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Implication of fractionated dose exposures in therapeutic gain

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1. Introduction

Radiation therapy pursues killing tumor cells while sparing normal cells from the radiation exposure. Stereotactic radiosurgery (SRS) is a cancer treatment modality that delivers a high dose in a single operation. In brain cancer radiosurgery, dose of around 20 Gy is delivered by single operation [1]. This high-dose single operation shortens the treatment course, but can increase the risk of normal cell damage. Normal cell damage can be reduced by employing multi-directional exposures for an increasing number of isocenters [2].

In this study, we investigated whether therapeutic benefits would be expected by employing new dose fractionation patterns at a high-dose single operation.

2. Materials and Methods

2.1 Cell and cell culture

Rat normal diencephalon cells (ATCC, CRL-2005) and rat gliosarcoma cells (ATCC, CRL-2200) were used in this study. Both cell lines were cultured on T-25 plastic flasks (NUNC) with medium containing 10 % fetal bovine serum (FBS; ATCC) and 90 % Dulbecco's modified Eagle's medium (DMEM; HyClone) at 37 ^{o}C in a humidified incubator with 10 % CO_2. Cells were sub-cultured before confluence occurred. Medium was changed every third day.

2.2 Irradiation

Radiation exposure was carried out in the hard X-ray irradiation facility at Seoul National University. The X-ray beam tube (450-D08, YXLON, Germany) was operated at 350 kVp. Total 15 Gy of dose was delivered in each of four different patterns: a single exposure, uniform-dose exposures, exposures of increasing dose, and exposures of decreasing dose. The fractionated dose delivery patterns are summarized in Fig. 1. There were five fractional exposures in fractionated dose delivery. Beam-off time was 2 min between beam exposures. The non-uniform fractional doses ranged from 0.3 Gy to 5.6 Gy to make the total dose of 15 Gy. The single exposure of 15 Gy took 7.5 min.

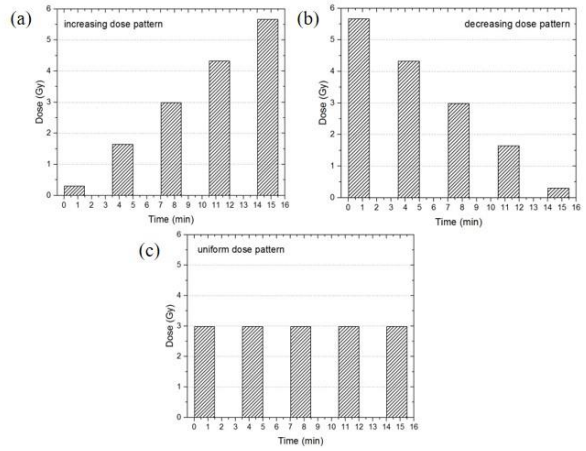

Fig. 1 Dose patterns in fractionated dose delivery: (a) increasing, (b) decreasing and (c) uniform doses with 2 min beam-off time between beam exposures.

2.3 Clonogenic assay

After irradiation, cells were washed with Dulbecco's phosphate buffered saline (DPBS; Gibco), trypsinized with TrypLE Express (Gibco) and then seeded on 6-well plates (NUNC). In 10-12 days, cell colonies were dyed with Giemsa (Sigma-Aldrich) and counted. The clonogenic survival was counted for the cells that form more than 50 clones.

2.4 Statistical analysis

Student's t-test was performed to determine whether the observed data were significantly different from each other. Significance was indicated by $p < 0.05$.

3. Results

3.1 Clonogenic survival of rat normal diencephalon cells

The surviving fractions of rat normal diencephalon cells were obtained for four different dose patterns. As shown in Fig. 2, cells better survived by 41 to 43 % from fractionated radiation exposures than from a single-dose exposure. The difference in surviving fraction from a single exposure was significant ($p < 0.05$) at exposures of uniform and increasing dose patterns.

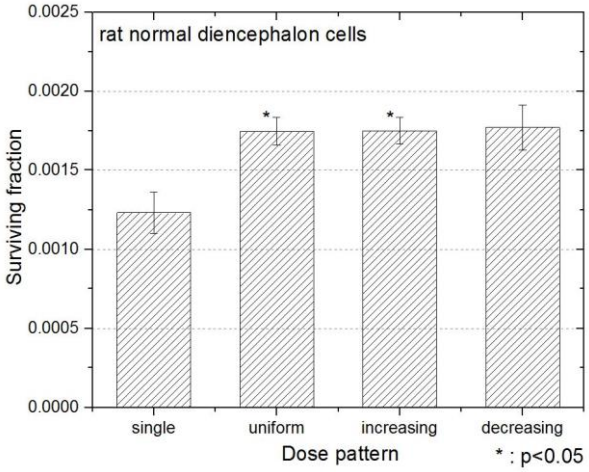

Fig. 2 Clonogenic cell surviving fractions of rat diencephalon cells for radiation exposures at four different dose patterns toward the same total dose of 15 Gy.

3.2 Clonogenic survival of rat gliosarcoma cells

Given in Fig. 3 are the surviving fractions of rat gliosarcoma cells from radiation exposures in four different dose patterns. As compared to the single-dose exposure, cells better survived by 20 to 58 % from fractionated dose exposures. The difference was significant only at a decreasing dose pattern.

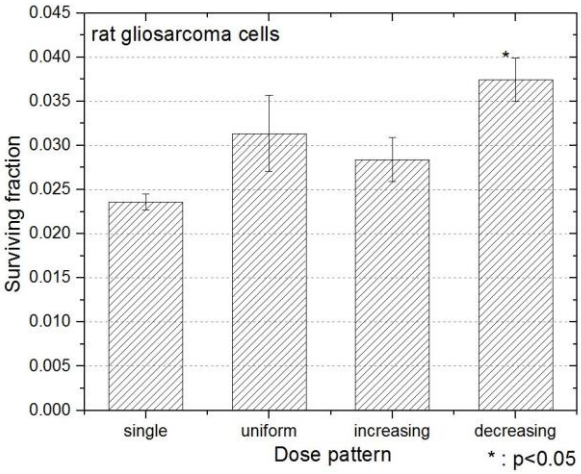

Fig. 3 Clonogenic cell surviving fractions of rat gliosarcoma cells for four different dose patterns toward the same total dose of 15 Gy.

3.3 Sensitivity of normal and tumor cells to dose patterns

Both normal and tumor cells responded with an enhanced clonogenic survival to the fractionated dose exposures in comparison with that to a single-dose exposure. For normal cells, the gain in surviving fraction expected from dose fractionation was similar at around 40 % in three dose exposure patterns. For tumor cells, the gain in surviving fraction was the smallest at 20 % from the increasing dose pattern and the greatest at 58 % from the decreasing dose pattern. From uniform dose pattern, the gain of tumor cell survival was 32%.

4. Conclusion

The conventional single-dose operation in brain tumor radiosurgery is performed by delivering fractionated uniform doses [3]. According to Figs. 2 and 3, the conventional radiosurgery might have obtained some therapeutic benefit by employing the fractionated uniform-dose exposures instead of a single-dose exposure. We suggest that further therapeutic gain be expected by employing the fractionated radiation exposures in an increasing dose pattern.

Until ensuring our suggestion, the significance in gain of cell surviving should be verified for all three dose patterns with both normal and tumor cells. The investigation whether normal and tumor cells show the same responses to the fractionated dose exposures at lower and higher than 15 Gy of total dose is also reserved for future work.

REFERENCES

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