

$p < 0.01$) but otherwise had no differences in Gleason score or number/location of metastases compared to those that received MDT. Within the entire cohort, log-rank testing demonstrated WNT mutations were associated with significantly worse OS ($p = 0.01$) but not rPFS ($p = 0.97$). Among patients treated with systemic therapy alone, WNT was associated with significantly worse 3-yr rPFS (12% vs 64%; $p < 0.01$) and OS (3-yr OS 69% vs 98%; $p = 0.01$). In patients treated with MDT +/- systemic therapy, no difference was observed in either 3-yr rPFS (59% vs 34%, $p = 0.26$) or 3-yr OS (100% vs 98%; $p = 0.60$).

Conclusion: WNT pathway mutations are associated with a worse OS in men with omCSPC that appears to be most pronounced in patients receiving systemic therapy alone. Given these findings, MDT may hold an important role in the initial management of WNT-mutated omCSPC.

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Evaluation of a Functional Assay for Radiosensitivity in the Pediatric Prospective Cohort ARPEGE

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Purpose/Objective(s): Approximately 900 children/adolescents are treated with radiotherapy (RT) every year in France. However, among the 80% of survivors, the cumulative incidence of long-term morbidity – including second malignancies – reach 73.4% thirty years after the cancer diagnosis. Identifying a priori the subjects at risk for RT sequelae is a major challenge of pediatric oncology. Individual radiosensitivity (IRS) of children/adolescents is unknown at this time. The cellular response to radiation depends on the recognition and repair of radiation-induced DNA double-strand breaks (DSB). Unrepaired DSB as well as a delay in the intra nuclear activation of the pATM protein are common features to patients with RT toxicity. From these conclusions, we proposed and retrospectively validated a functional IRS immunofluorescence assay based on Radio-Induced ATM Nucleoshuttling (RIANS) (Granzotto et al, 2016). The purpose of this study was to define prospectively the predictive impact of RIANS assay in children.

Materials/Methods: Patients of the ARPEGE prospective open-label, non-randomized multicenter clinical trial were included in the study and prospectively evaluated for early toxicities. For each patient, skin samples were collected prior RT to raise a primary dermal fibroblast line and carry out in blind the RIANS assay. Different endpoints were measured: residual double-strand breaks at 24 h (γ H2AX marker), pATM foci at 10 min and 1 h (pATM marker) and micronuclei at 24 h respectively after ex vivo radiation

(2 Gy). The procedures were repeated in triplicates in blind in two independent expert centers (Neolys and Institut de Cancerologie de Lorraine). In parallel early toxicity was reported according to NCI-CTCAE v4.0 three months after the completion of RT. Patients with grade < 2 or ≥ 2 toxicity were considered as radioresistant (RR) and radiosensitive (RS) respectively. We correlated the parameters of the RIANS assay according to toxicity with logistic regression.

Results: Among the 29 analyzable patients, 37 % exhibit brain cancers, 10% Hodgkin lymphomas, 10% nephroblastoma, 10% neuroblastoma, 10% Ewing cancer and 13% malignant mesenchymal cancer. The mean delivered dose was 32.5 Gy (range 1,5 - 60 Gy) with fractionation between 1.5 to 2 Gy. 16/29 (56%) patients were clinically considered as RS. There was no significant difference in total dose delivered between the two groups. Among the radiobiological factors tested, the number of Micronuclei at 24h post irradiation provided the best discrimination among RS patients (p -value= 0.0216). Overall, the RIANS assay provided the following performance: sensitivity=0.82, specificity=0.70 and AUC=0.75 (0.550-0.888).

Conclusion: ARPEGE is the first study to document the distribution of IRS in such a population. Screening hypersensitive patients would be a major step forward in the management of cancers, opening a way to personalized pediatric oncology.

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Microbiota-Derived I3A Accelerates Intestinal Stem-Cell-Mediated Epithelial Development after Ionizing Radiation

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Purpose/Objective(s): The intestine is a highly radiosensitive tissue that is susceptible to structural and functional damage due to systemic as well as localized radiation exposure. Unfortunately, no effective prophylactic or therapeutic agents are available at present to manage radiation-induced intestinal injuries (RIII). Gut microbiome play pivotal roles in intestinal homeostasis. Several studies have demonstrated the potential of gut microbiome and metabolites as a therapeutic for RIII. Our results demonstrate that microbiota-derived Indole-3-carboxaldehyde (I3A) plays a pivotal role in promoting ISC-mediated epithelial development.

Materials/Methods: Male C57BL/6J mice were treated with 13Gy of Whole abdominal irradiation (WAI). Probiotics or I3A were gavage before (once a day for 30 days) WAI. The survival and body weight were recorded, while the severity of RIII was evaluated by HE staining, Immunohistochemistry (IHC) and TUNEL assay of gut tissues for each irradiated group. Meanwhile, stool samples were obtained 6h and 3.5d after irradiation. Gut microbiome were measured by 16S rRNA sequencing, and metabolites were detected by LC-MS analysis.

Results: Compared to the control, probiotics (Lactobacillus plantarum, Bifidobacterium longum, Lactobacillus paracasei) treatment significantly increased survival rates by 50% ($P < 0.05$) and improved clinical scores of mice after WAI. HE staining of jejunum tissues showed that probiotics mitigated RIII, as reflected by the dramatic attenuation of crypt-villi architecture destruction. IHC results showed that probiotics treatment remarkably increased the Lgr5⁺ cells, Paneth cells, and Ki67+ cells ($P < 0.001$) per crypt, indicating that probiotics promoted proliferation and differentiation of ISC after WAI. The most highly enriched metabolites from the feces of probiotics treatment mice in the tryptophan metabolic pathway, with a threefold change seen in level of I3A. Specifically, I3A -treated groups showed survival rates of ~20%, with the protection persisting for > 200 days after radiation. In addition, mice fed the I3A daily for 3 days before IR had significantly more Lgr5⁺, Paneth cells,