Cancer burden, radiotherapy utilisation, and outcomes

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This work is presented on behalf of the GTFRCC Working Group #1 Members

Purpose/Objective: To estimate the number of cases of cancer that would benefit from radiotherapy (RT) by country, the survival and local control benefits of radiotherapy and to calculate projections of demand and benefit to 2035 for input to GTFRCC investment framework.

Methods: The CCORE model of optimal utilisation of RT and Globocan data on cancer incidence and projections by country were used to calculate the number of cases with an indication for RT where RT was the treatment of choice. The estimate does not include non-melanomatous skin cancer or benign conditions. Survival and local control benefit were calculated by meta-analysis of available results for each radiotherapy indication for the 10 most common cancers that comprise 75% of the world cancer burden. Palliative benefit was not included.

Results: In 2012 there were 14 million new cases of cancer in the world. 7 million (50%) would benefit from RT. More than half of the cases were in Low and Middle Income Countries. For the 10 most common cancers, 1.3 million cases would have a local control benefit and 0.5 million would have a survival benefit from RT if all patients were treated according to guidelines. By 2035, 12 million cases would have an indication for RT and the benefit for the 10 most common cancers would be local control for 2 million and improved survival for 0.8 million.

Conclusion: In 2012 7 million cases of cancer require radiotherapy. This will increase to 12 million by 2035.
annual rate of 3% in the base case analysis. We conducted sensitivity analyses to investigate how variation in overall survival with and without RT, RT demand, projected GDP growth rates, and operational and infrastructure costs per fraction impacted projections.

**Results:** In the base case “rapid” investment scenario, a total of 24,383,261 discounted life years are gained by 2035 through scaling up radiotherapy capacity. This represents 4,131,981 LYs in upper-middle, 11,006,360 LYs in lower-middle, and 9,245,240 LYs in low-income countries. This results in a total of 124,389,936,346 USD discounted net monetary benefits accrued through productivity gains. Different investment scenarios and costing packages impact the rate of return.

**Conclusion:** The health and economic benefits from improving access to radiotherapy capacity are projected to be substantial. Despite the capital costs associated with implementing radiotherapy infrastructure, the adoption of a long-term perspective demonstrates that in addition to the large health gains generated, the economic gains of radiotherapy investment are likely to offset programmatic costs. Scaling up radiotherapy capacity may be considered a cost-saving intervention, which may warrant priority within the health budgets of LMIC.

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**SP-0540**

Modulation of tumour vasculature: effects on hypoxia and tumour regrowth

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The structure and mechanics of tumour vasculature as well as oxygen consumption by the cancer determines the levels of tumour hypoxia. Vascular structure is affected by remodeling that can be altered after agents inhibition of oncogenic signaling in the cancer cells. Inhibition of the RAS-PI3K signalling pathway leads to morphological changes resulting in increased perfusion and decreased vascular tortuosity. At the same time inhibition of the pathway also affects tumor hypoxia. Vascular structure is affected by oxygen consumption by the cancer determines the levels of angiogenic stimulator, FGF2 by recruited myeloid cells. In radiation we find increased deposition of the potent angiogenic stimulator, FGF2 by recruited myeloid cells. In another oncologic setting, liver metastasis, we can show that myeloid cells recruited to the liver colonies are induced to express FGF2 and that inhibition of FGF2 reduced the liver colony growth. These studies raise the possibility of FGF2 as a target for therapy in the setting of fractionated radiation therapy.

**SP-0541**

The PI3K/mTOR pathway regulates oxygen metabolism via pyruvate dehydrogenase (PDH)-E1a phosphorylation

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**Purpose:** Inhibition of the PI3K/mTOR pathway decreases hypoxia within SQ20B human head and neck cancer xenografts. We set out to understand the molecular mechanism underlying this observation.

**Experimental Design:** We measured oxygen consumption using both a Clark electrode and an extracellular flux analyzer. We made these measurements after various pharmacologic and genetic manipulations.

**Results:** Pharmacologic inhibition of the PI3K/mTOR pathway or genetic inhibition of Akt/PI3K decreased the oxygen consumption rate (OCR) in vitro in SQ20B and other cell lines by 30-40%. Pharmacologic inhibition of this pathway increased phosphorylation of the E1a subunit of the pyruvate dehydrogenase (PDH) complex on Ser293, which inhibits activity of this critical gatekeeper of mitochondrial respiration. Expressing wild type PTEN in a doxycycline-inducible manner in a cell line with mutant PTEN led to an increase in PDH-E1a phosphorylation and a decrease in OCR. Pre-treatment of SQ20B cells with dichloroacetate (DCA), which inhibits PDH-E1a phosphorylation by inhibiting dehydrogenase kinases (PDKs), reversed the decrease in OCR in response to PI3K/Akt/mTOR inhibition. Likewise, introduction of exogenous PDH-E1a that contains serine to alanine mutations, which can no longer be regulated by phosphorylation, also blunted the decrease in OCR seen with PI3K/mTOR inhibition.

**Conclusions:** Our findings highlight an association between the PI3K/mTOR pathway and tumor cell oxygen consumption that is regulated in part by PDH phosphorylation. These results have important implications for understanding the effects PI3K pathway activation in tumor metabolism and also in designing cancer therapy trials that use inhibitors of this pathway.

**OC-0542**

Biganuvides and cancer: microenvironmental and anti-proliferative effects at in vivo achievable concentrations

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**Purpose/Objective:** The anti-diabetic biguanides metformin (MET) and phenformin (PHEN) works by partial inhibition of respiration, and may have antineoplastic effects. Inhibition of respiration induces energetic stress and activation of the AMPK stress-signaling pathway possibly causing reduced tumor growth or cell death. Inhibition of respiration may also improve tumor oxygenation and thus radiosensitize tumors. Unfortunately, nearly all studies demonstrating anticancer effects of biguanides have used supraphysiological drug concentrations in vitro and ignored that cellular uptake depends on organic cation transporters (OCTs). The purpose of this study is to provide evidence for or against directly