Mathematical model of drug transport to determine chemotherapeutic outcomes in patients with cancer metastases in the liver

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***Short abstract* - There are many biobarriers that the tumor drugs have to overcome to reach their target site, however a thorough understanding of all these challenges is yet to be elucidated. To comprehend these barriers, we along with our collaborators will reflectively examine the diffusion of chemotherapy drugs in cancer metastases in the human liver by evaluating measurements from histopathological samples and a mathematical model of transport that surmises the fraction of dead tumor cells depending upon various physical, measureable patient specific parameters. Results from this work can be improvised into clinical applications that anticipate the effects of chemotherapy on patient outcomes [1].**

I. PURPOSE

Hepatic metastases associated with the carcinomas of the gastrointestinal tract are the most common cause of malignant neoplasms found in the liver in 40% of patients dying from cancer [2]. In patients with hepatic metastases, chemotherapy is routinely administered to treat the disease and improve the outcomes [2]. Conventional chemotherapy drugs are non-specific between cancerous and normal cells, thereby reducing the effectiveness of the treatment [3]. In order to effectively combat cancer, chemotherapeutic drugs must diffuse through the interstitium and enter the tumor mass [4]. However, these drugs face formidable challenges to enter the tumor microenvironment as these drugs can be espoused and retained in cells close to blood vessels and also become sequestered by binding to tissues such as the extracellular matrix, the endosomes or the DNA inside the cells. High interstitial fluid pressure also plays a role in discouraging drug uptake in tumor tissue [5]. Many tumors have a poor vasculature and the chemotherapeutic drugs have to travel through multiple layers which pose an obstruction for effective treatment of the tumor mass [6].

Three main physiological barriers that cause poor localization of drug molecules in the tumor tissue have been identified: (i) variation in amount of blood supplied to tumor; (ii) increased interstitial pressure; (iii) large transport distances to tumor sites [7]. Although research has been done to overcome these barriers through technologies such as nanomedicines, scarce evidence exist to address the effects of the tumor microenvironment and the biobarriers within it [8, 9]. Previous studies have implied the tumor microenvironment to play a substantial role in the variation of chemotherapy [10, 11]. To better understand how tissue scale transport of chemotherapeutic agents affect tumor response to chemotherapy, mathematical modeling based on fundamental biophysical principles can be used [1]. This will not only help to better predict patient response to chemotherapy, but also lead to better treatment outcomes in clinical settings.

II. CONCLUSION

Preliminary data suggests that the mathematical model could accurately predict results of chemotherapeutic outcomes among cancer metastasis in liver.

III. REFERENCES

[1] Pascal, J et al. (2012) Diffusion barriers cause physiologic resistance of colorectal cancer liver metastases to chemotherapy in patients. Submitted to Proceedings of National Academy of Sciences.

[2] Cui Y, Zhang X-P, Sun Y-S, Tang L, & Shen L (2008) Apparent Diffusion Coefficient: Potential Imaging Biomarker for Prediction and Early Detection of Response to Chemotherapy in Hepatic Metastases. Radiology 248(3):894-900.

[3] 4. Cho K, Wang X, Nie S, Chen Z, & Shin DM (2008) Therapeutic Nanoparticles for Drug Delivery in Cancer. Clinical Cancer Research 14(5):1310-1316.

[4] Sinek J, Frieboes H, Zheng X, & Cristini V (2004) Two-Dimensional Chemotherapy Simulations Demonstrate Fundamental Transport and Tumr Response Limitations
Involving Nanoparticles. Biomedical Microdevices 6(4):297-309.

[5] Tredan O, Galmarini CM, Patel K, & Tannock IF (2007) Drug Resistance and the Solid Tumor Microenvironment. Journal of the National Cancer Institute 99(19):1441-1454.

[6] Cowan DSM & Tannock IF (2001) Factors that influence the penetration of methotrexate through solid tissue. International Journal of Cancer 91(1):120-125.

[7] Jain RK (1990) Physiological Barriers to Delivery of Monoclonal Antibodies and Other Macromolecules in Tumors. Cancer Research 50(3 Supplement):814s-819s.

[8] Blanco E, et al. (2011) Molecular-targeted nanotherapies in cancer: Enabling treatment specificity. Molecular oncology 5(6):492-503.

[9] Ferrari M (2010) Frontiers in cancer nanomedicine: directing mass transport through biological barriers. Trends in Biotechnology 28(4):181-188.

[10] Simpson-Herren L & Noker PE (1991) Diversity of penetration of anti-cancer agents into solid tumours. Cell Proliferation 24(4):355-365.

[11] Simpson-Herren L, Noker PE, & Wagoner SD (1988) Variability of tumor response to chemotherapy II. Contribution of tumor heterogeneity. Cancer Chemotherapy and Pharmacology 22(2):131-136.

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