Tracheobronchial Replacement and / or Pulmonary Vessels by a Cryopreserved Arterial Allograft TRACHEOBRONC-ARTCode : P091203

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1 General Information

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2 Summary

Title and Research Code: Tracheobronchial Replacement and / or Pulmonary Vessels by Cryopreserved Arterial Allograft; TRACHEOBRONC-ART study

Inclusion site:
Hôpital Avicenne, Assistance Publique des Hôpitaux de Paris, Bobigny, Université Paris XIII

Coordinator Investigator: Pr Emmanuel Martinod - Pôle Activité Cancérologique Spécialisée

Participating teams:
Specialized Cancer Activity Pole (Pr. Dominique Valeyre) including Thoracic and Vascular Surgery, Pneumology, Medical Oncology.
Emergency Department Hospital: Anesthesia and ICU

Rational:
Proximal tumor lesions of the thorax are the leading cause of cancer deaths worldwide. The treatment providing the best survival to patients with non-metastatic proximal tumor lesion is complete surgical resection. Peripheral malignant tumors are usually treated with lobectomy, a procedure characterized by low morbidity and mortality. Proximal malignant tumors, on the other hand, are associated with a greater problem since local invasion leads, in the majority of cases, to pneumonectomy. This intervention is associated with a very high morbidity and mortality. The mortality can reach 21% at 90 days, even 24% in case of right pneumonectomy performed after a neo-adjuvant treatment in some centers of reference. In a minority of cases, resection with direct bronchial anastomosis [RAB] associated with lobectomy can be performed instead of pneumonectomy if anatomical conditions permit. Preservation of the lung parenchyma is crucial, firstly to avoid major complications of pneumonectomy and secondly to offer a better quality of life at longer term. However, controversies still persist, with some studies showing a significant increase in the incidence of loco-regional recurrence after RAB lobectomy. Surgical treatment of proximal tumor lesions does not, therefore, present a satisfactory solution because of its postoperative risks (pneumonectomy, resection of carina) and loco-regional recurrence (lobectomy with RAB, resection of carina). The possibility of performing a bronchial replacement would allow a longer bronchial resection with greater oncologic safety margins, a satisfactory anatomical reconstruction after extensive bronchial resection, a maximum preservation of the pulmonary parenchyma and therefore of the respiratory function, a strong limitation of the indications of pneumonectomy (and therefore its many complications in the short, medium and long term). Finally, in some cases where there is invasion of the pulmonary vessels, the use of a cryopreserved arterial graft could avoid, as at the bronchial or arterial, a pneumonectomy and its complications or a resection with anastomosis of the artery [RAAP].
Experimental work has been carried out since 1997 on the topic of tracheal replacement by an aortic graft by a team led by the principal investigator of this project. Fifty-one sheep were operated on in three successive studies: replacement of the anterior segment of 2 tracheal rings with an autologous arterial patch (n = 10), segmental replacement of the trachea by aortic autograft (n = 21) and aortic allograft fresh (n = 20) without immunosuppressive therapy. An endoprosthesis was placed in case of extensive replacement (n = 41). The postoperative course was simple in 46 cases. There was no stenosis apart from the first study, anastomotic release or graft rupture. Removal of the stent was possible after 6 months. The pathological study showed a progressive transformation of the aortic graft into a tissue similar to that of the trachea comprising a continuous epithelium (squamous, mixed then mucociliary) and neo-formation of immature cartilage then organized in rings with a maximal follow-up of 3 years. This work has thus shown the possibility of obtaining a tracheal regeneration from an aortic graft. The technique was extended to replace the carina (n = 15) with similar results as those obtained with tracheal replacement. We then proposed to evaluate the bronchial and / or pulmonary artery replacement by an arterial allograft on the same animal model (n = 20). There was no peri-operative mortality and the intervention was particularly well supported from a clinical point of view by all the animals. Three cases of early postoperative atelectasis were observed and treated by bronchial fibrosis. During the study (maximum follow-up = 24 months), only 2 complications (lung abscess) led to premature sacrifice of the animals. In the remaining 18 cases, the sacrifice was made on the scheduled date. The removal of the stent remained without clinical impact. In 4 cases, non-stenotic endobronchial granuloma was observed. From a histological point of view, a progressive tissue

transformation of the graft led to a re-epithelialization initially of squamous, then mixed or respiratory type and the appearance of neo-cartilage.
These favorable experimental results allow, today, to consider a clinical application in humans of this new surgical technique in the context of the proximal CBP whose excision would be a superior lobectomy with RAB, pneumonectomy or resection of carina.
In addition, some cancerous or non-cancerous lesions of the trachea, in therapeutic impasse, can also justify a replacement of the airways by cryopreserved aortic allograft + endoprosthesis according to the same protocol

Primary outcome:
To evaluate the feasibility of bronchial replacement and / or pulmonary vessels or trachea by a cryopreserved arterial allograft for the surgical treatment of proximal tumor lesions of the thorax
The primary endpoint will be 90-day survival

Secondary outcome:
To assess the morbidity associated with this procedure: Postoperative complications (bronchial congestion, atelectasis, pneumonia, lung re-expansion defect, tracheal, bronchial or broncho-vascular fistula, empyema, bronchial stent-related, thrombosis of the artery or pulmonary vein ...), Postoperative leakage, drain removal, Hospital length of stay.

Methodology:
Open Study, Cohort, monocentric, multidisciplinary (see participating teams)

Inclusion criteria:
Patient over the age of 18; proximal tumor lesion whose surgical excision requires resection of carina, pneumonectomy, lobectomy with RAB and / or RAAP, immediately or after neo-adjuvant chemotherapy and with EFR allowing the proposed pulmonary resection; proximal tumor lesion whose surgical resection requires pneumonectomy but with EFR allowing only lobectomy; proximal tumor lesion requiring surgical resection requiring pneumonectomy in a patient over the age of 70 (major risk of death at 90 days); extensive cancerous or non-cancerous lesions of the trachea without bronchial involvement in therapeutic impasse; Surgical eligibility (indication of surgical treatment) retained during a collegial discussion (Multidisciplinary Consultation Meeting); Information of the patient and informed and written consent.

Non-inclusion Criteria:
Minor or incapacitated, under guardianship or under judicial protection; proximal or distal tumor lesion whose surgical resection is technically possible by simple lobectomy without RAB; tumor lesion that can not be resected completely due to locoregional invasion; N3 ganglion invasion (contralateral neoplastic lymph node involvement); M1 metastatic lesions unless there is a single resectable metastasis; Allergy to iodinated contrast media; Operability balance not allowing lobectomy; Isolated tracheal lesion that can be simply resected-tracheal anastomosis; Patient unable to comply with the requirements of the study; Patient not affiliated to a social security scheme (beneficiary or beneficiary).

Course of the study:
The clinical trial will be conducted according to the following steps:
- Indication retained according to inclusion and non-inclusion criteria
- Collective decision of surgical treatment in Multidisciplinary Meeting (RCP)
- Announcement of the therapeutic strategy proposed to the patient (J-30 □ 15j)
- Preparation of the intervention (after obtaining consent until D0): Preparation of the patient for the intervention according to the usual recommendations; Control of cryopreserved arterial allografts; Control of a covered metallic stent (Silmet) and / or silicone suitable for CT measurements at the company Novatech.
- Surgical procedure (D0): bronchial and / or arterial or tracheal replacement by a cryopreserved arterial allograft according to the excision time performed according to the usual rules used in thoracic surgery.
Postoperative follow-up (from D0 to D + 90 days):
From D0 to the exit of the hospital: Postoperative follow-up to detect and treat possible complications. Postoperative management will be done according to the rules observed for any patient who had a major excision for a tumor lesion or an extensive lesion of the trachea. Bronchial fibroscopy (conventional or virtual) will be carried out systematically before discharge of the patient.

At D30±7 d / D60±7 j / D90±7 d: Systematic consultation by the referent specialist doctor of the patient. A clinical examination will be carried out as well as the search for complications (dehiscence of the graft, displacement of the silicone stent, fistula, granulomas, thrombosis of the pulmonary artery ...) or of a loco-regional recurrence of the tumor lesion (requiring pathological confirmation by directed biopsies). Additional examinations may be requested;

- Stent removal: In the current state of knowledge, it is impossible to predict the kinetics of bronchial regeneration in humans and thus the possibility of ablation of the stent. The decision to remove the stent will not occur, in principle (unless stent change is necessary), during the feasibility study period (90 days). The elements concerning the removal of this stent, if it is withdrawn, will be collected as part of the patient's usual follow-up.

Summary of benefits, if any, and foreseeable risks known to those who are suitable for research:

As part of this study, we set ourselves the goal of obtaining more encouraging results than those found for conventional surgery in terms of morbidity and mortality at 90 days.

Serious Adverse Events expected from surgical treatment or study procedures

- Related to surgery: death, postoperative respiratory distress, complete atelectasis of the remaining lobe or postoperative pneumonia requiring prolonged artificial ventilation, tracheostomy, lack of pulmonary re-expansion, empyema requiring surgical revision, fistula (tracheal, broncho-pulmonary, broncho-vascular, broncho-oesophageal), infection, prolonged air leakage beyond 21 days,
- Transplant-related: allograft rupture, allograft dilation, thrombosis of the pulmonary artery or vein, fibrosis and allograft retraction by an excessive inflammatory reaction, impaired tissue regeneration and the formation of a neo-bronchus, intolerance of the endoprosthesis placed in place temporarily (inflammatory granuloma, hemorrhage, ...), migration of the stent, obstruction of the stent.

Duration of the study: 5-year inclusion period / 4-month patient participation (1 month between inclusion and intervention and 90 days of follow-up) / total duration of 7 years and 4 months (88 months)

Main criterion:

Survival at 90 days

Secondary criteria:

- Postoperative complications: bronchial obstruction, atelectasis, pneumonia, pulmonary re-expansion defect, tracheal, bronchial or broncho-vascular fistula, empyema, bronchial stents, thrombosis of the pulmonary artery or vein, other (cardiac complications , thromboembolic ...) daily during hospitalization and then at day 30, day 60 and day 90 postoperative
- Duration of postoperative air leakage, Duration until removal of drains, length of hospital stay

Calculation of the number of subjects & Statistical analysis:

As this trial was a feasibility study, a small number of patients (n = 20) were selected.

However, it will make it possible to estimate the proportion of survivors (of the order of 80% or more with a precision of about +/- 17.5%

If a patient is included but can not have surgery in the meantime, he will be replaced. We admit the possibility of including up to 30 patients in this study.

Expected results

Evidence of the feasibility and good tolerance of bronchial replacement and / or pulmonary artery or trachea by a cryopreserved arterial allograft for the surgical treatment of proximal tumor lesions

Decrease in postoperative morbidity and mortality, improved survival at 90 days.

SIGNATURE Page OF A PROTOCOL OF BIOMEDICAL RESEARCH

By the investigator COORDONNATOR and the representative of the PROMOTER

Biomedical research N ° P091203

Title : *"Tracheobronchial Replacement and / or Pulmonary Vessels by Cryopreserved Arterial Allograft. TRACHEOBRONC-ART "*

Version N° 6.0 of : 24/03/2016

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3 Scientific Justification and General Description of the Research

3.1 justification for research and prerequisites

Proximal tumor lesions of the thorax represent the leading cause of cancer deaths in the world[1,2]. The treatment providing the best survival to patients with a non-metastatic tumor lesion is complete surgical resection. International clinical practice guidelines state that proximal stage I, stage II, and certain stage III subgroups (revised classification, 1997[3]) should be treated with or without surgery, depending on the case, with chemotherapy and / or pre- or postoperative radiotherapy [4-7]. The 5-year survival of operated patients with a proximal tumor lesion decreases rapidly with increasing stage (pIA = 67%, pIB = 57%, pIIA = 55%, pIIB = 39%, pIIIA = 23%)[3].

Peripheral malignant tumors are usually treated with lobectomy, a procedure characterized by low morbidity and mortality[8,9]. Proximal malignant tumors, on the other hand, are associated with a greater problem since local invasion (bronchial and/or vascular) leads, in the majority of cases, to pneumonectomy. This intervention, particularly on the right side, is associated with a high morbidity and mortality10-12[10-12]. Mortality can be as high as 21% at 90 days13, or even 24% in cases of right-sided pneumonectomy after neo-adjuvant therapy in some referral centers (Memorial Sloan Kettering Cancer Center, New York)[14]. The high mortality rate after pneumonectomy can be explained by major complications such as bronchial fistula, pulmonary edema or pneumonia (occurring on the contralateral lung) and pulmonary embolism. In the longer term, the quality of life and the respiratory function can be altered after pneumonectomy[10]. Indeed, this major surgery of thoracic surgery induces a hyper-inflation of the remaining lung associated with a mediastinal displacement (important after right pneumonectomy) which can lead to a compression of the distal trachea or the main bronchus (between the big vessels and the rachis) but also to a decrease in venous return with disabling symptoms. Lung resection progressively leads to significant functional respiratory impairment and therefore quality of life.
In a minority of cases, bronchial resection with direct anastomosis [RAB] associated with superior lobectomy can be performed instead of pneumonectomy if anatomical conditions permit. Originally born from the need to provide surgical resection to patients with altered pulmonary function, RAB lobectomy has shown benefits in some clinical studies. Indeed, the preservation of the pulmonary parenchyma is crucial, on the one hand to avoid the major complications associated with pneumonectomy[15-17] and on the other hand to offer a better quality of life at longer term [18]. However, there is still a controversy regarding the benefit of performing superior lobectomy with RAB in patients with proximal tumor lesions who may be candidates for pneumonectomy. Criticism is indeed raised by some studies that have noted a significant increase in the incidence of loco-regional recurrence after lobectomy with RAB, especially in case of stage N1[19-20]. Loco-regional recurrence after RAB lobectomy can be explained by the persistence of ganglionic tumor foci (this can be corrected by high-grade ganglion dissection, especially at the level of pulmonary fissures) but also by the narrowness of the lymph nodes. margins of carcinological safety. An associated resection with direct anastomosis of the pulmonary artery may be the necessary complement to a superior lobectomy with RAB or be performed when there is arterial infiltration by the tumor[21,22]. In some cases, pneumonectomy is indicated only because of significant arterial invasion that does not allow lobectomy with pulmonary artery resection-anastomosis [PAAP]. The use of a cryopreserved arterial graft could avoid, as at the bronchial level, a pneumonectomy and its complications. In some cases of extensive arterial invasion, the interposition of a vascular substitute has already been proposed[23]. Finally, in some cases, invasion of the pulmonary veins also leads to pneumonectomy. The use of a cryopreserved arterial graft could avoid, as at the bronchial or arterial level, a pneumonectomy and its complications.
Finally, some more rare cases of proximal tumor lesions are treated by carinal resection, which is most often associated with parenchymal excision of the pneumonectomy type. The risks of this intervention include those of pneumonectomy (high morbidity and mortality, functional consequences) and lobectomy with RAB (loco-regional recurrence). Therefore, the resection of the carina, in particular with associated pneumonectomy, is not recommended outside a few series[24-26].

Surgical treatment of a proximal tumor lesion does not, therefore, present a satisfactory solution because of its postoperative risks (pneumonectomy, resection of carina) and locoregional recurrence (lobectomy with RAB or RAAP, resection of the carina). The possibility of bronchial and / or pulmonary artery replacement in the surgical treatment of proximal tumor lesions would render obsolete the main complaints made to the procedures used for this type of injury, namely pneumonectomy, lobectomy with RAB and resection of the carina.

Thus, the use of a bronchial substitute and / or pulmonary vessels would allow:

- longer bronchial resection and / or pulmonary artery with consequent larger oncological safety margins
- a satisfactory anatomical reconstruction after extensive bronchial, arterial or venous resection
- a maximum preservation of the pulmonary parenchyma and therefore of the respiratory function
- a strong limitation of the indications of pneumonectomy (and thus of its numerous complications in the short, medium and long term).

Moreover, some cancerous or non-cancerous lesions of the trachea, in therapeutic impasse, can also justify a replacement of the airways by cryopreserved aortic allograft + endoprosthesis according to the same protocol.

Replacement of the trachea with an aortic graft

Experimental work conducted since 1997 by a team led by the project coordinator in the Laboratory of Cardiac Grafts and Prostheses [LEGPC] of Pr. Alain Carpentier (Broussais Hospital, Paris V University) on the topic of tracheal replacement with an aortic graft has made it possible to consider the first clinical applications in humans to treat malignant tumors extended trachea.

Primary malignant tumors of the trachea are much rarer than proximal tumor lesions (2 to 6 new cases / million / year). The curative treatment is a complete resection with direct anastomosis. Tracheal sections must be in a healthy zone. It is now possible to propose the resection of half the length of the trachea (5-6 cm) in adults and one-third in children. It should be noted, however, that from a 4 cm resection, the morbidity and mortality of the intervention increases significantly. When the lesions are too extensive, the patients are referred to a palliative treatment using tracheal endoscopy (desobstruction, stent) and / or radio-chemotherapy whose effectiveness is very low. The treatment of extensive lesions must therefore involve a tracheal substitute

In the light of the considerable progress made in the area of organ or tissue substitution, the replacement of a tracheal segment, which is mainly intended for the passage of air between the external environment and the lungs, could appear as relatively simple. However, more than fifty years of experimental research on the animal model did not solve the many problems posed by tracheal replacement and the discovery of an ideal substitute material. The characteristics of the ideal tracheal substitute seem today, however, well defined: relative lateral rigidity and longitudinal flexibility; possibility of re-epithelialization, at best respiratory type; bio-compatibility; integration with surrounding tissues with no chronic inflammation, granulation tissue and erosion; resistance to infection; lack of use of immunosuppressive therapy; simple and reproducible surgical technique. Schematically, there are 5 main lines of research. Implantation of synthetic prostheses has led to major complications (migration, dislocation, erosion, infection, obstruction) due to the lack of incorporation into adjacent tissues[28]. The use of chemically preserved, cold or lyophilized bio-prostheses has generated non-functional scar tissue. Tracheal allografts evolved into necrotic tissue ischemia and posed the major problem of the need to use immunosuppressive agents in cancer. Various autografts (skin, fascia, muscle, cartilage, dura mater, esophagus, intestine, bladder ...) have been evaluated in the context of poorly reproducible surgical procedures and with an absence, ultimately, of restoration of tracheal function. Tissue engineering, after a long period of development, still seems subject to the instability of structures formed "in vitro".

In 1997, we proposed an original solution: the use of an aortic graft. Fifty-one sheep were operated in three successive studies: replacement of the anterior segment of 2 tracheal rings with an autologous arterial patch[29,30] (n = 10), segmental replacement of the trachea by aortic autograft[31,32] (n = 21) and fresh aortic allograft [33]
(n = 20) without immunosuppressive therapy. A silicone endoprosthesis (Novatech□, La Ciotat, France) was placed in case of extensive replacement (n = 41). Postoperative evaluation was

clinical, fibroscopic and pathological after sacrifice of animals with a maximum follow-up duration of up to 3 years. In the allograft study, aortic ram tissue was used for replacement of a tracheal segment of ewes (n = 6). The technique of PCR33 (detection of the SRY gene of the Y chromosome) made it possible to study the origin of the tissue modifications observed. The postoperative course was simple in 46 cases. There was no stenosis apart from the first study, anastomotic release or graft rupture. Removal of the stent was possible after 6 months. The pathological study showed a progressive transformation of the aortic graft into a tissue similar to that of the trachea with a continuous epithelium (squamous, mixed then mucociliary) and neo-formation of immature cartilage and organized in rings. The search for the Y chromosome in the newly formed cartilage was negative. This work has thus shown the possibility of obtaining a tracheal regeneration from an aortic graft. The well-known possibilities of epithelial repair from the native trachea have been confirmed. Cartilaginous regeneration, a phenomenon that has never been reported with other substitutes, has been possible from recipient cells derived from native trachea or circulation. This biological process was subsequently reproduced in pigs[34] by another team. In the LEGPC (Broussais Hospital, Paris V University), the technique was extended to the replacement of the carina using a bifurcated arterial allograft and a Y stent[35]. The clinical and pathological study on 15 operated ewes showed similar results, with in particular a good respiratory tolerance and obtaining a transformation of the aortic allograft in a tissue comprising a respiratory epithelium and a cartilaginous neo-formation within deadlines varying from 9 to 12 months. The subsequent association of an omentum or dorsal muscle flap relieved the various vascular and infectious complications that had been encountered in our first experimental series.

How can one explain that an aorta is transformed into a trachea?

These experimental works have embarked on a new pathway, that of induced tissue regeneration and the use of biological structures (the aorta) to repair others (the trachea) or modify them according to their function, the latter phenomenon having already been observed, for example, after cardiomyoplasty[36].

We know today that tracheal regeneration from an aortic graft is done from the recipient's cells and not from the aortic cells. Studies are underway to demonstrate the intervention of local or bone marrow mesenchymal stem cells, a process already identified for the repair of other organs[37-39] but also at the level of the trachea [40]. The exact role of the aorta remains to be defined since only this type of biological graft has led to such a complete regeneration. Significant inflammation in the graft, as well as signals from regenerating epithelial and cartilage cells, appear to be key components of tissue repair.

Why is immunosuppressive therapy not necessary?
The main immunogenic cells of the vessels are in the vascular endothelium. Once the vessel is extracted from its natural environment, these fragile cells are destroyed and the aorta behaves like a tissue almost inert from the immunological point of view. It should be noted here that the transplanted aorta is not the subject of any particular blood or tissue compatibility research. In clinical practice, arterial allografts are frequently used, without immunosuppressive therapy, for vascular prosthetic infections41 and no acute rejection has been observed.

What type of aortic graft to use in humans?
Autograft should not be favored in humans because it is too invasive in patients who are weakened by extensive cancer of the trachea. Because of the similar results obtained with an allograft and without rejection reaction, the use of a fresh allograft should therefore be preferred in the context of a multi-organ collection or better cryopreserved allograft available. in tissue banks. We have just demonstrated the superiority of cryopreserved allograft on allografts freeze-dried or preserved by glutaraldehyde[42] .

Tracheal replacement in humans
On the basis of the experimental work, and after favorable opinion of the National Consultative Committee of Ethics and the Agency of Biomedicine, six patients in therapeutic impasse were the subject, (as compassionate and then as part of a research biomedical) of a tracheal replacement performed by the collaboration of several teams in France (CHU Lille, CHU Nice, CHU Avicenne APHP) from 2005. These patients had extensive tracheobronchial tumors, radiation-resistant and chemo-resistant, not accessible to conventional surgery and whose short-term evolution could have been marked by asphyxia and death. The first two replacements were made from a fresh aorta graft[43], the next four from a cryopreserved aortic graft. In all cases, lesions observed intra-operatively were more extensive than the preoperative assessment predicted. In addition to an extensive tumor resection and the use of aortic graft to replace the missing air segment, the act involved for three patients the reconstruction of the hull. For two patients, the tumor extension also required resection of the pulmonary parenchyma (right upper lobectomy for one and left pneumonectomy for the other). A stent (Novatech®, La Ciotat, France) in silicone (cylindrical in one case, in Y in five cases) was set up per-operatively to avoid the respiratory collapse of the aortic graft (internal guardian) and myoplasty (pectoralis major) has been used to protect the graft and facilitate its revascularization. Even if the macroscopic and histological evolution seems to be superimposable on what has been observed in animals, it is still too early to know whether, in the long term, the transformation of the grafts into neo-trachea will be sufficient to allow the removal of the internal tutor. All patients were alive at 90 days. The morbidity was high, related to infectious or anastomotic complications and in one case to paraplegia. To date, the first 2 patients have died, one of a metastatic evolution, the other a haemoptysis. The last 4 patients are alive, without recurrence with an average duration of follow-up of 32 months. Three returned to normal full-time work. Re-epithelialization of the graft was observed. The current question is to know what will be the possibilities of ablation of the stent since the regeneration phenomena seem delayed in the man with regard to the cartilage (with nevertheless a neo-trachea present) and that it exists, in half of the cases, an asymptomatic fistula with the esophagus.

The prospects of experimental research
Current research aims to characterize the cells responsible for transforming a tissue as differentiated as the aorta into a new differentiated tissue such as the trachea. Based on the hypothesis of colonization of the arterial graft by local mesenchymal stem cells or from the bone marrow of the recipient, a major research project on the lagomorphic model is underway (LEGPC collaboration, Broussais Hospital, Paris V University and Center for Cardiovascular Repair, University of Minnesota, Minneapolis).

The use of an aortic graft stiffened by a temporary stent as a tracheal substitute led, in animals, to unexpected tissue regeneration in the form of a functional "neo-trachea" comprising a respiratory epithelium and cartilage. These encouraging results have led to the first clinical applications in

France in patients with malignant tumors extended trachea hitherto incurable. Even if it is necessary to remain cautious, it is legitimate to ask, as did the review *Chest*[44], if the ideal tracheal substitute has not been discovered. The clinical evaluation and the scientific work must be amplified in order to offer a standardized surgical treatment to complex tracheal lesions and to explain this new concept of induced tissue regeneration. Parallel to this work, was published the first human case of tracheobronchial replacement by a graft resulting from tissue engineering[45].
This was the replacement of a short segment in a patient with post-tuberculosis stenosis. A tracheobronchial graft taken from a brain-dead patient was decellularized. Tracheal epithelial cells were removed from the recipient and then cultured and finally seeded on the graft using a bioreactor. The evolution was favorable with a follow-up period of 4 months. The question that arises today is whether this technique will be applicable to cancerous lesions in the future. Indeed, the use of epithelial cells taken from the recipient and then cultured and the time to obtain the graft (several months) condemn today its indication in the field of malignant tumors extended trachea.

Bronchial replacement and / or pulmonary artery by an arterial allograft

In view of the very encouraging results of our work on the replacement of the trachea and carina with aortic graft, we have proposed to evaluate, on the same animal model of the ewe, the bronchial replacement with an arterial allograft. This is an unresolved problem in thoracic surgery for which the discovery of an effective solution would allow the near disappearance of the pneumonectomy, an intervention with a morbidity and mortality rate too high as well as unacceptable functional consequences, and the lobectomy with RAB associated with major risks of recurrence (see above).

Material and methods

A left superior lobectomy with replacement of a bronchial segment by an arterial allograft supported by a silicone stent (Dumon®, Novatech®, La Ciotat, France) was performed in 20 ewes.

Three experimental groups were formed:

- **groupe I** : left bronchial replacement by fresh arterial allograft (n = 5);
- **groupe II** : left bronchial replacement by cryopreserved arterial allograft (n = 10);
- **groupe III** : bronchial replacement and replacement of the left pulmonary artery by a cryopreserved allograft (n = 5).
-

In order to improve local vascularization and to create a mechanical barrier between bronchial anastomoses and the adjacent pulmonary artery, an intercostal muscle flap was used in all cases. The evaluation criteria were clinical, fibroscopic and histological at 2, 4, 6, 12, 18 and 24 months. Removal of the stent was performed at 9 months (n = 1) and 12 months (n = 2) of the procedure. For animals that had pulmonary arterial replacement with a cryopreserved arterial allograft, the permeability and macroscopic appearance of the arterial graft were evaluated at sacrifice.

The sacrifices of animals have been programmed according to their group:

- **groupe I** : at 2, 4, 6, 12 and 18 months of the procedure (one animal at each interval);
- **groupe II** : at 2, 4, 6, 12 and 18 months of the procedure (two animals at each interval);
- **groupe III** : at 2, 6, 12, 18 and 24 months (one animal at each interval).

After explantation, the grafted area was opened longitudinally on its posterior side and the bronchial stent was extracted. The graft was examined macroscopically, appreciating its integrity, rigidity and permeability as well as the presence of abnormalities. Two longitudinal sections of the graft, including the two areas of anastomosis, were made and included in paraffin. Two sections with a microtome of 4 µm thick were made from each block, then stained with hematoxylin-eosin-saffron and orcein. Histological transformations of the grafts were examined by light microscopy

Results

There was no perioperative mortality and the intervention was particularly well supported from a clinical point of view by all the animals. Three cases of early postoperative atelectasis were observed and treated by bronchial fibrosis. During the study (maximum follow-up = 24 months), only 2 complications (lung abscess) led to premature sacrifice of the animals. In the remaining 18 cases, the sacrifice was made on the scheduled date. The removal of the stent remained without clinical impact. In 4 cases, non-stenotic endobronchial granuloma was observed. Macroscopic examination of the specimens showed, in all cases, perfect continuity between the grafted area and the adjacent bronchial tree. The graft was replaced by a dense tissue with a lower stiffness than the bronchial wall. Longitudinal contraction of the grafted area was observed on all samples. Ossification at the level of the intercostal muscle flap partially covering the bronchial circumference was observed in all cases. No narrowing of the bronchial lumen due to ossification of the intercostal muscle has been demonstrated. A progressive histological transformation of the arterial graft into the bronchial position led to a re-epithelialization initially of squamous, then mixed or respiratory type and the appearance of neo-cartilage. There was no difference between fresh and cryopreserved arterial allografts. The grafted area remained a tubular structure, gradually becoming stiffer. Regarding arterial pulmonary replacement by a cryopreserved arterial allograft, the histological analysis found the following aspects: thickening of the intima, disappearance of the smooth muscle cells, good conservation of the elastic fibers in the internal part of the media. The outer part of the media has been characterized by a regressive inflammation over time, and by the existence of elastic fiber zones in degradation or calcification. The grafted arterial zone remained permeable.

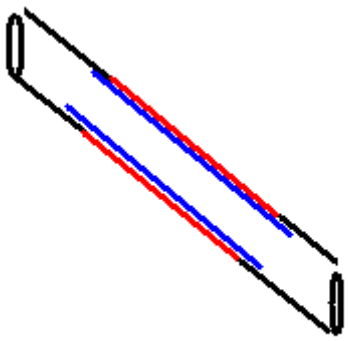
The part of this study concerning bronchial replacement was published in The Annals of Thoracic Surgery[46].

These very favorable results make it possible to envisage a clinical application in humans of this new surgical technique in the context of proximal tumor lesion, the removal of which would be a superior lobectomy with RAB, RAAP or a pneumonectomy.

The bronchial replacement technique with an arterial allograft is detailed by intraoperative views in animals in Appendix 1.

3.2 General description of the graft being investigated and the medical device used during the surgery:

The bronchial and / or arterial replacement evaluated in this trial will require the use of a cryopreserved arterial allograft (research subject). As part of this surgery, and a temporary stent will be used.



bronchial segmental replacement (bronchus = black, arterial allograft = red, stent = blue)

- **Graft: cryopreserved arterial allograft**

    - the arterial grafts (aorta, human iliac arteries or aortic bifurcation from a multi-organ collection) for bronchial replacement and possibly the pulmonary artery will come from the Saint Antoine tissue bank of the EFS Ile de France. The grafts are cryopreserved at -80 ° C. according to an authorized method.
    - Henri Mondor Tissue Bank of the EFS Ile de France obtained on May 07, 2010 the renewal of its authorization of activity not the AFSSAPS (BT / 10 / M / 003).
    - Applications will be made to Dr. A. Fialaire-Legendre (or his replacement in case of absence), responsible for the Tissue Bank and referent of this clinical research protocol.
    - *The protocols for freezing and thawing cryopreserved arterial allografts are detailed in Appendix 2.*

- **STENT**
    - The use of a stent is mandatory, as our studies have shown, because of the natural elasticity of the arterial tissue.
    - Ablation was possible in animals after tissue regeneration was observed.
    - The custom-made metallic endoprosthesis (made on the basis of fibreoptic and computed tomography data) will be delivered by Novatech ®, La Ciotat, France or supplied by that same company with respect to the silicone reference stent.
    - *The characteristics of Silmet or silicone stents marketed by Novatech ® are detailed in Appendix 3.*

3.3 Summary of available non-clinical trial and clinical trial results relevant to relevant biomedical research.

Refer to section 3.1 for tracheobronchial replacement with aortic allograft.

3.4 Summary of benefits, if any, and foreseeable risks known to those who are suitable for research.

Summary of benefits, if any, and foreseeable risks known to those who are suitable for research::

- **Expected benefits:**
    - The literature review shows in some referral centers that mortality at 90 days after neoadjuvant chemotherapy and right pneumonectomy can reach 24%.
    - In this study, we set ourselves the goal of achieving a 90-day survival of at least 76% (90-day mortality less than 24%), more encouraging results than those found in conventional surgery.
    - Data collected in the postoperative period will be evaluated and compared to literature data for major lung resections:
        - postoperative complications: bronchial obstruction, atelectasis, pneumonia, defect of pulmonary re-expansion, tracheal, bronchial or broncho-vascular fistula, empyema, bronchial stents (migration, rupture, granuloma formation, obstruction, infection, hemoptysis), thrombosis of the pulmonary artery or vein, others (cardiac complications, thrombo-embolic ...)
        - Postoperative bubbling time,
        - Ablation of the drains
        - length of hospital stay

- **Serious Adverse Events expected from surgical treatment or study procedures**

The expected SAEs are

Those related to surgery whatever it is:

- death,
- postoperative respiratory distress, complete atelectasis of the remaining lobe or postoperative pneumonia requiring prolonged artificial ventilation

- lack of pulmonary re-expansion
- empyema requiring surgical revision,
- fistula (tracheal, broncho-pleural, broncho-vascular, broncho-oesophageal),
- nosocomial infection,
- prolonged bronchial bubbling ≥21 days or requiring revision

Those related to the practice of an allograft including the stent is::

- o rupture of the allograft,
- o dilation of the allograft,
- o thrombosis of the pulmonary artery or vein
- o fibrosis and retraction of the allograft by an excessive inflammatory reaction,
- o Deficiency of induced tissue regeneration and neo-bronchial formation
- o intolerance of the endoprosthesis placed in place temporarily (inflammatory granuloma, hemoptysis, ...),
- o migration of the stent, rupture of the stent
- o obstruction of the stent, infection.
- o Stenosis upstream and downstream of the prosthesis
- o risk of tissue perforation and hemorrhage with haemothorax / haemoptysis

3.5 Description and rationale for the use of the medical device (s) or in vitro diagnostic medical device (s), and the duration of treatment, if any;

The cryopreserved arterial allograft and stent will be used according to the rules and recommendations in force. The duration of follow-up will be 90 days.

3.6 The research will be conducted in accordance with the protocol, the good practices and the laws and regulations in force

- o Patient over 18 years old
- o Proximal tumor lesion whose surgical excision requires resection of carina, pneumonectomy, lobectomy with RAB and / or RAAP, immediately or after neo-adjuvant chemotherapy and with EFR allowing the proposed pulmonary resection
- o proximal tumor lesion whose surgical resection requires pneumonectomy but with EFR allowing only lobectomy
- o proximal tumor lesion whose surgical resection requires pneumonectomy in a patient over the age of 70 (major risk of death at 90 days)
- o Extensive lesions of the trachea, cancerous or not, trachea without bronchial involvement in therapeutic stalemate.
- o Surgical eligibility (indication of surgical treatment) retained during a collegial discussion (Multidisciplinary Collaborative Meeting)
- o Informed and written consent.

3.7 References to scientific literature and relevant data serving as a reference for research.

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4 Objectives of the research

4.1 Primary outcome

To evaluate the feasibility of bronchial replacement and / or pulmonary vessels or trachea by a cryopreserved arterial allograft for the surgical treatment of proximal tumoral lesions of the thorax. The primary endpoint will be 90-day survival.

4.2 Secondary outcome

To evaluate the morbidity associated with this intervention::

- Postoperative complications: bronchial congestion, atelectasis, pneumonia, pulmonary re-expansion defect, tracheal, bronchial or broncho-vascular fistula, empyema, bronchial stents, thrombosis of the pulmonary artery or vein, other (complications cardiac, thrombo-embolic ...)
- Postoperative air leak, removal of drains
- Hospital length of stay

Note:
The objective of this study is not, initially, to compare the results of the evaluated technique with those of pneumonectomy or lobectomy with RAB (case-control study). This is a feasibility study which aims to say whether this new technique is feasible without major complications in relation to the data of the literature. The primary endpoint will be 90-day survival, which can reach 24% in some international series from reference centers.

5 Research Design

5.1 Specific statement of the main evaluation criteria and, if applicable, secondary evaluation criteria

Main criterion:
Survival at 90 days

Secondary criteria:

- Postoperative complications: bronchial congestion, atelectasis, pneumonia, pulmonary re-expansion defect, bronchial or broncho-vascular fistula, empyema, bronchial stents (migration, rupture, granuloma formation, obstruction, infection, hemoptysis), thrombosis pulmonary artery or vein, other (cardiac complications, thrombo-embolic ...) daily during hospitalization and on D30, D60 and D90 postoperative
- Postoperative bubbling time
- Duration until removal of drains
- Hospital length of stay

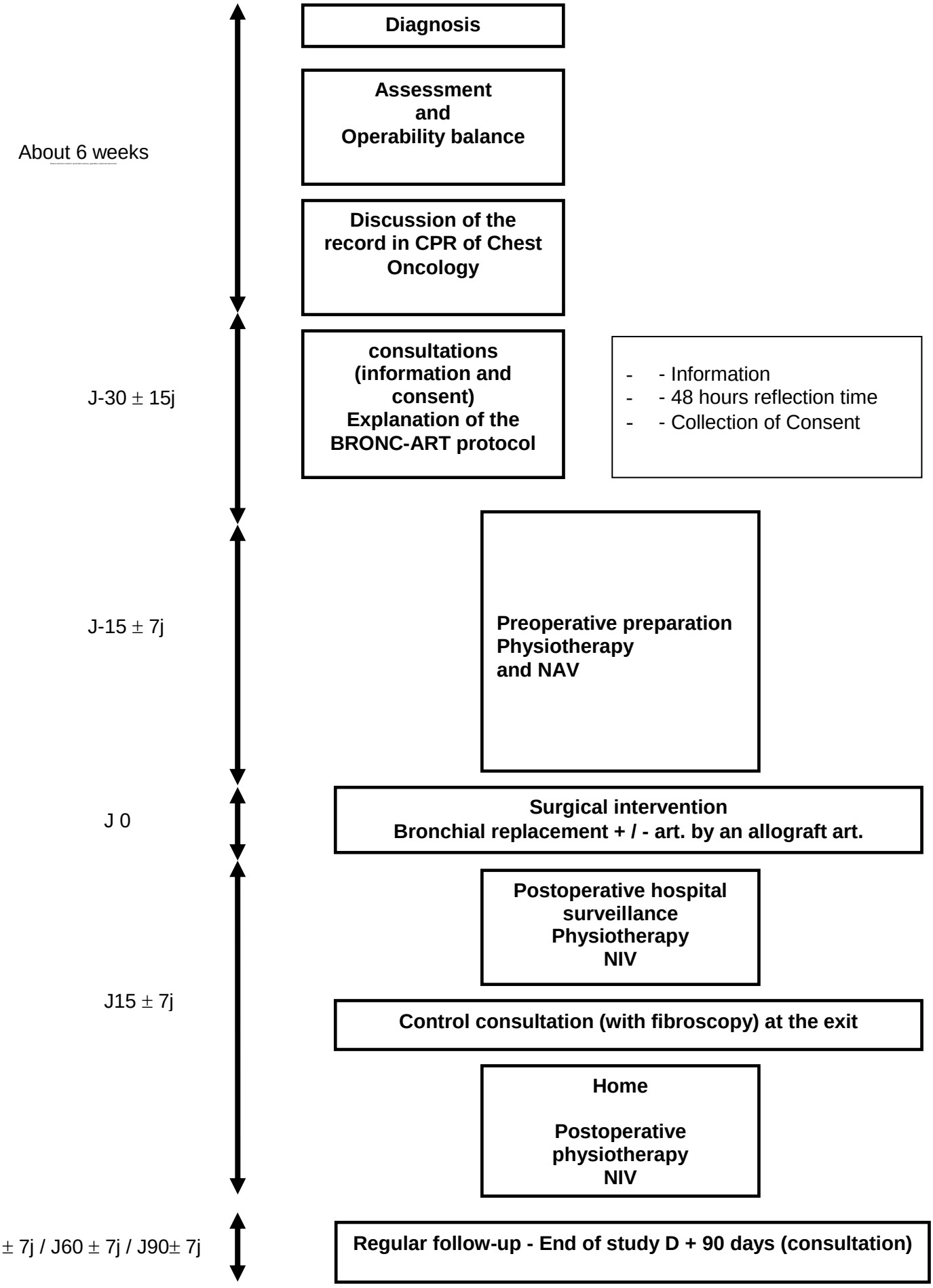
5.2 Description of the research methodology, accompanied by its schematic presentation specifying in particular the visits and examinations planned.

- **Methodology:**

Open Study, Cohort, monocentric.

Multidisciplinary: Pôle Specialized Cancer Activity (Prof. Dominique Valeyre) including Thoracic and Vascular Surgery, Pneumology, Medical Oncology
Emergency Department Hospital: Anesthesia-Resuscitation (Clinical Unit for Continuous Surveillance and Resuscitation)
Avicenna Hospital, Public Assistance of Paris Hospitals, Bobigny, Paris XIII University

- **Scheme of the study:**



5.3 Description of the evaluation parameters (other than those related to security discussed in 7) and methods to measure, collect and analyze these parameters;

The data in the observation book will be collected as soon as the patient is included in the protocol until it is stopped.

5.4 Description of measures taken to reduce and avoid analysis bias :

The study is a feasibility study, non-randomized, open. There are therefore no possible measures to avoid the biases.

5.5 Detailed description of the surgical procedure under investigation (allograft) and the medical device related to this procedure (stent) ;

The use of the cryopreserved arterial allograft and the stent will be performed according to the protocol detailed in section 4.2 and according to the recommendations in force (use of vascular allografts in humans, use of tracheobronchial stents in the patient. 'man).

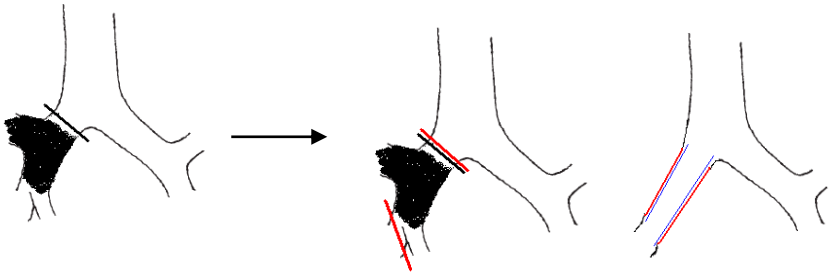
5.6 Traceability of arterial grafts and medical devices: :

Arterial grafts: The Promoter will ensure the traceability of the graft used for a given patient in the form of a checklist which will be completed by the thoracic surgeon and kept in the observation book. No specific labeling for research will be done on the pouch containing the graft and the transport container.

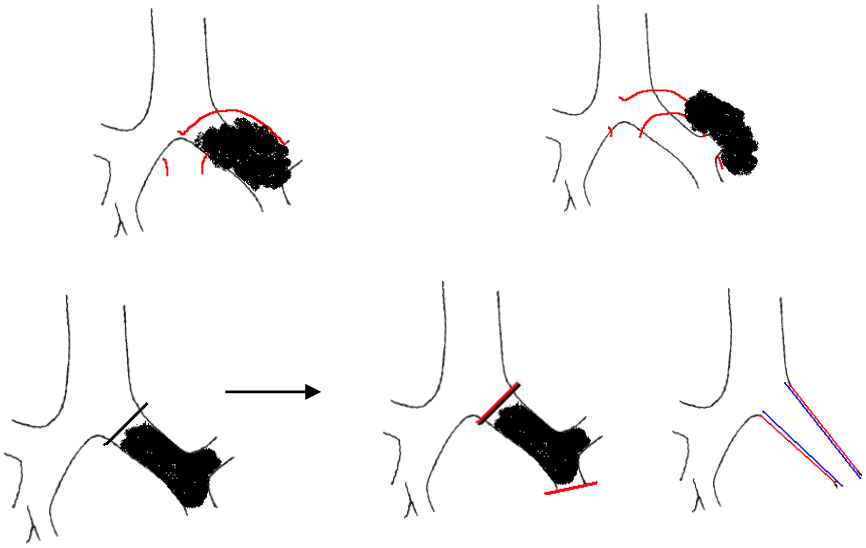
Medical device (DM): The DM supplied by NOVATECH (commercial boxes in sterile unit packaging) will mention at least a labeling stating: Public Assistance Hospitals of Paris, DRCD, Saint Louis Hospital, 75010 Paris / BRONC-ART / Device for Biomedical research for a specific use in research. The DM will be delivered by this company to the PUI Avicenne who will provide the dispensing to the investigative service according to the terms and conditions specific to this center.

Diagram of the intervention according to the indication::

- The indications include :
  - proximal tumor lesion whose surgical excision requires resection of carina, pneumonectomy, lobectomy with RAB and / or RAAP, immediately or after neo-adjuvant chemotherapy and with EFR allowing the proposed pulmonary resection
  - proximal tumor lesion whose surgical resection requires pneumonectomy but with EFR allowing only lobectomy
  - proximal tumor lesion whose surgical resection requires pneumonectomy in a patient over the age of 70 (major risk of death at 90 days)
- Indications of pneumonectomy:

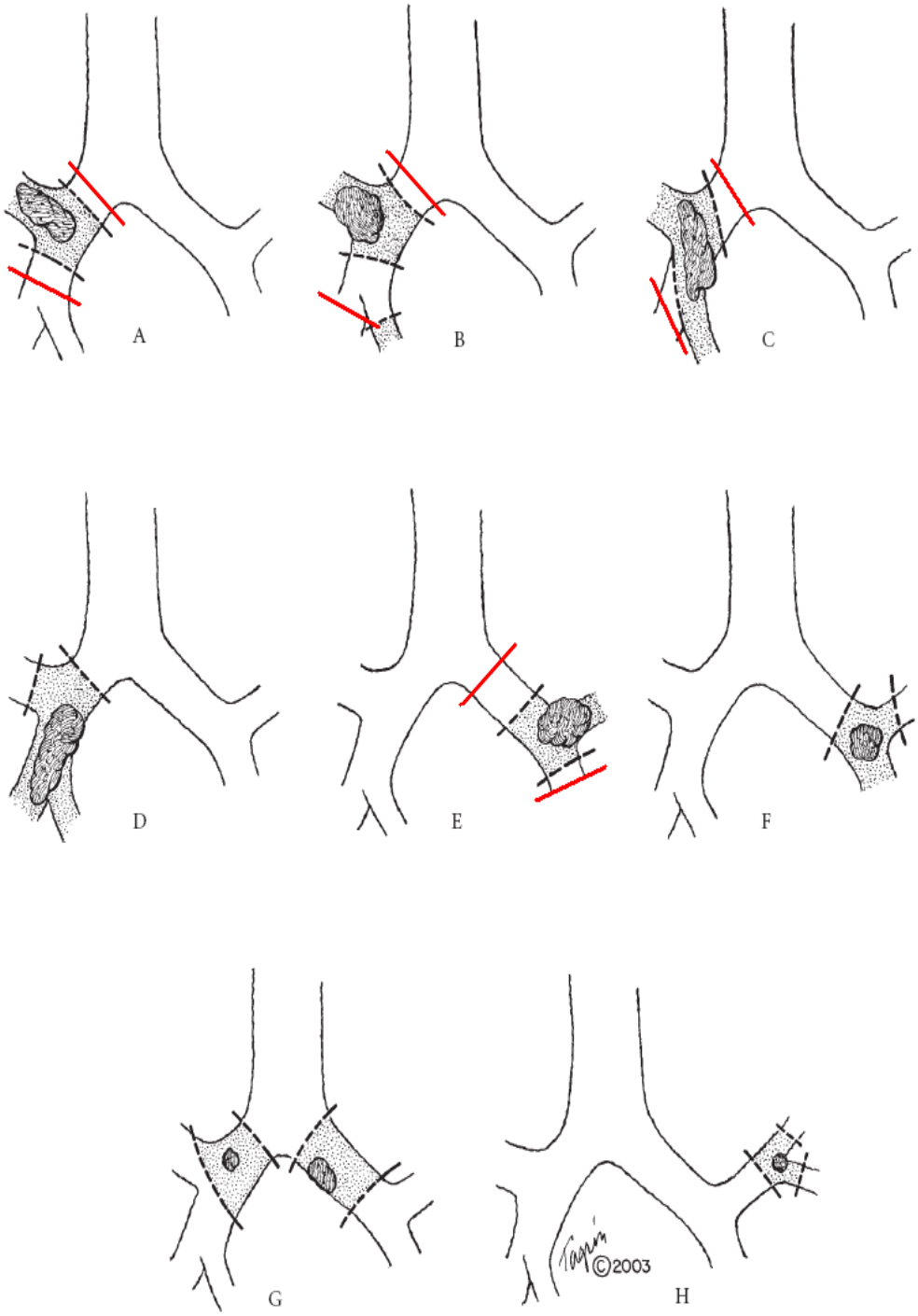


To avoid a pneumonectomy D, a superior bilobectomy with preservation of the lower lobe and bronchial replacement by an arterial allograft stiffened by a silicone stent is performed.
To avoid pneumonectomy G, an upper lobectomy with preservation of the lower lobe and

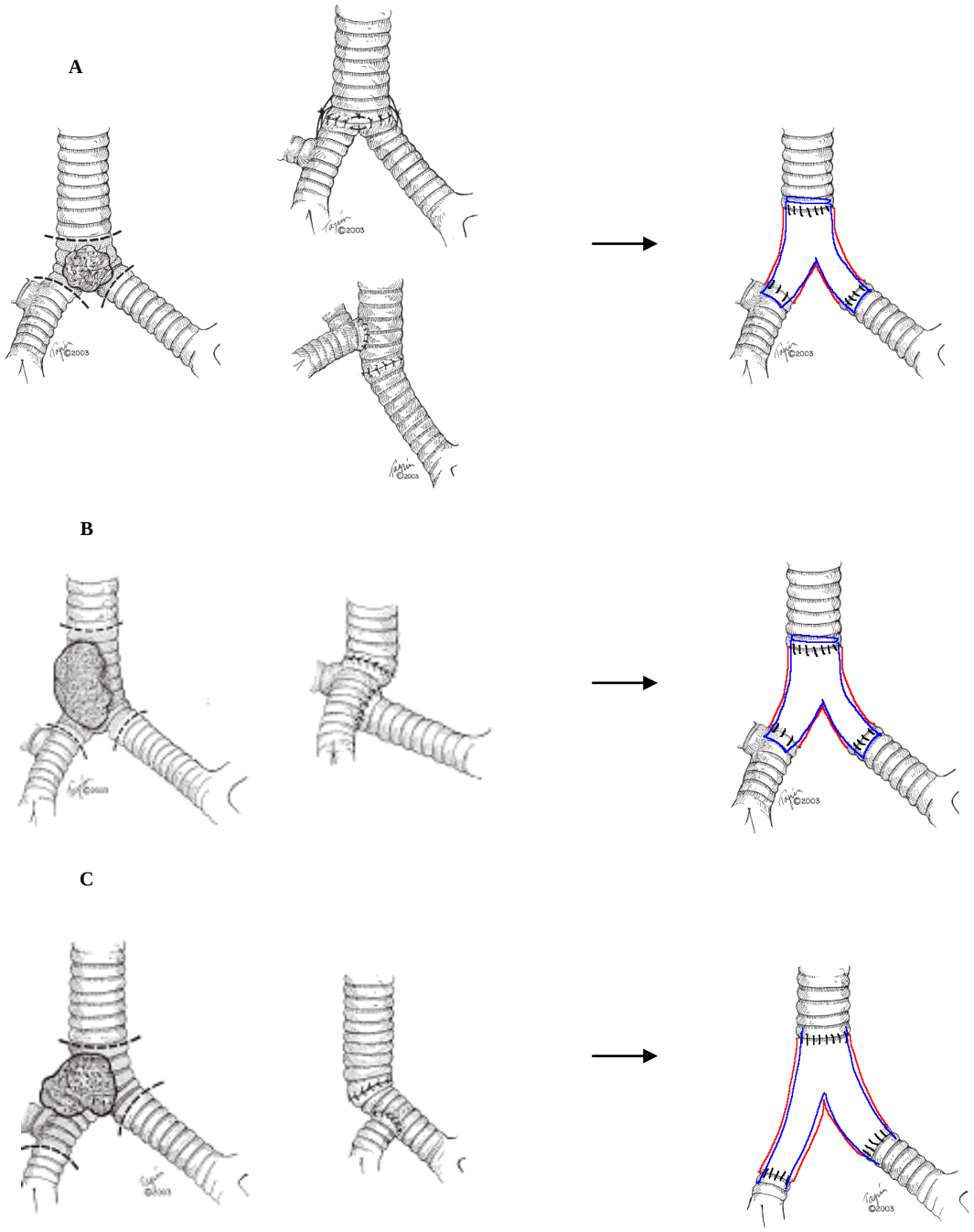


bronchial replacement by an arterial allograft stiffened by a silicone stent is performed.
To avoid pneumonectomy in case of massive invasion of the pulmonary artery, replacement of the pulmonary artery by an arterial allograft is performed in isolation or associated with a bronchial replacement with the interposition of a flap.

Indications of lobectomy + RAB: among all the identified cases where a lobectomy with RAB is envisaged (resection limits: black lines, figures A to H), some may be highly dependent on a bronchial replacement, which makes it possible to increase the margin oncology (resection limits: red lines, figures A, B, C, E); others do not seem to be part of the potential indications (Figures D, F, G, H).

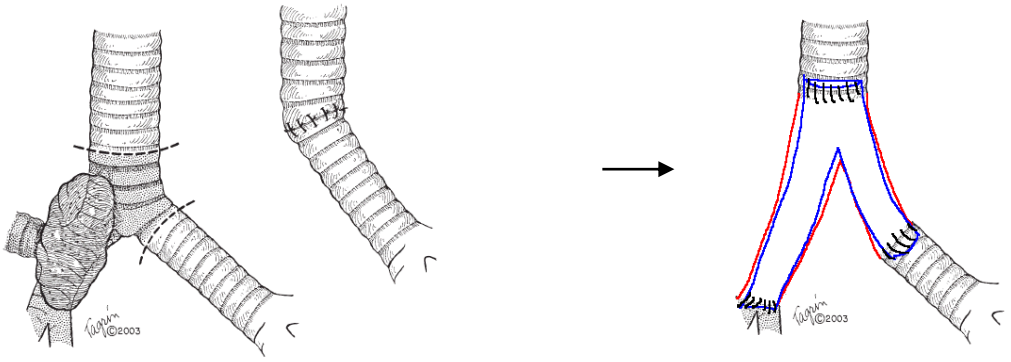


- Indications of carinal resection: all the surgical interventions described in the literature can be modified in the direction of a bronchial replacement by a bifurcated allograft. This allows, moreover, in cases where a pneumonectomy must be associated with the carina resection to avoid it and thus to preserve lung parenchyma free from cancer and functional. Moreover, this technique implies, in all cases, an increase in the safety margins of resection, a crucial point to avoid the risk of loco-regional recurrence.



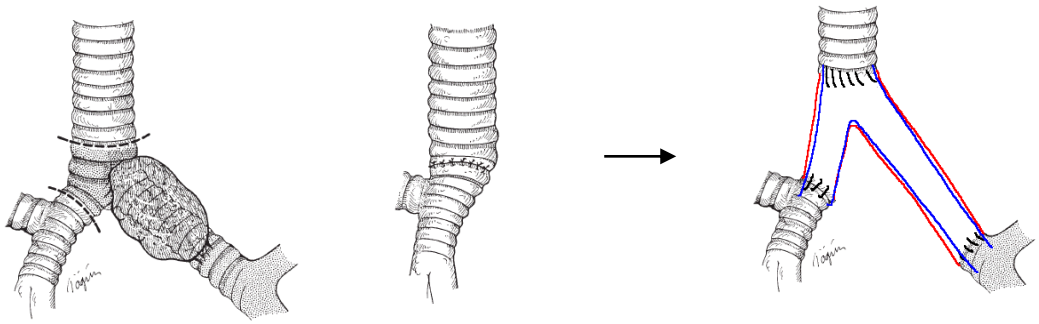
The techniques of resection of carina isolated without lung resection [case A and B] or with right superior lobectomy [case C] are modified in the direction of a bronchial replacement by a bifurcated arterial graft stiffened by a silicone stent, also bifurcated ..

D



The technique of resection of carina with pneumonectomy D [case D] is modified in the direction of a bronchial replacement by a bifurcated arterial graft stiffened by a silicone stent, also bifurcated. Thus, it is possible to preserve the lower lobe D and possibly the middle lobe in some cases

E

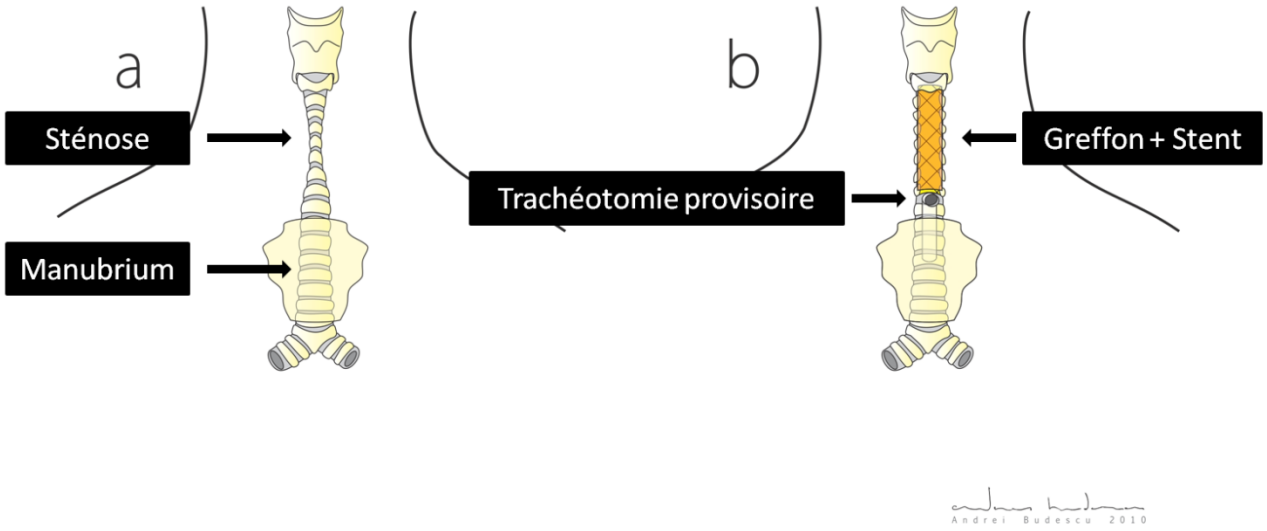


The technique of resection of carina with pneumonectomy G [case E] is modified in the direction of a bronchial replacement by a bifurcated arterial graft stiffened by a silicone stent, also bifurcated. Thus, it is possible to preserve the lower lobe G and possibly the upper lobe G in some cases.

Several clinical cases illustrating the indications in humans of bronchial replacement by an arterial allograft are reported in Appendix 3

- General description of the graft being investigated and the medical device used during surgery::

The surgical innovation evaluated in this trial for the treatment of benign or cancerous tracheal stenosis in therapeutic impasse will require the use of a cryopreserved arterial allograft (research object). As part of this surgery, and a temporary stent will be used..



5.7 Expected duration of participation, and description of the timeline and duration of all research periods, including follow-up;

5.7.1 Duration of the study

Duration of the inclusion period: 7 years

Duration of participation of the patient: 4 months (1 month before the intervention, 90 days of follow-up).

Total duration of the study: 7 years and 4 months (88 months)

5.7.2 Chronology

Pre-therapeutic assessment: *: standardized, resulting in the eligibility or not of the patient*

- Bronchial fibroscopy with directed biopsies and in the case of negativity: CT-guided trans-parietal puncture if possible and retained by CPR.
- loco-regional and remote extension assessment (cTNM): thoracic computed tomography with hepatic and adrenal sections (injection of contrast medium), positron emission tomography (PET) + MRI or cerebral CT. Verification or not (according to the opinion of the RCP) of the N2 or N3 invasion by mediastinoscopy with biopsies directed in case of mediastinal fixation to PET.
- Respiratory Functional Explorations: spirometry, blood gas with postoperative predictive FEV1 calculation and ventilation / perfusion scintigraphy in cases where the respiratory function is limited (postoperative predictive FEV1 at about 1/3 of the theoretical value).).
- Operability report: Anesthesia consultation, cardiovascular assessment (cardiac ultrasound, Doppler and lower limbs echo-Doppler ultrasound, supra-aortic trunk ultrasound) and other examinations depending on the clinical context.

This assessment is indicated for a better understanding of the scheme, but it is upstream of the research, it corresponds to the examinations carried out classically upstream of a conventional surgical procedure.

Course of the study:

The clinical trial will be conducted according to the following steps::

- **Collegial decision of surgical treatment in Multidisciplinary Concertation Meeting**

(RCP)

- any eligible patient will be presented in CPR for a collegial agreement on the surgical indication
- indication of surgery immediately or after neoadjuvant chemotherapy will be discussed.
- a report will be made at the end of the CPR and sent to the corresponding doctors of the patient.

- **Announcement of the therapeutic strategy proposed to the patient (J-30±15j)**
  - the inclusion will be offered to the patient, in the presence of one or more members of his family or friends of his choice.
  - The type of intervention proposed, the expected benefits as well as the risks incurred will be detailed to the patient.
  - a newsletter will be given to the patient.
  - An informed consent form will be signed by the patient after a reflection period of at least 48 hours.

- **Preparation of the intervention (after obtaining consent until D0)**
  - Preparation of the patient by a strong recommendation of smoking cessation if necessary (consultation at the anti-smoking center), by intensive respiratory physiotherapy and non-invasive ventilation for at least 15 days (usual procedure)
  - Computed tomography of the chest with contrast injection (in the absence of allergy to iodine) and 3D reconstruction with study of the anatomical relationships of the tumor; measurement of the diameters of the main bronchus, the lower lobe bronchus and the length between these two markers; measurement of the diameters of the pulmonary artery at its emergence of the pericardium and the inferior lobar artery. For hull replacements, measures will be made, in addition, at the level of the trachea and the 2 bronchial trees (usual procedure).
  - Control of cryopreserved arterial allografts: an aortic graft or two iliac grafts will be systematically requested to cope not only with bronchial replacement but also with the possibility of replacement of the artery or pulmonary vein. For hull replacements, a bifurcated graft will be requested (specific to the search).
  - Stent control (Novatech®, La Ciotat, France) adapted to CT measurements (specific to research).
- **Graft: cryopreserved arterial allograft**
  - Arterial grafts (aorta, human iliac arteries or aortic bifurcation from a multi-organ collection) for bronchial replacement and possibly the pulmonary artery will come from the Saint Antoine tissue bank of the EFS Ile de France. The grafts are cryopreserved at -80 ° C. according to an authorized method.
  - Henri Mondor Tissue Bank of EFS Ile de France has obtained the renewal of its activity authorization by AFSSAPS on May 7, 2010 (BT / 10 / M / 003).
  - Requests will be made to Dr. A. Fialaire-Legendre (or his replacement in case of absence), responsible for the Tissue Bank and referent of this clinical research protocol.
  - Freezing and thawing protocols for cryopreserved arterial allografts are detailed in Appendix 2.

- **Stent**
  - The use of a stent is mandatory, as our studies have shown, because of the natural elasticity of the arterial tissue.
  - Its ablation was possible in animals after tissue regeneration was observed.
  - The custom-made metal endoprosthesis (made on the basis of fibreoptic and computed tomography data) will be delivered by Novatech®, La Ciotat, France or supplied by the same company for the silicone reference stent.
  - The various stents sold by Novatech® are detailed in Appendix 3.

- **Surgical procedure: bronchial or tracheal replacement (D0)**

The surgical procedure is carried out in the same way as for a conventional intervention, the specificities related to the allograft are, the allograft replacement in the point 5 /, the interposition of the allograft in the point 6 / and the control fibroscopic in point 8 / of the paragraph below.

1 Conventional anesthesia performed according to the reference systems used during any major or tracheal pulmonary resection surgery (including in particular selective pulmonary intubation if possible), antibiotic prophylaxis according to the protocol approved by the Local Committee for the Control of Hospital Nosocomial Infections.
The surgical procedure will be conducted according to the reference techniques used in thoracic surgery for major pulmonary resection and according to the experience gained during the development of the surgical operation in animals.
2 Postero-lateral thoracotomy. Preparation of the intercostal or dorsal flap by the thoracic and vascular surgeon who operates the patient. Thorough exploration of the thoracic cavity: indication for a superior lobectomy with bronchial replacement +/- replacement of the pulmonary artery or vein according to the invasion, contraindications = loco-regional invasion, metastases located in the lower lobe and histologically proven by extemporaneous anatomo-pathological examination, pleural, pericardial metastases or other localizations.
3 Opening of the mediastinal pleura at the level of the hilum, section of the triangular ligament and control of the different vessels (with pericardotomy if necessary), opening of the fissure (s) and dissection of the pulmonary artery and its branches. Creation of a pulmonary bridge forward and backward with stapling with automatic forceps. Arterial and venous vascular ligation. Estimation of the need for a simple ligation of the arterial branches, an arterial resection-anastomosis or a replacement of the pulmonary artery or vein by a cryopreserved arterial allograft.
NB: on the left side, parenchymal resection will be at least an upper lobectomy; on the right side, a superior bilobectomy (resection of the upper lobe and middle lobe). These two interventions, which differ according to the side due to the anatomical characteristics, can, on the other hand, be considered as equivalent from a functional point of view.
4 Bronchial resection in the main bronchus and lower lobe bronchus with estimation of the possibility of preservation of the apical bronchus of the lower lobe. If there is a need for sacrifice of the apical bronchus of the lower lobe, parenchymal resection complementary to the apical segment of the lower lobe.
5 Bronchial replacement by cryopreserved arterial allograft sutured by 2 continuous superposition of absorbable son 4/0 and stiffened by the endoprosthesis placed by the operative field or natural pathways. Fixation of the stent at the proximal and distal anastomoses by several points of nonabsorbable thread. Extemporaneous pathological study of bronchial limits. In case of invasion, complementary bronchial cut until obtaining a healthy tissue.
6 6 If necessary, resection of the pulmonary artery or vein after heparin injection by the general route (50 IU / kg), clamping of the proximal and distal pulmonary artery or of the inferior pulmonary vein. Direct anastomosis of the pulmonary artery or interposition of a cryopreserved arterial allograft sutured by 2 nonabsorbable 5/0 sutures. Purge and declamping;
7 Full and radical ganglionic treatment according to the usual recommendations.
8 Fibroscopic examination at the end of the procedure: checking for the absence of abnormalities and the correct positioning of the stent, which must, in particular, cover the anastomoses.
9 Control of hemostasis and aerostasis.
Interposition of the muscle flap isolating the bronchial reconstruction of the pulmonary artery.
11 Closure plan by plan on 2 chest drains according to the usual technique.
12 For hull replacements, the surgical technique will be adapted to anatomical cases: approach (sternotomy or postero-lateral thoracotomy in the 4th intercostal space), wide resection to move into a healthy zone, bifurcated tracheobronchial replacement by adapting the length of the legs at the extent of the resection, customized bifurcated endoprosthesis according to the CT measurements).

- **Postoperative follow-up (from day 0 to discharge from hospital)**

- Postoperative follow-up in the Continuous Care Unit, in the Resuscitation Unit or in the Surgical Unit (depending on the clinical condition) performed by the surgical team, anesthesia-intensive care, pulmonology and thoracic oncology; aiming to detect and treat possible complications. Postoperative management is done according to the rules observed for any patient who had a major excision for tumor lesion. The discharge of the hospital is decided collegially by the various stakeholders. Bronchial fiberoptic (conventional or virtual) will be performed systematically before discharge.
- The patient leaves the hospital with a stent holder card clearly indicating the clinical signs that must evoke a complication and the action to take.
- At the end of the pathology report, a ranking according to the international classification of CBP (pTNM and stage) is carried out in a collegiate manner by the various stakeholders of the clinical research protocol.
- The decision of adjuvant treatment by radiotherapy and / or chemotherapy is decided collegially in CPR.

- **Postoperative follow-up (at D30±7 d / D60±7 d / D90±7 d)**

- Follow-up: a consultation will be carried out systematically at 30, 60 and 90 days by the referring specialist doctor of the patient. A clinical examination will be performed. Additional examinations may be requested: chest x-ray, computed tomography chest CT scan for complications (dehiscence of the graft, removal of the silicone stent, fistula, granulomas, thrombosis of the pulmonary artery ...) or a loco-regional evolutionary recovery of the tumor lesion (requiring pathological confirmation by directed biopsies), positron emission tomography, bronchial fiberoptic, biological examinations. A report is written and sent to all participants in the clinical research protocol

- **Removal of the stent**

- Data from animal experiments and human clinical applications on aortic graft replacement of the trachea, carina and bronchi showed significant differences depending on the species and the tracheobronchial portion grafted. Endoprosthesis ablation was possible, with no functional consequence, from 6 months at the level of the sheep trachea. In man, the phenomena of tracheobronchial regeneration seem delayed so that some patients undergoing surgery (replacement of the trachea by aortic allograft) still have a tracheal endoprosthesis more than 2 years after the intervention. In ewes, the results observed after bronchial replacement (regeneration in the form of a neo-bronchus with cartilage neoformation) have just allowed the removal of the stent (n = 2) without any respiratory consequence. In the current state of knowledge, it is impossible to predict the kinetics of bronchial regeneration (epithelial repair and cartilage neoformation) in humans and therefore the possibility of ablation of the stent.
- The decision to ablate the stent will not occur, in principle (unless stent change is required), during the feasibility study period (90 days). The elements concerning the removal of this stent, if it is withdrawn, will be collected as part of the usual follow-up of the patient

The pre- and post-surgical management of the patients included in this research protocol is no different from that usually performed in the medical-surgical treatment of a tumor of the thorax. The only non-systematic examination that became available in this study is bronchial fibroscopy (conventional or virtual) after discharge.

5.8 Description of the rules of permanent or temporary cessation

- The participation of a person in research*;*

The termination of the research protocol for a person will follow a possible death or after a period of 90 days.

- part or all of the research;

An independent monitoring committee (Data Safety Monitoring Board) will be set up. The finding of morbidity or excess mortality in relation to the data of the literature may lead to the proposal by this committee of a suspension or a definitive cessation of the test. The stopping rules will be the subject of a text validated by the committee. In this event, the need for a stop will be considered in a collegial way by the steering committee of the study and submitted to the promoter who will make the decision. The study may of course be stopped by decision of the competent authority or the sponsor for other major reasons that appeared during the trial.

5.9 Arrangements for maintaining the blind and procedures for lifting the blind, where appropriate; Not applicable

5.10 Identification of all the data to be collected directly in the observation books, which will be considered as source data.

Different data will be collected in an observation notebook:

Administrative data:
- 1st letter of first and last name, Sex, Date of Birth.
- Date of presentation of the file in CPR
- Date of inclusion in the BRONC-ART protocol (signature of informed consent)

Physical data :
- Weight
- Cut
- BMI (Weight / Height2)
- Performans Status (PS)
- ASA score

Medical data containing the main antecedents and co-morbidities specifying in particular:
- Smoking (in pack-years, effective weaning or not)
- Diabetes
- Immunosuppression
- Renal failure
- Heart failure
- Respiratory failure
- Neo-adjuvant treatment

Preoperative bronchial fibroscopy data +/- puncture / CT
- descriptive scheme
- Result of biopsies
- Puncture / CT if performed

Pre-operative extension assessment
- CT chest with hepatic and adrenal sections
- PET scanner
- MRI or cerebral CT
- Mediastinoscopy if performed
- other

Functional respiratory data:
- Respiratory Functional Explorations (EFR) with VEMS, CV, DLCO
- Possible data from the Pulmonary Ventilation / Infusion Scintigraphy

- Calculation of postoperative predictive FEV1
- Blood gases (PaO2, PaCO2, Ph, Oxygen saturation)

Operability balance

- cardio-vascular assessment (cardiac ultrasound, aorta and lower limbs ultrasound, echo-doppler of supra-aortic trunks)
- other examinations depending on the clinical context

Neo-adjuvant treatment

- chemotherapy
  - drugs used
  - number of cures
  - effect on the tumor mass (TDM)
- radiotherapy
  - dose
  - number of sessions
- other

Data concerning the surgical intervention

- Intervention date
- Look first
- Operated side
- Resection performed
- Associated resection
- Type of stent used
- Type of reconstruction and flap of protection
- Diagram of the intervention
- Duration of the intervention
- Antibiotic prophylaxis protocol surrounding the surgical procedure
- Possible complications or per-operative difficulties

Postoperative clinical data :

- Daily nursing team record of respiratory rate, blood pressure, heart rate, oxygen saturation and body temperature measurement, collated in a table
- Duration of bubbling and drainage
- Complications followed daily during hospitalization: bronchial congestion, atelectasis, pneumonia, lung re-expansion defect, tracheal, bronchial or bronchovascular fistula, empyema, bronchial stents, thrombosis of the artery or vein pulmonary, other (cardiac complications, thrombo-embolic ...)

Postoperative radiological data

- Daily chest X-ray (analyzed by a radiologist) in search of atelectasis in particular)
- Possible CT

Postoperative fibroscopic data

- Date (D)
- Data from postoperative fibroscopy

Postoperative complications

- - Date (D)
- - Type
- - Possible treatment

Histological data

- Histological type of the tumor
- Pathology stage (TNM)
- Complete resection (R classification)

Administrative post-operative data

- Hospital length of stay
- Length of stay in a unit of continuous care, in intensive care

Followed

- Output (J)
- Consultation J30, J60, J90:
    - Clinical status analysis, CT, fibroscopy, PET scan
    - Follow-up of complications: bronchial congestion, atelectasis, pneumonia, pulmonary re-expansion defect, tracheal, bronchial or broncho-vascular fistula, empyema, bronchial stents, thrombosis of the pulmonary artery or vein, other (cardiac complications, thromboembolic ...)

6 Selection and exclusion of people from research

6.1 Criteria for inclusion of people who are suitable for research

- Patient over 18 years old
- proximal tumor lesion whose surgical excision requires resection of carina, pneumonectomy, lobectomy with RAB and / or RAAP, immediately or after neo-adjuvant chemotherapy and with EFRs allowing the proposed pulmonary resection
- proximal tumor lesion whose surgical resection requires pneumonectomy but with EFR allowing only lobectomy
- proximal tumor lesion requiring surgical resection requiring pneumonectomy in a patient over the age of 70 (major risk of death at 90 days)
- Extensive lesions, cancerous or not, of the trachea without bronchial involvement in therapeutic stalemate.
- Surgical eligibility (indication of surgical treatment) retained during a collegial discussion (Multidisciplinary Collaborative Meeting)
- Informed and written consent.

6.2 Criteria for non-inclusion of individuals who are suitable for research

- Sick or mentally incompetent, under guardianship or under judicial protection
- proximal or distal tumor lesion whose surgical resection is technically possible by simple lobectomy without RAB
- tumor lesion that can not be resected completely due to loco-regional invasion
- isolated tracheal lesion that can be simply resected-tracheal anastomosis
- N3 ganglion invasion (contralateral neoplastic lymph node invasion)
- Metastatic lesions M1 unless there is a single resectable metastasis
- Patient allergic to iodinated contrast media
- Operability balance not allowing lobectomy
- Patient unable to comply with the requirements of the study
- Sickness affiliated to a social security scheme (beneficiary or beneficiary)

6.3 Procedure for premature termination of the use by the medical device (s) or in vitro diagnostic medical devices, the procedure of excluding the search of the persons who are suitable for the procedure stopping the use and monitoring of the person as part of the research, specifying:

a) Criteria and modalities for premature termination of treatment with the medical device (s), or exclusion of a person from research;
Implantation of an allograft is irreversible apart from performing a new procedure (complement pneumonectomy). A postoperative complication can not lead to the arrest or exclusion of a person from research except in the case of a collegial decision to re-intervene. Implantation of the stent is reversible. The appearance of a complication related to the stent may lead to its removal or change after collegial discussion.
b) Terms and timing of collection for these data;
Screening for postoperative complications will be performed by a daily clinical examination of the patient and additional examinations (chest X-ray, thorax CT, blood gas, bronchial fibroscopy ...)
c) How to replace these persons, if any:
Any.
d) How to follow these people.
Follow-up of patients who have had a postoperative complication will be performed in hospital until improvement or recovery according to usual and recommended practices. The follow-up will be continued in all cases at the exit of the patient until cure of the complication.

7 Security assessment

7.1 Description of the security evaluation parameters

• Adverse event

Any harmful event occurring in a person who is amenable to biomedical research, whether or not this event is related to the research or the product to which this research relates (Article R. 1123-39 of the Public Health Code)

• Adverse effect of a medical device

Any harmful and adverse reaction to a medical device or any incident that could have caused this reaction if appropriate action had not been taken, in a person who is amenable to research or to the user of the medical device (Art. R. 1123-39 of the Public Health Code)

- **Adverse event or incident related to an element or product of the human body**

Adverse event: The adverse reaction occurring in a patient, living donor or recipient, related or likely to be related to a product or activity of collection, collection, manufacture, preparation, processing, preservation, transport, distribution, assignment, importation, exportation, distribution, attribution, transplant or administration (article R.1211-31 of the Public Health Code)

Incident: the incident related to the activities mentioned above, due to an accident or an error, likely to cause an undesirable effect on the patient, the living donor or the recipient (article R.1211-31 of the code of the public health)

- **Event or serious adverse event**

Any event or adverse reaction that results in death, endangers the life of the person who is suitable for research, requires hospitalization or prolongation of hospitalization, causes a significant or lasting disability or disability, or results in by an abnormality or congenital malformation.

- **Serious adverse event or serious incident related to an element or product of the human body**

Serious Adverse Event: the undesirable effect that may result in death or life-threatening illness, disability or disability, or the onset or continuation of hospitalization or other morbid conditions, or likely to recur. in one or more patients, living donors or recipients (Article R.1211-31 of the Public Health Code)

Serious incident: the incident likely to lead to serious undesirable effects (Article R.1211-31 of the Public

- **Unexpected adverse event of a medical device**

Any adverse event of the product the nature, severity or development of which does not agree with the information given in the CPP's opinion, the instruction leaflet or the instructions for use when it is the subject of a CE marking, and in the protocol or brochure for the investigator where it is not so marked, and where appropriate in the technical file relating to the products, procedures and methods used in the context of the research.

- **New fact**

Any new safety data, which may lead to a reassessment of the benefit and risk ratio of the research or associated medical device, or which may be sufficient to consider modifications in the use of the allograft or medical device, in conduct of research.

7.2 Methods and schedule for measuring, collecting and analyzing safety assessment parameters

7.2.1 Steering Committee

It will consist of the project initiators, the biostatistician in charge of the project, the representatives of the promoter and the URC appointed for this research.
It will define the general organization and conduct of the research and coordinate the information.
He will initially determine the methodology and will decide in the course of research of the behavior to be held in the unforeseen cases, will supervise the progress of the research in particular in terms of tolerance and undesirable events.

7.2.2 Independent Oversight Committee

An independent monitoring committee will be established prior to the commencement of clinical research.

It will have an advisory function when the sponsor will call on him on medical points such as tolerance and adverse events. It will be made up of people from outside the research community, including a clinician specialized in the pathology studied, a materiovigilant and a methodologist / biostatistician.

The finding of morbidity or excess mortality in relation to the data of the literature may lead to the proposal by this committee of a suspension or a definitive cessation of the test. The stopping rules will be the subject of a charter validated by the committee. In this event, the decision will be made in a collegiate manner by the steering committee of the study (in which a representative of the sponsor is located) and the promoter. The study may of course be stopped by decision of the competent authority or the sponsor for other major reasons that appeared during the trial.

7.3 Procedures put in place for recording and reporting adverse events

7.3.1 Non-serious adverse events:

Any undesirable event - not serious according to the previous definition - observed during the research and in its after-effects should be reported in the observation notebook in the section provided for this purpose.

Only one event must be reported per item. The event may correspond to a symptom, a diagnosis or a complementary examination result deemed significant. All the clinical or para-clinical elements allowing to better describe the corresponding event must be reported

7.3.2 Serious Adverse Events (SAEs):

Investigators must immediately notify the sponsor of serious adverse events and serious incidents and new developments as defined above.

The investigator completes the forms of serious adverse events (the research observation book) and sends them to the DRCD by fax to 01 44 84 17 99 and without delay (Article R1.1123-50 of the code of the public health), if possible an immediate telephone call to the 01 44 84 17 80/17 92 in case of death or a vital threat.
The investigator must also inform the CRU in charge of the investigation of the occurrence of the SAI or serious incident.
For each serious adverse event or serious incident, **the investigator should provide an opinion on the causal relationship of the event with each allograft, medical device and any other treatments.**

Obtaining information relating to the description and evaluation of an adverse event may not be possible within the time allotted for the initial declaration.

Also, the relevant clinical evolution concerning the SAEs, the serious incidents and the new facts as well as the results of the possible clinical assessments and the diagnostic and / or laboratory examinations, or any other information allowing an adequate analysis of the causal link will be reported :

- **on the initial declaration of EIG if they are immediately available,**
- **either later and as soon as possible, by faxing a new completed EIG declaration (and stating that it is an EIG follow-up and the tracking number).**

All statements made by the investigators will identify each subject participating in the search by a **unique code number** assigned to each of them.

In the event of the notified death of a subject participating in the research, **the investigator will communicate to the promoter all the additional information requested** (report of hospitalization, autopsy results ...).

Any new developments in research or in the context of research, from literature or ongoing research, should be notified to the sponsor.
Reporting of serious adverse events to the Health Authorities and the CPP
It will be provided by the Pharmacovigilance Pole of the DRCD, after evaluation of the seriousness of the adverse event, the causal link with each graft and / or medical device of the study and the other possible treatments as well as the unexpected nature of the undesirable effects. .
All suspicions of an unexpected serious adverse reaction will be reported by the sponsor to the appropriate authorities within the legal timeframes.

Any safety data or any new fact that could significantly modify the assessment of the benefit and risk ratio of a medical device used in the research, or research, or which could lead to consider modifications concerning the modalities of use of the medical device or conduct of research, will be transmitted by the sponsor to the competent authorities, the Committee for the Protection of Persons and research investigators.
For example :
a) any clinically significant increase in the frequency of occurrence of an expected serious adverse reaction;

b) suspicions of unexpected serious adverse reactions occurring in participants who have completed the research and who are notified by the investigator to the sponsor, as well as any follow-up reports;

c) any new fact concerning the conduct of the research or the development of the medical device, where this new fact is liable to jeopardize the safety of the participants. For example:

- a serious adverse event likely to be related to research investigations and diagnostic procedures and which could modify the course of this research,
- a significant risk for the research population, such as a lack of effectiveness of the medical device used in the treatment of a life-threatening disease,
- Significant safety results from a recently completed animal study
- an early stop or a temporary interruption for safety reasons of a search conducted with the same medical device in another country,
- an unexpected serious undesirable effect related to a non-experimental drug needed to perform the test (eg "challenge agents", emergency treatment)

d) the recommendations of the independent Data Monitoring Committee (DMC) or Data Safety Monitoring Board (DSMB), if applicable, if they are relevant for the safety of persons,

e) any unexpected serious adverse reaction transmitted to the sponsor by another promoter of biomedical research in a third country concerning the transplant and / or the medical device.

7.4 Provisions to be taken to ensure safety in the event of failure of the medical device including in case of isolated dysfunction of the device without clinical impact as well as in case of misuse;

Any patient with an adverse event should be followed until resolution or stabilization of the patient.

Follow-up of patients who have had a postoperative complication will be performed in hospital until improvement or recovery according to usual and recommended practices.

In all cases the follow-up will be continued from the exit of the patient until complete cure of the complication.

• If the event is not serious, the evolution will be noted on the corresponding page of the report in the section provided for this purpose.

• If the event or incident is serious or if a new fact is observed, an EIG follow-up will be sent to the DRCD.

7.5 Expected serious side effects related to treatment or study procedures

The expected SAEs reported in Annex 4 are:

<u>Those related to surgery whatever it is:</u>

- death
- postoperative respiratory distress, complete atelectasis of the remaining lobe or postoperative pneumonitis requiring prolonged artificial ventilation, ~~tracheostomy~~,
- lack of pulmonary re-expansion
- empyema requiring surgical revision,
- fistula (tracheal, broncho-pleural, broncho-vascular, broncho-oesophageal),
- nosocomial infection,
- prolonged bronchial bubbling ≥21 days or requiring revision

<u>Those related to the practice of an allograft including the stent is:</u>

- rupture of the allograft,

- dilation of the allograft,
- thrombosis of the pulmonary artery or vein
- fibrosis and retraction of the allograft by an excessive inflammatory reaction,
- Deficiency of induced tissue regeneration and neo-bronchial formation
- intolerance of the endoprosthesis placed in place transiently (inflammatory granuloma, hemoptysis ...),
- migration of the stent,
- obstruction of the stent and infection
- Stenosis upstream and downstream of the prosthesis
- risk of tissue perforation and hemorrhage with haemothorax / haemoptysis

8 Statistics

8.1 Description of planned statistical methods, including schedule of planned interim analyzes

This is a feasibility study whose analysis will be essentially descriptive.

All quantitative parameters will be summarized descriptively for each time they are collected. The descriptive statistical analysis will include for each quantitative parameter at each time: mean, standard deviation, minimum, maximum, median and quartiles, number of missing values. The qualitative parameters will be expressed by the frequency of distribution and the associated 95% bilateral confidence intervals. In case of non-validity of the asymptotic approach, exact confidence intervals will be used.

No interim analysis is planned beyond those conducted by the independent monitoring committee.

8.2 Expected number of people to be included in the research, and expected number of people in each research location with its statistical justification.

As this trial was a feasibility study, a small number of patients (n = 20) were selected.
However, it will make it possible to estimate the proportion of survivors (of the order of 80% or more with a precision of about 17.5%
If a patient is included but can not have surgery in the meantime, he will be replaced. The replacement rate can be estimated at about 10% or a forecast of 22 patients.
For added security, we admit the possibility of including up to 30 patients in this study.

8.3 Degree of statistical significance expected.

All results will be presented with their 95% bilateral confidence interval.

8.4 Statistical criteria for stopping research (to be described according to the medical context of the research).

The independent monitoring committee will adopt stopping rules to stop the study in case of excessive mortality compared to that generally accepted for this type of pathology.

8.5 Method of taking into account missing, unused or invalid data.

Given the type of patient, it is not possible to have missing data on the main criterion.
In case of missing data on the other criteria, the last available values will be used.

8.6 Management of changes made to the initial strategy analysis plan.

Any major changes to the initial analysis plan presented in the protocol will be subject to amendment.

8.7 Choosing who to include in the analyzes

All patients having the procedure under study will be analyzed.

9 Right of access to data and source documents

Persons having direct access in accordance with the legislative and regulatory provisions in force, in particular Articles L.1121-3 and R.5121-13 of the Public Health Code (for example, investigators, persons in charge of quality control, Instructors, Clinical Research Assistants, Auditors, and all others involved in the testing) take all necessary precautions to ensure the confidentiality of information about experimental drugs, tests, and those who are suitable for them. in particular as regards their identity and the results obtained. Data collected by these people during quality checks or audits are then made anonymous.

10 Quality control and quality assurance

The research will be framed according to the promoter's standard operating procedures.
The conduct of the research in the investigative centers and the handling of the subjects will be done in accordance with the Declaration of Helsinki and the Good Practices in force.

10.1 Monitoring procedures

The CRA representatives of the sponsor will visit the investigating centers at the rate corresponding to the protocol of follow-up of the patients in the protocol, the inclusions in the different centers and the level of risk which has been attributed to the research.

- Opening visit of each center: before inclusion, for an implementation of the protocol and acquaintance with the different stakeholders of biomedical research.

- During the following visits, the notebooks will be reviewed as the CRA progresses. The principal investigator of each center as well as the other investigators who include or follow-up the people involved in the research commit to receive the CRAs at regular intervals.
During these on-site visits and in accordance with Good Clinical Practice, the following will be reviewed:
• Respect of the protocol and procedures defined for the research,
• Verification of informed consents of patients
• Examination of the source documents and comparison with the data reported in the logbook regarding accuracy, missing data, consistency of the data according to the rules enacted by the promoter's procedures.

- Closing visit: recovery of observation books, check-up at the pharmacy, documents of biomedical research, archiving.

10.2 Transcription of data in the observation book

All information required by the protocol must be provided in the observation booklet and an explanation given by the investigator for each missing data.
The data should be transferred to the observation book as it is obtained whether it is clinical or para-clinical data. The data must be copied in a clear and readable way in black ink in these notebooks (this in order to facilitate duplication and computer entry).
The erroneous data found on the notebooks will be clearly crossed out and the new data will be copied to the notebook with the initials and date by the member of the investigator team who made the correction.
The anonymity of the subjects will be ensured by a code number and the initials of the person who is ready to search on all the documents necessary for the search, or by erasing by the appropriate means of the personal data on the copies of the source documents, intended for research documentation.

The computerized data on a file will be declared to the CNIL according to the procedure adapted to the case.

11 Legal and ethical considerations

The sponsor is defined by law 2004-806 of August 9, 2004. In this research, the AP-HP is the promoter and the Department of Clinical Research and Development (DRCD) who performs the regulatory tasks.
Before starting the search, each investigator will provide to the research sponsor's representative a copy of his ***curriculum vitæ*** signed and dated and which resume his registration number with the College of Physicians.

11.1 Request for authorization from Afssaps

To be able to start the search, the AP-HP as a promoter must submit an application for authorization to the competent authority Afssaps. The competent authority, defined in Article L.1123-12, decides on the safety of persons who are suitable for biomedical research, considering in particular the safety and quality of the products used in the course of research in accordance with where applicable, the standards in force, their conditions of use and the security of the persons with regard to the acts practiced and the methods used, as well as the arrangements for monitoring persons.

11.2 Request for advice to the Committee for the Protection of Persons

In accordance with article L.1123-6 of the Public Health Code, the research protocol must be submitted by the promoter to a Committee for the Protection of Persons The opinion of this committee is notified to the competent authority by the promoter before starting the search.

11.3 Modifications

The sponsor must be informed of any plans to modify the protocol by the coordinating investigator. The changes must be qualified as substantial or not.
A substantial change is a modification that may somehow change the guarantees provided to those who are amenable to biomedical research (modification of an inclusion criterion, extension of a duration of inclusion , participation of new centers, ...).

After the beginning of the research, any substantial modification of the research on the initiative of the promoter must obtain, prior to its implementation, a favorable opinion of the committee and an authorization from the competent authority. In this case, if necessary, the committee ensures that new consent from the people involved in the research is collected.

In addition, any extension of the research (profound modification of the therapeutic regimen or of the included populations, prolongation of the treatments and or therapeutic acts not initially envisaged in the protocol) will have to be considered as a new research.
Any substantial modification must be submitted **by the promoter** for an authorization request to Afssaps and / or a request for an opinion from the CPP.

11.4 CNIL Declaration

The law provides that the declaration of the computerized file of personal data collected for research must be made before the actual start of the search.

A reference methodology specific to the processing of personal data operated in the context of biomedical research defined by law 2004-806 of August 9, 2004, as falling within the scope of articles L.1121-1 and following of the Public Health Code has been established by the CNIL in January 2006.

This methodology allows a simplified reporting procedure when the nature of the data collected in the search is compatible with the list provided by the CNIL in its reference document.
When the protocol benefits from a data quality control by an CRA representing the promoter and falls within the scope of the CNIL simplified procedure, the DRCD as promoter will ask the person responsible for the computer file to commit in writing on compliance with the MR06001 simplified reference methodology.

11.5 Information Note and Informed Consent

Written consent must be obtained from anyone suitable for research prior to the completion of any action required by biomedical research, after a reflection period of at least 48 hours.

11.6 Final report of the research

The final report of the research will be written in collaboration by the coordinator and the biostatistician for this research. This report will be submitted to each investigator for opinion. Once a consensus has been reached, the final version must be endorsed by the signature of each investigator and sent to the sponsor as soon as possible after the actual end of the research. A report drawn up in accordance with the reference plan of the competent authority must be sent to the competent authority and to the CPP within one year, after the end of the search, meaning the last monitoring visit of the competent authority. last topic included. This delay is reported at 90 days in case of premature termination of the search.

12 Data Processing and Retention of Research Documents and Data

Research documents under the Biomedical Research Act must be archived by all parties for a period of 30 years after the end of the research (duration related to a cell therapy practice).
(see PCB, Chapter 8: Essential Documents)

This indexed archive contains:

- The copies of authorization letters from Afssaps and the mandatory notice of the CPP
- The successive versions of the protocol (identified by the version number and the version date),
- Correspondence with the promoter,
- Consents signed by the subjects under sealed cover (in the case of minor subjects signed by the holders of parental authority) with the list or register of correspondence,
- The completed and validated observation notebook of each subject included,
- All specific appendices to the study,
- The final report of the study from the statistical analysis and quality control of the study (double transmitted to the sponsor).
- Any audit certificates made during the research

The database that has been the subject of the statistical analysis must also be archive by the person responsible for the analysis (paper or computer).

13 Insurance, Scientific Commitment and Delegation of Functions

13.1 Insurance

The Assistance Publique - Hôpitaux de Paris is the promoter of this research. In accordance with the law on biomedical research, she has taken out insurance with the company GERLING KONZERN for the duration of the research, guaranteeing her own civil liability as well as that of any intervener (doctor or staff involved in the realization of the research) (law n ° 2004-806, Art L.1121-10 of the CSP).
The Assistance Publique - Hôpitaux de Paris reserves the right to interrupt the search at any time for medical or administrative reasons; in this event, a notification will be provided to the investigator.

13.2 Scientific commitment

Each investigator will commit himself to respect the obligations of the law and to carry out the research according to the B.P.C, respecting the terms of the declaration of Helsinki in force. To do this, a copy of the **scientific commitment** dated and signed **by each investigator** of each clinical department of a participating center will be given to the sponsor's representative.

13.3 Delegation of functions

The principal investigator of each service may delegate certain functions. To do this, a copy of the **delegation of functions form**, dated and signed **by each stakeholder concerned**, will be completed indicating the delegated functions and a CV will be requested by the Promoter.

14 Publication rules

The AP-HP owns the data and no use or transmission to a third party can be made without its prior consent.
The first signatories of the publications will be the people who really participated in the development of the protocol and its development and the writing of the results.

As a precaution, a writing committee should be established and the order of the signatories can be defined in advance.

The Assistance Publique-Hôpitaux de Paris must be mentioned as the promoter of biomedical research and as financial support if necessary. The terms "Assistance Publique- Hôpitaux de Paris" must appear in the address of the authors.