Validation of ERCC1/2 signature as radiosensitivity biomarker for tumor and normal tissues in NSCLC

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A genetic analysis of non-small cell lung cancer (NSCLC) patients on the phase III NRG Oncology RTOG 0617 clinical trial assessing radiation dose discovered that high dose radiation therapy is associated with shorter survival times among patients with a radiation-sensitive genotype in DNA repair pathway. These findings were presented at the virtual edition of the American Society for Radiation Oncology's (ASTRO) Annual Meeting in October 2020.

The NRG-RTOG 0617 analysis reviewed blood and DNA samples from the 321 eligible patients who participated in the study. The primary focus was to externally validate blood cell ERCC1 and ERCC2 genetic signatures as a radiosensitivity biomarker for tumor and normal tissues. Previous findings in stage I and IV NSCLC patients indicate that high dose radiotherapy typically leads to improved survival, better tumor control, and better survival in inoperable NSCLC.

"Single nucleotide polymorphisms (SNPs) signature in DNA repair pathway and its interaction with radiation dose could provide personalized radiation prescriptions to patients depending on their genotypic signature, and this could improve survival outcomes," said Feng-Ming (Spring) Kong, MD, Ph.D., FACR, FASTRO of the Clinical Oncology Center, the University of Hong Kong—Shenzhen Hospital; and Li Ka Shing Faculty of Medicine, The University of Hong Kong; Department of Radiation Oncology, Case Western Reserve University, and the lead author of the NRG-RTOG 0617 abstract. "Previously, the data that indicated the potential for ERCC1 and ERCC2 genes to be biomarkers for normal and tumor tissue in NSCLC patients had only been performed in single institution trials. It was imperative to validate these findings in a multi-institutional clinical setting."

Patients who participated on the initial NRG-RTOG 0617 trial were randomly assigned to receive either standard radiation (RT) dose (60 Gy) or high RT dose (74 Gy). Among the 321 eligible patients, 275 patients had both ERCC1 and ERCC2 SPNs signatures conducted. The median follow up time for the trial was 68 months. Of the 163 patients assigned to 60 Gy arm, 67 patients carried the resistant genotype signature and had a median survival time (MST) of 22 months compared to the radio-sensitive genotype's MST of 31 months (P=0.076, HR= 1.4 [95%CI: 0.96-2.01]). There were 112 patients assigned to the 74 Gy arm and 36 of these patients were carrying the resistant genotype signature and had a MST of 31 months (95% CI, 20-52). This was significantly better than the MST of 20 months for the sensitive signature type patients on the 74 Gy arm (p=0.025, HR= 0.59 [95% CI: 0.37-0.94]). These results confirm the hypothesis that patients with the radio-sensitive genotype have better survival with 60 Gy, whereas patients with the radiation-resistant genotype fair better in the 74 Gy arm with regard to survival. Interestingly, 63% patients from this study were classified as radiation sensitive according to this signature, and this at least partially explains the result of better survival in patients in the 60 Gy arm.

These findings could benefit from further prospective validation through a study with a larger sample size, and suggest the need of future study on personalized radiation prescription in treating patients with lung cancer.

More information: Kong FMS, Jin JY, Hu C, Wang W, Bogart J, Garces YI, Narayan S, Robinson CG, Kavadi VS, Rothman J, Koprowski CD, Gore E, Welsh J, Gaur R, MacRae RM, Cannon G, Machtay M, Bradley JD, Lu B. (2020, October). RTOG0617 to externally validate blood cell ERCC1/2 genotypic signature as a

radiosensitivity biomarker for both tumor and normal tissue for individualized dose prescription. Paper presented at the annual meeting of the American Society for Radiation Oncology. Virtual meeting platform.

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