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.

Symposium with Proffered Papers: Tumour metabolism and radioresistance

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 leads to decreased oxygen consumption. Together then the result of RAS-PI3K inhibition is decreased tumour hypoxia and increased tumour growth delay after radiation therapy.
While decreased hypoxia during radiation therapy should increase efficacy, recurrence of tumours after therapy could be expected to require neoangiogenesis. Inhibition of angiogenesis using an antibody to notch ligand DLL4 led to superadditive reduction in tumour regrowth after radiation. However these studies cannot fully describe the events that might occur after fractionated radiation. After fractionated 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
Biguanides 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