T01- 75: Introducing information on gut microbiota into toxicity modeling: preliminary results from the MICRO-LEARNER trial

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BACKGROUND AND PURPOSE

A mono-institutional trial (MICRObiota, infLammatory Environment, clinicAl and Radiomic features as predictors of Normal tissue response in radiotherapy for prostatE and head-and-neck canceR – MICROLEARNER; ClinicalTrials.gov NCT03294122), was set up in 2017 to investigate the role of gut/saliva microbiota in driving radio-induced toxicity after RT for prostate (PCa) and head&neck cancers.
Preliminary data for PCa are here presented, with particular focus on introduction of information on gut microbiota into a normal tissue complication probability model (NTCP) for acute gastro-intestinal toxicity in the PCa cohort.

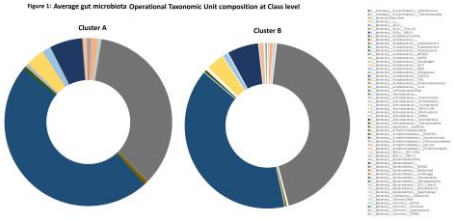
MATERIALS AND METHODS

For this initial evaluation 20 patients were selected: 10 with G0 and 10 with G2 acute intestinal toxicity. All patients were without any intestinal symptom at baseline (G0 before radiotherapy).
All patients received conventional (78Gy @2Gy/fr) or moderately hypofractionated (65Gy @2.6Gy/fr).
Gut microbiota measurement was performed before radiotherapy (baseline) and at the end of treatment.
The bacterial 16S ribosomal-RNA reads were analyzed and pooled in Operational Taxonomic Units (OTUs).
Grade 2 (G2) CTCAE acute intestinal toxicity was the primary endpoint of this preliminary analysis.
Unsupervised clustering was used to separate the patients into 2 microbiota clusters, based on relative abundance of OTUs at bacterial class level in microbiota before radiotherapy start (baseline microbiota).
Information on microbiota clustering was introduced as a dose-modifying factor into a logit NTCP model (characterized by D50=dose associated to 50% toxicity probability and steepness parameter k).
Mean dose to the rectum was chosen as dosimetric predictor (as already found in the literature.

RESULTS

Unsupervised clustering identified 13 patients included in a first microbiota cluster (A) and 7 in a second cluster (B), average OTU composition for patients in clusters A and B are presented in fig. 1. Figure 1 also reports on bacterial classes which were present with significantly different (p-value<0.01) abundance in clusters A and B.
4/13 (31%) and 6/7 (86%) patients with toxicity were found in clusters A and B, respectively (p=0.019). Microbiota clustering resulted in AUC=0.75 (95%CI=0.51-0.91) for toxicity discrimination.
An NTCP model including only mean rectal dose had D50=49Gy, k=16 (AUC=0.85, 95%CI=0.62-0.97).
When clustering was introduced, the fitted parameters were k=20.5, D50=42Gy for cluster A vs D50=32Gy for cluster B: with microbiota clustering resulting in a dose-modifying factor of 0.76 (B vs A) (AUC=0.87, 95%CI=0.65-0.98). Introduction of information on microbiota clustering into NTCP modelling also resulted in significant improvement in goodness of fit and calibration. Model curves are reported in fig. 2.

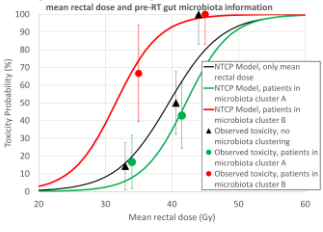
Figure 1: Average gut microbiota Operational Taxonomic Unit composition at Class level



The following bacterial classes are present with difference abundance in microbiota clusters A and B with p-value<0.01

Firmicutes_Other	--> more adundant in Cluster A
Firmicutes_Clostridia	--> more adundant in Cluster A
Chlorobi_BSV26	--> more adundant in Cluster A
Verrucomicrobia_Opitutae	--> more adundant in Cluster A
Nitrospirae_Nitrospira	--> more adundant in Cluster A
Proteobacteria_Other	--> more adundant in Cluster A
Gemmatimonadetes_Gemm-5	--> more adundant in Cluster A
Bacteroidetes_Bacteriodia	--> more adundant in Cluster B

Figure 2: Probability of acute grade 2 GI toxicity as a function of mean rectal dose and pre-RT gut microbiota information



CONCLUSIONS

A method was proposed to include whole microbiota information into NTCP models, without dramatically increasing the number of features to be included in the model.