

論 文 内 容 要 旨

報告番号	甲 先 第 243 号	氏 名	笈田 将皇
学位論文題目	Study on the effects of intercellular radiosensitivity uncertainty using a biophysical model in radiotherapy (放射線治療における生物物理モデルによる細胞間放射線感受性の不確かさの影響に関する研究)		
<p>内容要旨</p> <p>Radiotherapy has developed as primary treatment options for cancer along with surgery and chemotherapy. Recently, more than half of all cancer patients have receiving radiation therapy during their course of illness. Theoretical studies based on the in vitro experiments in radiobiology have contributed to the development of radiotherapy. However, few of these still have led to demonstrable clinical gains.</p> <p>In macroscopic viewpoint, it can be clear that the surviving cells would decrease by a certain amount of radiation dose. In contrast, it is challenging that in microscopic viewpoint, no one still predict which cell die or survive by radiation. These uncertain phenomena would be needed a much more robust and relevant parameter to assess radiation effect stochastically since any cell that retains proliferative capacity can cause failure to cancer treatment.</p> <p>In this thesis, we investigate the distribution of uncertainty of cell survival due to radiation and application of treatment planning. Firstly, we evaluated the distribution of uncertainty of cell survival due to radiation and assessed the predictions of tumour response using three different in vitro experimental cell cultures with EMT6/KU mouse mammary tumour cells. We then discussed the relationship between in vitro radiosensitizing activities with etanidazole (ETZ) and uncertainties in characteristics of cell survival using radiobiological parameters. Secondary, we assessed the usefulness of TCP/NTCP model and stochastic biological model applying for Gaussian distribution as the intercellular uncertainty of tumour in the treatment planning.</p> <p>The result from a fundamental study using EMT6 cells showed that the α parameters (mean \pm SD) were $0.257 \pm 0.188 \text{ Gy}^{-1}$, $0.078 \pm 0.080 \text{ Gy}^{-1}$, and $0.182 \pm 0.116 \text{ Gy}^{-1}$ in normoxic cell, hypoxic cell, and hypoxic cell plus ETZ cultures, respectively. The β parameters (mean \pm SD) were $0.0159 \pm 0.0208 \text{ Gy}^{-2}$, $0.0076 \pm 0.0113 \text{ Gy}^{-2}$, and $0.0062 \pm 0.0077 \text{ Gy}^{-2}$,</p>			

respectively. The D_{50} parameters (mean \pm SD) were 3.2 ± 2.5 Gy, 6.4 ± 2.7 Gy, and 3.7 ± 1.4 Gy, respectively. The α and D_{50} values were significantly different between the normoxic cell culture and hypoxic cell culture ($p < 0.01$), respectively. The use of radiosensitizers under the hypoxic conditions improved radiosensitivity.

The result from an application study using the treatment planning showed that TCP values mostly depended on the BED_{10} (i.e. irradiated dose to the volume of tumor), which contributed to the cell killing of the tumour directly. While, NTCP values mostly depended on the BED_3 (i.e. irradiated dose to the volume of normal tissues), which contributed to the cell killing or cell repairing of the normal tissues directly as to the α/β ratio. Our data have suggested that the optimal fractionation protocol in the treatment of prostate cancer relates to the value and uncertainties of biological parameters such as α/β ratio, γ and D_{50} , respectively. Also, it is indicated that the contributions to the variation of TCP were much higher with the uncertainties of D_{50} rather than that of α/β ratio and γ . However, our study did not mention the factors of uncertainties related to radioresistance such as radiation-induced bystander effect, the environment of cell circumstances of hypoxia, cancer stem cell and so on. Several clinical studies suggested that hypofractionated protocols would have benefit for low α/β ratio tumor such as prostate cancer treatment with capable of reducing normal tissue complication. Our data suggested that these uncertainty effects would be relatively small in conventional fractionated protocol with 74-78Gy/35-39fr or 75.6-81Gy/45fr. However, in the case of a hypofractionated protocol such as 40Gy/5fr, the effects would be slightly greater in both TCP and NTCP. From these results, the increase of total radiation dose, as well as precise determination of these biological parameters, would minimize these impacts. In addition, our data and several studies showed that hypofractionated schedule treatments with uncertainties of biological parameters might increase normal tissue complications unnecessarily. Therefore, the challenges to apply these uncertainties for the biological model of various clinical protocols are further studies.

論文審査の結果の要旨

報告番号	甲 先 第 2 4 3 号	氏 名	笈田 将皇
審査委員	主査 松木 均 副査 中村 嘉利 副査 宇都 義浩		
学位論文題目	Study on the effects of intercellular radiosensitivity uncertainty using a biophysical model in radiotherapy (放射線治療における生物物理モデルによる細胞間放射線感受性の不確かさの影響に関する研究)		
審査結果の要旨	<p>本研究は、様々な環境下における細胞間放射線感受性の不確かさを定量的に評価し、また臨床の放射線治療ではどの程度影響しうるのか、治療計画を通じて応用可能とすることを目標とする。乳がんマウス由来の EMT6 細胞を用いて基礎実験を行い、生存環境（酸素分圧）の違いに伴う放射線感受性の変化について LQ モデルを利用して解析した。解析結果から、α 成分のパラメータ（平均値\pm1 標準偏差）は、常酸素細胞、低酸素細胞、低酸素細胞に増感剤を加えたもので、それぞれ $0.257 \pm 0.188 \text{ Gy}^{-1}$, $0.078 \pm 0.080 \text{ Gy}^{-1}$, $0.182 \pm 0.116 \text{ Gy}^{-1}$ となった。同様に、β 成分のパラメータは、それぞれ $0.0159 \pm 0.0208 \text{ Gy}^{-2}$, $0.0076 \pm 0.0113 \text{ Gy}^{-2}$, $0.0062 \pm 0.0077 \text{ Gy}^{-2}$ となった。D_{50} パラメータは、それぞれ $3.2 \pm 2.5 \text{ Gy}$, $6.4 \pm 2.7 \text{ Gy}$, $3.7 \pm 1.4 \text{ Gy}$ となった。α および D_{50} の値は明らかに常酸素群と低酸素群で異なり、また同一群でも多少のばらつきを持ち、生存環境の違いだけでなく、同じ環境の細胞間でも放射線</p>		

感受性は大きく変動することが明らかとなった。続いて、上記の課題に対する検討として、臨床で用いられる3次元治療計画装置においてファントムおよび患者模擬データによる臨床治療計画から、腫瘍パラメータである α/β 比、 γ 、 D_{50} の違いや変動が腫瘍局所制御率(TCP)に、また正常臓器パラメータである α/β 比、 n 、 m が正常臓器副作用発生率(NTCP)にどのような影響を及ぼすかを検討した。結果として、腫瘍のTCPは BED_{10} に依存して増加し、 α/β 比、 γ 、 D_{50} はいずれも値が小さいほど低下する傾向があった。 α/β 比、 γ 、 D_{50} の変動に対するTCPの影響は、 α/β 比、 γ に比べて D_{50} の方が強く生じた。正常臓器のNTCPは BED_3 に依存して増加し、 m 値が大きいか、 n 値が小さいほど上昇する傾向があった。 α/β 比、 m 値、 n 値の変動に対するNTCPの影響は、高線量寡分割プロトコルにおいて m 値、 n 値に比べて α/β 比の方が強く生じた。これらの結果から、腫瘍および正常臓器への影響は、線量分割スケジュールの違い、生物学的パラメータの値や変動に依存することが明らかとなり、基礎実験で得られた知見とともに更なる治療計画の最適化へのアプローチに向けて応用可能な結果が得られた。

以上本研究は、放射線治療の臨床応用に向けて様々な環境下における細胞間放射線感受性の不確かさを定量的に評価した極めて重要な研究であり、本論文は博士(工学)の学位授与に値するものと判定する。