomarker, perfusion imaging



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Focal adhesion signaling and therapy resistance in cancer
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Purpose: Intrinsic and acquired resistance of tumor cells to therapy originates from multiple avenues. One avenue includes extracellular matrix (ECM) and proteins that facilitate cell interaction with ECM. These focal adhesion (FA) proteins coalesce at specific membrane sites as large multiprotein complexes functioning as signaling hubs and structural nexus. Molecular targeting of various FA proteins has shown promising preclinical data. Even more interesting are rather recent findings about activation of prosurvival bypass signaling under specific inhibition of integrins and their dependence on ECM stiffness.
Materials/methods: Different tumor models were investigated such as head and neck, pancreatic ductal carcinoma, glioblastoma. We performed a systematic targeting of FA proteins using siRNA or antibodies where applicable. In-vitro and in-vivo survival assays and a variety of mechanistic studies were conducted.
Results: To date, integrins turned out as most promising druggable candidates. Most interesting, molecular targeting generally showed to prominently induce unfavorable prosurvival signaling. Multitargeting strategies were successful to abrogate this bypass signaling and optimize radiochemosensitization.
Conclusions: Integrins and other FA proteins are promising cancer targets. Identification of underlying mechanisms is still the needle eye. From our data, multitargeting approaches on top of conventional radiochemotherapy look beneficial as specific tumor cell functions can be inhibited.

Keywords:
Focal adhesions, resistance, bypass signaling

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Evaluation study of in-beam PET performances with a Carbon ion linac (CABOTO)
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Purpose: In-Beam PET is a *well-established* method for dose monitoring in hadrontherapy, but its effectiveness is still limited by the accelerator duty cycle [1]. CABOTO [2, 3], CArbon BOoster for Therapy in Oncology, is an innovative development project of an efficient high-frequency linac for hadrontherapy that can accelerate ^{12}C ions and H_2 molecules up to 430 MeV/u, bunched in pulses of the order of 2-5 µs with a repetition rate of 360 Hz.
Thanks to its low duty cycle (less than 0.1%), CABOTO allows the γ-pair acquisition with PET during 99.9% of the treatment time. The main goal of this research is to describe how the CABOTO time-structure influences the in-beam PET images, reconstructed by acquiring the γ-coincidences during the irradiation time as well as in a period following it.
Methods and Materials: The study has been carried out performing several simulations with the FLUKA Monte Carlo code [4, 5] together with MATLAB routines written to take into account analytically the CABOTO time structure.
In a first set of simulations, the $ß^+$ emitter isotopes, produced by the interaction of a pencil beam (protons and ^{12}C-ions) with a water phantom, are identified. Due to the special time structure, the PET detector is sensitive also to γ-pair produced in the $ß^+$-decays of isotopes having half-lives ($T_{1/2}$) in the ms range; the most relevant ones are ^{13}O ($T_{1/2}$=8.6 ms), ^{12}N ($T_{1/2}$=11 ms), ^{9}C ($T_{1/2}$=126.5 ms), ^{8}B ($T_{1/2}$=770 ms). Considering the CABOTO time structure and the acquisition time window as defined before, the $ß^+$ activity versus time has been extrapolated for all $ß^+$ emitters.
A second set of simulations including a PET detector has been carried out, using a modified version of the routines originally developed in Fluka for conventional PET [6]. Arrival times of gamma pair coincidences on the PET detector have been scored and analysed in order to verify their correspondence to the beam irradiation profile. The history of each coincidence has been traced in order to identify the parent isotope, which helps to discriminate and evaluate the true signal versus the background noise. Based on this information, the PET images could be reconstructed from the true coincidences from both the online and offline signal, and quantify the differences.
Results & Conclusions: This work describes the results obtained in the study of the influence of CABOTO time structure on the PET scanner reconstruction. The $ß^+$ activity collected during the irradiation with a single pencil beam has been computed together with the estimated background during the irradiation. The effect of the very short half-life $ß^+$ emitters, which produce positrons of longer ranges, has been studied. Preliminary results obtained in a simulation on a real patient case, with all the beam spots delivered with the correct time structure, are also presented.

Keywords: in-beam PET, hadrontherapy, Monte Carlo

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