FEASIBILITY STUDY OF ENDOSCOPIC ULTRASOUND-GUIDED FINE-NEEDLE ASPIRATION (EUS-FNA) FOR THE ASSESSMENT OF HYPERMETABOLIC LYMPHADENOPATHIES IN THE LOWER, POSTERIOR AND MIDDLE MEDIASTINUM, DETECTED BY 18FDG PET-CT

APOGEE STUDY SUMMARY

(**A**pport de la **PO**nction **G**uidée sous **É**cho**E**ndoscopie – Contribution of Endoscopic Ultrasound Guided Aspiration)

Translation of version n°4 of 11/07/2016
Including the substantial modification n°1 of 12/10/2012
Including the substantial modification n°2 of 13/06/2013
Including the substantial modification n°3 of 04/08/2014
Including the substantial modification n°4 of 11/07/2016

N° IDRCB: 2012-A00985-38 – n° IB: 2012-01
NCT01892501

Coordinator
Prof Dominique BÉCHADE
Medical Oncologist
Department of Medical Oncology
Institut Bergonié
229, cours de l'Argonne – 33076 BORDEAUX Cedex
Tel: 05.56.33.78.71 – Fax: 05.56.33.33.83 – Email: d.bechade@bordeaux.unicancer.fr

Co-Coordinator
Dr Anne-Laure CAZEAU
Nuclear Medicine Specialist
Department of Nuclear Medicine
Institut Bergonié
229, cours de l'Argonne – 33076 BORDEAUX Cedex
Tel: 05.56.33.33.33 – Fax: 05.56.33.33.84 – Email: a.cazeau@bordeaux.unicancer.fr

Clinical and Epidemiological Research Unit
Prof Simone MATHOULIN-PELISSIER
Director
Institut Bergonié, Bordeaux

Dr Stéphanie HOPPE
Epidemiologist
Institut Bergonié, Bordeaux

Carine BELLERA
Biostatistician
Institut Bergonié, Bordeaux

Caroline LALET
Clinical Research Assistant
Institut Bergonié, Bordeaux

Clinical Trials Unit
Barbara LORTAL
Emilie TOULZA
Pharmacists
Institut Bergonié, Bordeaux

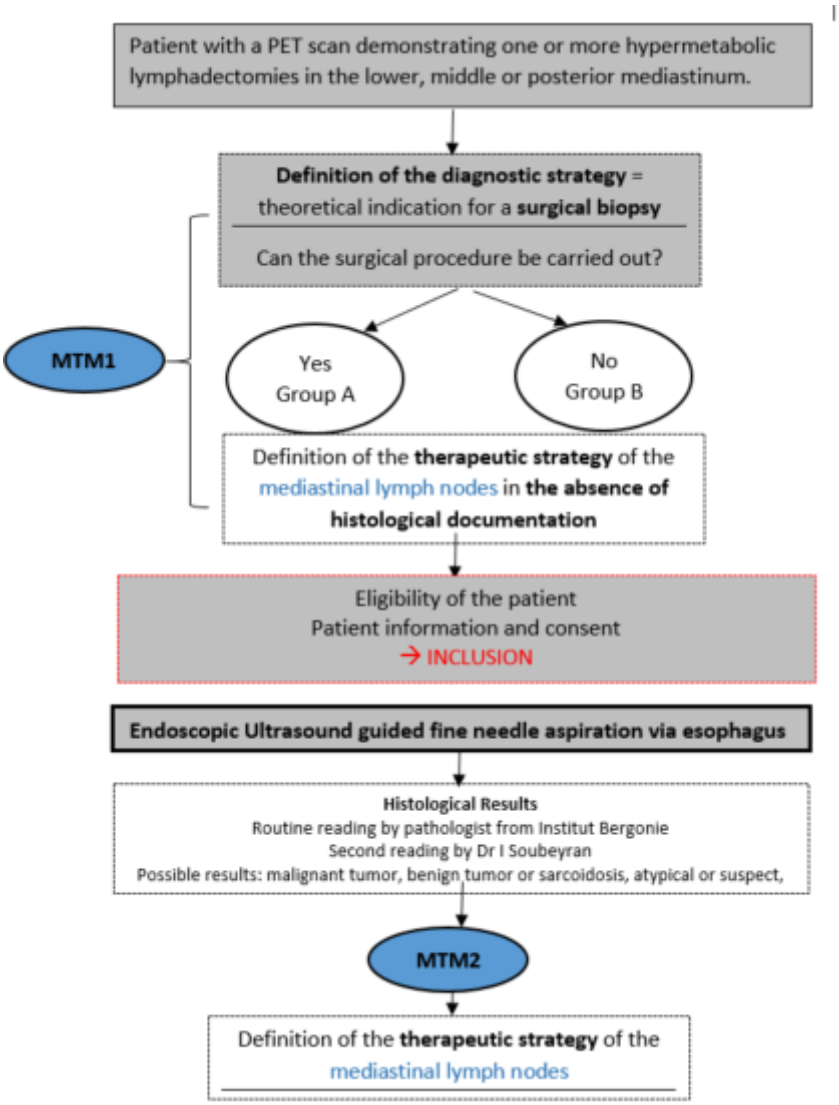
Pathology Department
Dr Isabelle SOUBEYRAN
Pathologist
Institut Bergonié, Bordeaux

PROMOTOR **INSTITUT BERGONIE**

SUMMARY

Study title	**Feasibility study of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) for the assessment of hypermetabolic lymphadenopathies in the lower, posterior and middle mediastinum, detected by 18FDG PET-CT**
Promotor	**Institut Bergonié**
Coordinator	**Prof Dominique BÉCHADE** **Institut Bergonié**
Indication	Mediastinal lymphadenopathies
Methodology	Single center study
Number of patients	50 patients
Study duration	End of inclusions: 31/12/2017 Follow-up duration: 1 year Study duration: 6 years Beginning of the study: 2nd semester 2012
Objectives / Endpoints	**Primary objective:** To assess the performance in terms of sensitivity of EUS-FNA for the characterization of mediastinal lymphadenopathies, hypermetabolic on PET, for new cancers or relapse. **Secondary objectives:** • Evaluate the negative predictive value of EUS-FNA for the characterization of mediastinal lymphadenopathies, hypermetabolic on PET, for new cancers or relapse. • Evaluate the impact of the combination of the two techniques on diagnostic and therapeutic management. This will be evaluated by: - the percentage of more invasive diagnostic procedures avoided (e.g. surgeries: mediastinoscopy, thoracoscopy) - the possible modification of the therapeutic strategy after endoscopic puncture, compared to the strategy that would have been envisaged after PET alone. • Evaluate the diagnostic performance of this method according to the stage of treatment (diagnosis, evaluation of the therapeutic response or suspicion of relapse), thoracic or extra-thoracic location and the pathological type of the tumor. • Compare tumor characteristics described on PET (size and intensity of lymphadenopathy fixation) in patients with a confirmed diagnosis of cancer and those with a diagnosis of benign pathology (using as reference EUS-FNA when it is positive and the follow-up at 1 year when it is negative), to define more efficient criteria for PET interpretation.
Inclusion criteria	1. Patients with a PET showing one or more hypermetabolic lymphadenopathies in the middle and/or lower and/or posterior mediastinum and requiring diagnostic certainty for therapeutic strategy decisions. 2. PET scan performed for the following indications: • Pre-therapeutic assessment of thoracic or extra-thoracic neoplasms (patients without a history of cancer). • Evaluation of the response to cancer treatment. • Suspicion of relapse in patients with a personal history of thoracic or extra-thoracic neoplasms. 3. PET with a positive result: • For lymphadenopathies with a small axis > 1cm: result greater than or equal to the hepatic background. • For lymphadenopathies with a small axis < 1cm: result strictly greater than the hepatic background noise. 4. Patient with an indication for a surgical diagnostic procedure (whether it is feasible or not).

	5. Lymphadenopathy(s) accessible to EUS-FNA via the esophagus, that is, allowing a technically feasible aspiration procedure from the esophagus (without recusing vascular structures). 6. Age ≥ 18 years old. 7. PET scan performed 6 weeks before endoscopy. 8. Platelets ≥ 70,000 / mm3; TP ≥ 60%. 9. Patient of childbearing age with negative pregnancy test and / or contraception. 10. Signed informed consent. 11. Patient affiliated to a social security scheme.
Non-inclusion criteria	1. General contraindication(s) to performing endoscopy. 2. Unfavorable anesthetic assessment (precluding general anesthesia). 3. Esophageal stenosis. 4. Coagulation disorders. 5. Pregnant or breastfeeding woman. 6. Inability to undergo medical monitoring of the trial for geographic, social or psychological reasons. 7. Adult patient under a legal protection measure or unable to express consent.
Study procedure	When a patient has a PET scan showing one or more hypermetabolic lymphadenopathies in the lower, middle or posterior mediastinum, his/her file is presented to a multidisciplinary consultation meeting MTM#1, ***to define the diagnostic strategy***: strategy chosen to perform a surgical biopsy to obtain histological documentation of the mediastinal lymphadenopathy with obvious impact on the therapeutic choices. The patient is eligible to participate in the study if the indication for mediastinoscopy is made. The patient is then informed of the study and signs the informed consent if s/he agrees to participate. We differentiate 2 groups of patients depending on the feasibility of the surgical procedure: Group A: surgical biopsy is possible Group B: surgical biopsy cannot be performed (medical or anesthetic contraindications): at that time, definition of the therapeutic strategy that would have been decided in the absence of histological documentation: • Surgery from the outset • Chemotherapy or other cancer treatment • Non-cancer treatment / patient management for suspected benign pathology • No treatment. The EUS-FNA via the esophagus is then performed for the 2 groups of patients (within a maximum of 6 weeks after the PET scan), under general anesthesia and endoscopic control, with a disposable 19-gauge needle (EchoTip, Cook Endoscopy) and with 3 needle passages per node. Pathology samples are taken: 3 tubes taken per lymph node (1 tube per needle passage), in most cases, only 1 lymph node will be taken: • 2 tubes for oncology analysis • 1 frozen tube for microbiological analysis (mainly tuberculosis) in the event of a negative oncology analysis and if there is evidence of a pathology The slides are then read by 2 different pathologists: routine reading by a pathologist from the Institut Bergonié then confirmatory reading by Dr I Soubeyran. Depending on the pathological results (5 to 6 days delay), the therapeutic

	strategy for the mediastinal lymph nodes is defined during a second MTM (MTM#2), making it possible to assess the impact of carrying out the EUS-FNA: • Surgery from the outset • Chemotherapy or other cancer treatment • Non-cancer treatment / patient management for suspected benign pathology • No treatment • Choice of another surgical diagnostic procedure (non-contributive result) Patients will be followed up for 12 months. Clinical and radiological data obtained during standard patient management will be collected. For patients who have had a negative biopsy, follow-up will consist of performing a thoraco-abdomino-pelvic scan at 6 and 12 months.
Study design	
Evaluation criteria	**The primary endpoint** is the **performance of EUS-FNA** after detection of lymphadenopathy by PET (index test). The performance will be evaluated by sensitivity. In the majority of cases, only one lymphadenopathy will be removed and diagnostic accuracy will be estimated per patient and not per lesion. • The **reference technique** (Gold standard) is follow-up for 12 months. In particular, we consider that there are: Diagnosis of malignancy: • if the management and the clinical and radiological follow-up established following EUS-FNA indicate the presence of a neoplastic

pathology, or
- if the thoraco-abdomino-pelvic scans carried out at 6 and 12 months after the EUS-FNA indicate the presence of progressive neoplastic pathology. In case of doubt and if the doctor taking care of the patient deems it necessary, additional examinations may be carried out to confirm this diagnosis.

Absence of malignancy: if the thoraco-abdomino-pelvic scans carried out 6 and 12 months after the EUS-FNA indicate the absence of progressive neoplastic pathology. In case of doubt and if the doctor taking care of the patient deems it necessary, additional examinations may be carried out to confirm this diagnosis.

• The technique evaluated is EUS-FNA. In particular, we consider that there is:
- Diagnosis of malignancy: if the histology carried out on the material taken by the endoscopic puncture shows a malignant tumor.
- Absence of malignancy: if the histology carried out on the material taken by the endoscopic puncture shows a benign pathology (benign tumor, sarcoidosis).
- Atypical, suspect or non-contributory result, diagnosis of malignancy / benignity impossible.

• The **sensitivity** corresponds to the rate of subjects with a diagnosis of malignancy (without taking into account atypical / suspect or non-contributory results) according to the EUS-FNA results (index test) among all the subjects considered to be suffering from a neoplastic pathology according to the reference test.

Secondary endpoints are:

• The **negative predictive value** of EUS-FNA will be evaluated. It corresponds to the rate of subjects with a diagnosis of benign pathology according to the reference test among all the subjects for whom EUS-FNA reveals a benign pathology (without taking into account atypical / suspect or non-contributory results).

Impact on care will be evaluated in 2 ways based on (i) clinical utility and (ii) concordance between the MTM1/ MTM2 therapeutic strategies.

The clinical utility of endoscopic ultrasound puncture (Groups A and B)
- The puncture will be considered to have clinical utility, if it makes it possible to avoid more invasive diagnostic procedures (mediastinoscopy or thoracoscopy for patients in group A) or if it allows the patient to benefit from an appropriate treatment (result of the malignant biopsy) or to avoid receiving an unjustified treatment (result of the benign biopsy): case of patients well classified in malignant / benign by the EUS-FNA.
- The EUS-FNA will be considered to have no clinical utility if the result of is invalidated by the reference examination, or if the result of the puncture does not allow a diagnosis to be made.

Agreement between MTM1 / MTM2 therapeutic strategies

In all patients, the **agreement between the therapeutic strategies** taken before and after the results of the EUS-FNA will be assessed.
- Therapeutic strategy for the mediastinal lymph nodes described at inclusion envisaged in MTM 1
  - Surgery from the outset
  - Chemotherapy or other cancer treatment
  - Non-cancer management in the event of a suspected benign pathology
  - No treatment
- Therapeutic strategy for the mediastinal lymph nodes described at inclusion envisaged in MTM2
  - Surgery from the outset
  - Chemotherapy or other cancer treatment
  - Non-cancer management in case of benign pathology
  - Other surgical diagnostic procedure

	○ No treatment • Agreement between the 2 strategies considered: for any discrepancy between the 2 strategies considered before the endoscopic puncture and after, the puncture will be considered to have had an impact on the treatment. • **Side effects** In all cases, the side effects associated with performing the EUS-FNA will be collected and classified according to the Clavien-Dindo classification of surgical complications [Clavien P et al. Ann Surg 2009; 250: 187-96].
Number of inclusions necessary	This project is an exploratory pilot study, the main objective of which is to evaluate the performance of EUS-FNA via the esophagus, carried out after a PET scan showing hypermetabolic lymphadenopathy. Again, the main judgment criterion is sensitivity. Due to the small amount of data available in the literature concerning the sensitivity and specificity of this examination, we did not calculate a number of patients necessary, but determined the number of patients taking into account the feasibility and recruitment criteria possible at Institut Bergonié as well as acceptable precision of the estimations. For 50 patients, we estimated that the precision of the sensitivity and specificity estimate would be 12% for an expected sensitivity of 95% (95% confidence interval: [89%; 100%]) [Kalade AV et al. Intern Med J. 2008 - sensitivity and specificity of EUS-FNA coupled with PET Scan, but for histology data, whereas in our project we will have cytology data].
Statistical analysis	**Patient characteristics at inclusion** The patients included will be described according to the following characteristics: • Compliance with eligibility criteria • Epidemiological characteristics The diagnosed mediastinal lymphadenopathy will be described: • On PET scan: injected dose, fixation time, location, size of the minor axis (mm), fixation grade (0 to 4), SUV max mediastinal vascular background, SUV max hepatic background, SUV max lymph nodes, SUV max tumor, N / T ratio, N / Liver ratio. • Endoscopic ultrasound: number of lymph nodes, location, shape, size, echogenicity, characteristics of the boundaries. • Quality of samples obtained by EUS-FNA. • Pathological characteristics: malignant tumor, benign tumor or sarcoidosis, atypical or suspect, non-contributory. **Definitions of the study populations** • Eligible population • All patients meeting the eligibility criteria. Patient eligibility will be established by the steering committee on a case-by-case basis. • Eligible and assessable population for the main criterion All the patients included in the study, for whom 1) the eligibility criteria are met, 2) the results of the endoscopic guided puncture are contributory. **Analysis of judgment criteria** • The characteristics of the patients at inclusion will be described from the eligible population • The main and secondary criteria will be described on the basis of the eligible and assessable population • Subgroup analyses, in particular by type of cancer, may be

	considered, but only on an exploratory basis. • Quantitative variables will be described using descriptive statistics (range, quartile and median). • Qualitative variables will be described on the basis of the proportions and presented with their 95% confidence interval.