EVALUATION OF IMMUNE REACTION AFTER RADIOFREQUENCY TREATMENT OF PULMONARY METASTASES IN COLORECTAL CANCER

ARFIM STUDY

Category 2 non-interventional research involving humans with minimal risks and constraints (RIPH 2)

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TITLE	**Evaluation of the immune response after radiofrequency treatment of lung metastases of colorectal cancer. ARFIM study.**
RATIONALE / BACKGROUND	Radiofrequency (RF) is now widely used in the percutaneous treatment of lung metastases of colorectal cancers. The pathophysiology of reactions induced locally by this ablation technique at metastatic sites is poorly known, particularly in terms of immunology. Some studies have shown that RF ablation may alter the environment and immunological mechanisms, not only at treated sites, but also at distant sites. However, this RF-induced immune response is insufficient to cause the regression of metastases at a distance from the treated site. From an immunological point of view, the importance of the PD-1/PD-L1 axis has been shown in tumour mechanisms of resistance to the immune system, in particular by inhibiting lymphocyte action. Combining RF with targeted anti-PD-1/PDL-1 therapies could therefore be an interesting therapeutic option to control metastases distant from those treated with RF.
OBJECTIVES	**Primary objective**: To evaluate the RF-induced immune response to lung metastases of colorectal cancers (CRC). The radiofrequency-induced immune response will be jointly evaluated in 3 ways: by measuring changes to lymphocyte infiltration of metastasis tumour stroma, by quantifying the PD-1 and PD-L1 interaction by immune Förster Resonance Energy Transfer (iFRET), and by assaying blood lymphocyte sub-populations. **Secondary objectives**: – To evaluate the impact of RF on tumour activity by measuring the level of circulating tumour cells and circulating DNA, along with as the expression of the PDL-1 ligand on tumour cells. – Clinical evaluation with monitoring of metastatic disease and especially RF-treated sites – Evaluation of procedure-related complications (RF and biopsies)

ENDPOINTS	**Primary endpoint**: Lymphocyte infiltration rate on histological analysis of metastases. Biopsy samples will be taken before RF and 4-6 weeks after the first RF in a second procedure on another initially untreated metastasis. A lymphocyte infiltration rate of 20% or more is considered significant. A comparative measurement of lymphocyte infiltration rates will be performed. A blood assay of NK, CD4, CD8 T cells and their HLADR+ activated sub-population, CD25+, CD38+, will be performed before, then 30 minutes after each RF, in order to evaluate distribution changes. **Secondary endpoints**: – Rate of circulating tumour cells and of circulating DNA before and after each RF (before RF, at 30 minutes and on D1 after RF). Quantification of PDL-1 ligand expression on tumour cells before and after RF from histological samples – Assessment of the progress of treated sites and of any distant metastatic disease by scans at 3, 6, 9 and 12 months, as part of standard follow-up. – Complications will be graded (1 to 5) according to version 5 of the NCI-CTAE scale.
STUDY DESIGN	Prospective single-centre pathophysiology study
INCLUSION CRITERIA	1. Patient aged 18 years or over. 2. WHO performance status ≤ 2. 3. Histologically confirmed colorectal cancer. 4. Resected primary tumour. 5. Lung metastases a. bilateral (or unilateral if: number ≥ 5 and requiring two interventions), b. maximum diameter ≤ 4 cm, c. stable or slowly progressive (radiologically defined), with or without chemotherapy, d. eligible for radiofrequency therapy. 6. Thorax-abdomen-pelvis CT scan and/or PET scan: a. performed within 8 weeks prior to inclusion, b. finding lung metastases of which no more than 10 can be treated with radiofrequency during both times (supplemental metastases being considered untreatable with radiofrequency due to their small size). 7. Inclusion criterion No. 7 was deleted during MS2. 8. Decision on local treatment taken during the multidisciplinary meeting or during an Interventional Radiology opinion meeting (no contraindication). 9. Life expectancy ≥ 3 months. 10. Free, informed and written consent signed by the participant and the investigator (on the day of inclusion at the latest and before any tests required by the study). 11. Patient with social security cover in accordance with Article 1121-11 of the French public health code.

EXCLUSION CRITERIA	1. Non-lung or liver metastases. 2. Contraindication to general anaesthesia. 3. Contraindication to radiofrequency treatment tumour localization (< 1 cm of the hilus), respiratory failure (FEV1 < 1 l), 4. Pregnant or breastfeeding woman. 5. Concomitant inclusion in another interventional radiology study. 6. Patient incapable of following and adhering to research procedures for geographical, social or psychological reasons. 7. Patient deprived of freedom or subject to a legal protective measure. 8. Previous treatment with hormone therapy.
STUDY TREATMENTS/STRATEGIES/PROCEDURES	Lung radiofrequency treatment of lung metastases of colorectal cancer. The procedure is performed under general anaesthesia. A RF needle is deployed, under strict asepsis, into the metastasis under imaging guidance. Once deployed, heating is performed to destroy the lesion. Each patient will undergo 2 procedures, to treat all metastases Biopsy samples are taken from a location before the heating phase.
STUDY SIZE	20 patients
STUDY DURATION	Duration of the inclusion period: 24 months Duration of participation of each patient: 12 months Total study duration: 36 months
DATA STATISTICAL ANALYSIS	**Number of subjects required** This exploratory study is not based on a statistical hypothesis but on feasibility criteria in terms of recruitment. 20 patients will be included in this study **Statistical analyses** Patient characteristics will be described for the eligible and eligible evaluable populations: • Compliance with eligibility criteria, • Socio-demographic characteristics, • Clinical and tumour characteristics, • Performing procedures (RF, radiological examinations). Analysis of primary and secondary endpoints: • will concern the eligible and evaluable population. • Quantitative variables will be described from mean values (+/- sd) if the normality hypothesis is met, and otherwise from non-parametric statistics (median, range, quartiles). • Qualitative variables will be described based on frequency, percentage and 95% confidence interval (binomial law).
EXPECTED BENEFITS	• Better understanding of radiofrequency-induced pathophysiological and immunological mechanisms of lung metastases • with the possibility of developing combined RF/immunotherapy treatments • an evaluation of metastatic disease activity with a new endpoint consisting of the circulating tumour cell (CTC) level