# **CANCER & HYPOXIA**







AREAS to avoid destruction by chemotherapy and radiation





Tissue/organ	Physoxia (median % O <sub>2</sub> )	Reference	Cancer	Hypoxia (median % $O_2$ )	Reference
Brain	4.6	8,9	Brain tumor	1.7	6,122
Breast	8.5	6	Breast cancer	1.5	6,123
Cervix (nullipara)	5.5	4,6	Cervical cancer	1.2	4,6
Kidney cortex	9.5	7	Renal cancer	1.3	124
Liver	4.0–7.3	125,126	Liver cancer	0.8	125,126
Lung	5.6	127	Non-small-cell lung cancer	2.2	127
Pancreas	7.5	128	Pancreatic tumor	0.3	128,129
Rectal mucosa	3.9	130	Rectal carcinoma	1.8	130

Table I Comparison of the oxygenation in organs and respective tumors

Barbara Muz, Pilar de la Puente, Feda Azab, Abdel Kareem Azab. Hypoxia 2015:3 83–92

### Many SOLID CANCERS ARE HYPOXIC when compared to normal tissue in the same organ





## HYPOXIA PROMOTES CANCER ACTIVITY

#### Hypoxia influences gene expression

- HIF-1a suppresses SCO2, TIGAR transcription and downregulates OXPHOS<sup>3</sup>
- Hypoxia directly increases DNA methylation by reducing TET activity<sup>2</sup>

#### Hypoxia increases tumour angiogenesis<sup>5</sup>

- 个 VEGF
- Angiogenesis
- Metastasis

1. DeBerardinis RJ, Cheng T.Oncogene 2010, 29:313-24. 2.Thienpont Nature 2016; 537, 63–68

- 3.R.Rajendran. Int J Oncol 2013;42:1961-1972
- 4. Zhang et al. Journal of Hematology & Oncology (2015) 8:83

5. Shweiki, D., Itin, A., Soffer, D., and Keshet, E. Nature (Lond.),359: 843–845, 1992.

#### Hypoxic pathways for energy generation

- Warburg effect
- Crabtree Effect
- Cancer cell uses glycolysis for energy generation
- Krebs cycle is hijacked for producing intermediates used for biosynthesis<sup>1</sup>

#### Hypoxia increases exosomes

- Transmit oncogenic nucleic acids/proteins
- Induce malignant transformation of normal cells<sup>4</sup>



### HYPOXIA IN A CANCER MAKES IT MORE MALIGNANT AND MORE RESISTANT TO THERAPY





### HIGHER DOSE OF RADIATION IS NEEDED TO KILL HYPOXIC CANCERS



**Ref:** Gray, L. H., Conger, A. D., Ebert, M., Hornsey, S., and Scott, O. C. Concentration of oxygen dissolved in tissues at the time of irradiation as a factor in radiotherapy. Br. J. Radiol., 26: 638–648, 1953.





### HYPOXIC CANCERS RECUR FASTER AND SHORTEN PATIENT SURVIVAL IN SPITE OF RADIATION



Shows the influence of MEDIAN OXYGENATION of head and neck tumors on disease-free survival after standard radiotherapy (Brizel et al)

Brizel, D. M., Sibley, G. S., Prosnitz, L. R., Scher, R. L., and Dewhirst, M. W. Tumor hypoxia adversely affects the prognosis of carcinoma of the head and neck.Int. J. Radiat. Oncol. Biol. Phys., 38: 285–289, 1997.



### MEDICAL RESEARCH HAS FOUND THAT HYPOXIA PROMOTES RESISTANCE TO CANCER CHEMOTHERAPY

- Hypoxic cells *in vitro* are resistant to some anticancer drugs<sup>1</sup>
- Hypoxia causes cells to stop or slow their rate of progression through the cell cycle and this affects the efficacy of many anticancer drugs that target rapidly growing cells<sup>2</sup> E.g. Bleomycin
- Hypoxia induces various hypoxic stress proteins that cause resistance to adriamycin<sup>3</sup>, etoposide<sup>4</sup>, and cisplatin<sup>5</sup>

 Tannock, I., and Guttman, P. Response of Chinese hamster ovary cells to anticancer drugs under aerobic and hypoxic conditions. Br. J. Cancer, 42: 245–248, 1981.
J Martin Brown. CANCER RESEARCH 59, 5863–5870, December 1, 1999
Proc. Natl. Acad. Sci. USA, 84: 3278–3282, 1987.
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Cancer Res., 54: 5808–5810, 1994

