

Stockholm, December 15, 2016

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Mr. Tatarintsev, Ambassador of the Russian Federation to the Kingdom of Sweden¹

Competent Authorities of the Russian Federation²

Petition for an Investigation of Research Misconduct

RE: “Tracheal Transplantation, Clinical Trial Protocol, Version A, February 5, 2012”, by Dr. Macchiarini and Request to the Karolinska Institutet to Report to Competent Russian Authorities of the Russian Federation

^{1,2} Complete list with contact information on p.17

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Introduction

This petition concerns the "Tracheal Transplantation Clinical Trial Protocol, Version A" signed by Dr. Paolo Macchiarini (PM) as "Leading Scientist, Karolinska Institutet" on February 5, 2012 (1, 2) which was approved by **The Ethical Commission** at the State Budgetary Educational Institution for Higher Education "Kuban State Medical University" of the Ministry of Health Care and Social Development of the Russian Federation on February 15, 2012 (protocol 9) (3) and May 29, 2012 (protocol 11) (4).



Exhibit 1. Front page of the Tracheal Transplantation Clinical Trial Protocol, Version A, February 5, 2012. Russian original (left) with English translation (right):

Tracheal Transplantation

Clinical Trial Protocol

in "Molecular and Cellular Biology, Biotechnology, Regenerative Medicine" as part of the Russian Government Grant Federation for governmental support of scientific research conducted under the supervision of leading scientists at Russian institutions of higher educational training according to contract "19" October 2011 N2 11.034.31.0065 between the Ministry of Education and Science of the Russian Federation and the State Budgetary Educational Institution of Higher Professional Education "Kuban State Medical University," the Ministry of Health and Social Development of the Russian Federation and the leading scientist Paolo Macchiarini performing scientific research for the time period October 19, 2011 to December 31, 2013.

Together with the ethical approval of the Clinical Trial Protocol (protocol) which was issued by **The Local Ethics Committee at GBUZ "Krasnodar Regional Clinical Hospital No. 1, n.a. S.V. Ochapovsky Department of Health Care Krasnodar Krai"** on May 31, 2012 (protocol 49) (5) PM received ethical approval to implant synthetic tracheae in humans.

In the 40-page protocol PM refers to the two patients (with special focus on patient nr. 2) who had undergone elective (the two patients' conditions were not immediately life threatening) synthetic tracheal implantations at Karolinska University Hospital in June and November 2011 (6, 7). In the text clinical findings are presented that PM uses to support the conclusion that these procedures were clinically successful without any negative effects or complications ([1, 2] pp. 6, 8, 9, 15, 17, 26, 27). On the basis of these conclusions from the Karolinska cases PM wishes to continue and expand the program of synthetic tracheal implantations ([1, 2] pp. 25-26) despite the lack of any previous animal data (8, 32), implying potential success of this procedure before starting up these high risk experiments in humans. It must also be pointed out that these two experimental Karolinska implantations by PM were executed without ethical approval (9, 10, 11, 12, 13, 14, 15, 16) and without permission from the Swedish Medical Products Agency (MPA) (17, 18). After the protocol was approved the patients Julia Tuulik and Alexander Zozulya were the first two Russian "patients" transplanted in Krasnodar on June 19 and 21, 2012 respectively (19, 20, 21).

The following review of the Clinical Trial Protocol Version A from February 5, 2012, will prove that the clinical findings presented by PM of the two patients operated at Karolinska have no correlation to their actual clinical outcome as demonstrated in the patient medical records, in the recorded bronchoscopic film material and in the radiological reports. PM has thereby consciously been providing misleading and fraudulent results of the procedure the patients have been subjected to in order to attain approval and multimillion dollar funding (22, 23, 24, 25, 26) of these high risk experiments on humans in Russia.

The text of the protocol where PM presents falsified data and misleading conclusions have been marked in yellow. Under each Russian text section a translation is attached as well as a page reference from the original document. For each statement separate comments are provided with references to hyperlinked documents (pp. 39-45), specific images from bronchoscopic recordings and radiological exams (pp. 18-38) as well as appendices (pp. 46-55) in order to demonstrate evidence of serial fabrication and manipulation.

Translation of the original protocol consists of 29 of the total 40 pages. The untranslated pages consist of images and technical tables which do not change the implications of the translated text. The contents of the documents and page numbers have been preserved between the original and translated versions to simplify comparison.

Along with this petition the following documents are attached:

1. Original Russian version of the "Tracheal Transplantation Clinical Trial Protocol, Version A, February 5, 2012" (1).
http://www.circare.org/info/pm/plan_rus.pdf
2. Our English translation of the protocol (2).
<http://www.circare.org/info/pm/macchiarini-trachealtransplant-protocol-20120205.pdf>

Original bronchoscopic films will be supplied upon request.

Text sections on pp. 7-8:

На сегодняшний день, две операции по трансплантации трахеи с использованием синтетического искусственного биокаркаса были успешно выполнены доктором Маккиарини совместно с коллегами из Каролинского института в Стокгольме, Швеция. При первой операции (июнь 2011 г.) использовали нанокompозитный биокаркас из POSS-PCU (полиэдрический олигомерный силсесквиоксан), а при второй операции (ноябрь 2011 г.) использовали нановолоконный композитный биокаркас из ПЭТ (полиэтилентерефталат). В обоих случаях наблюдали люминальное вращение здоровых клеток эпителия дыхательных путей.

На Рис. 2 показаны результаты бронхоскопии и эпителиальные клетки дыхательных путей после операции с применением ПЭТ-композитного нановолоконного биокаркаса в ноябре 2011, биокаркаса того же типа, что предлагается в данном протоколе. Бронхоскопия и паттерн окрашивания клеток демонстрируют появление нормальной слизистой оболочки на биокаркасе через неделю после пересадки.

Exhibit 2A, pp. 7-8: "To date, two tracheal transplantations with bioengineered synthetic scaffolds have been successfully performed by Dr. Macchiarini together with colleagues from Karolinska Institutet in Stockholm, Sweden. In the first operation (June 2011) a nanocomposite bioengineered synthetic scaffold made of POSS-PCU (polyhedral oligomeric silsesquioxane) was used, while in the second operation (November 2011) a nanocomposite bioengineered synthetic scaffold made of PET (polyethylene terephthalate) was used. In both cases luminal ingrowth with healthy cells of respiratory epithelium was observed.

Fig. 2 shows the bronchoscopy results with respiratory epithelial cells after the operation in November 2011 when a bioengineered synthetic PET-nanocomposite bioscaffold was used, which is the same type of bioscaffold which is proposed in this protocol. The bronchoscopy and the pattern of stained cells show the presence of a normal mucosa in the bioscaffold at one week after transplantation."



Exhibit 2B, p. 7: "Fig. 2: A. Bronchoscopy of the PET-nanocomposite trachea one week after implantation (November 2011), showing presence of a normal mucosa on the bioscaffold. B. Ciliated respiratory..." [Text continues on p. 8].

эпителиальные клетки (белая стрелка), полученные после бронхоскопического соскабливания из центра пересаженной трахеи через неделю после имплантации. Тот факт, что биопсия из центра трансплантата была сделана почти сразу после имплантации, позволяет предположить, что эти клетки возникли вследствие дифференциации стволовых клеток, а не путем непосредственного распространения обычного эпителия в проксимальных или дистальных зонах трансплантата.

Exhibit. 2C, p. 8: ***“...epithelial cells (white arrow) obtained from a brush biopsy from the center of the transplanted trachea one week after implantation. The fact that this biopsy was done almost immediately after transplantation, allows us to assume that the cells derive from the differentiated stem cells, and not from the spread of normal epithelial cells from the proximal or distal end of the transplant.”***

Comments to exhibits 2A, B, C:

1. *“In both cases luminal ingrowth with healthy cells of respiratory epithelium was observed.”*

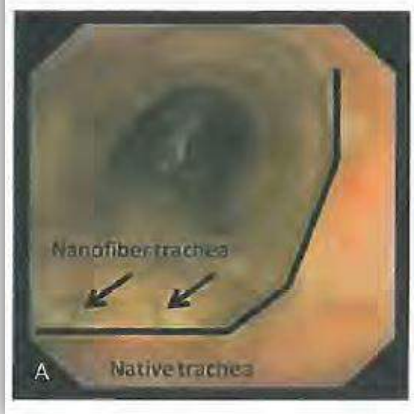
The statement is false. No evidence of luminal ingrowth with healthy cells of respiratory epithelium in the synthetic scaffolds has been verified in the 2 patients’ referred to in the protocol in the time period before (or after) PM authored these false statements. On the contrary:

- a. All the registered biopsies from Case 1 (at 10 weeks, 5½ and 8 months* and 1 year* after implantation) as well as Case 2 (at 5 days and 8 weeks after implantation) show no signs that indicate that a normal respiratory lining has covered the plastic trachea.
(Biopsies Case 1: Appendices 1, 2, 3, 4, 5 and Case 2: Appendices 6, 7, 10).
- b. All bronchoscopic films from Case 1 (at 10 weeks, 5½ and 8 months* and 1 year* after implantation) as well as Case 2 (at 8 weeks after implantation) show clear evidence of serious pathology without any signs of epithelialization, vascularization or tissue ingrowth in the synthetic scaffolds.
(Bronchoscopic images, Case 1: pp. 18-21, 27-31, and in Case 2: pp. 32-37).
- * The finding at 8 months as well as 1 year after the implantation of Case 1 were procured after PM signed the study plan on Feb. 5, 2012 but have been attached to prove the presence of serious pathological findings before, during and after PM signed the document, and during the approval process of the protocol (from February to the end of May 2012 (1, 2, 3, 4, 5).

2. *“Fig. 2 shows the bronchoscopy results with respiratory epithelial cells after the operation in November 2011...”, “The bronchoscopy and the pattern of stained cells show the presence of a normal mucosa in the bioscaffold at one week after transplantation.”*

These statements are misleading and false. The image in the figure 2A postulates to show Case 2’s bronchoscopy at one week. This image is identical to the image that was presented as a day 3 after implantation image in the awarded scientific poster publication *“First in Man Synthetic Nanofiber Trachea”* by Johnson, **Jungebluth, Macchiarini**, Aug. 2, 2012 which was petitioned as research fraud to the Karolinska Institutet on Aug. 30, 2016 (27, 28, 29):

На Рис. 2 показаны результаты бронхоскопии после операции с применением биокаркаса того же пациента в ноябре 2011, биокаркаса того же пациента. Бронхоскопия и паттерн окрашивания слизистой оболочки на биокаркасе



RESULTS – POST SURGERY

Photograph of tracheal graft sutured into position (left) and a representative bronchoscopy 3 days after the surgery (right). Notice the vascularization and tissue in-growth of the implanted synthetic trachea and lack of inflammatory response from the surrounding tissue demonstrating biocompatibility and acceptance of the nanofiber scaffold.

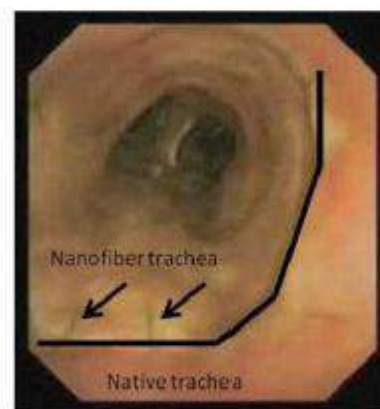


Exhibit 3. Image (left) from the Clinical Trial Protocol version A (p. 7) stated to depict the bronchoscopic view in Case 2 **at one week**. The identical image (right end side) presented in the fraudulent scientific poster publication “First in Man Synthetic Nanofiber Trachea” stated to demonstrate the bronchoscopic view in the same patient at **3 days** after implantation (published in August 2012).

In the patient's (Case 2) medical records there exists no formal procedural report of a bronchoscopy postulated by PM to have been performed at specifically one week (7 days) after implantation of the plastic tracheal scaffold, which is a standard routine if such an intervention is performed especially in such a unique patient. Instead there was a routine bronchoscopy performed at day 5 (Nov. 22, 2011) by a pulmonology resident physician (non-specialist) without any experience in tracheal surgery or transplantation who in the bronchoscopy report described the findings as:

“The graft is well positioned and gives the impression of a smooth and even pink mucosal lining...”

A macroscopic description of the surface structure and colour does not verify that the graft was lined with respiratory or any other kind of epithelium. The graft was already “smooth” and “pink” at the time of implantation surgery 5 days earlier on Nov. 17, 2011 (30, 31). Subsequently this postulation is only a visual impression made by somebody still under training and with no experience within the field and cannot be used to verify the existence of a “normal mucosa” in the synthetic graft as stated by PM.

The claim by PM of a normal mucosa present in the synthetic scaffold is however clearly disproven by the following examinations and findings:

- Detailed bronchoscopy report by a senior ENT-physician on Nov. 28, 2012, **11 days** after implantation, states (Appendix 8):

*“The implant is patent and **there are no signs of tissue ingrowth yet.**”*

- b. Detailed bronchoscopy report by the same senior ENT-physician on Dec. 6, 2011, **19 days** after implantation *did not verify any signs of vascularization* of the scaffold.
- c. Detailed bronchoscopy report by a senior ENT-physician on Jan. 10, 2012, **8 weeks** after implantation, states (Appendix 9):

“Exfoliation of the outer layer of the graft. Sutures are clearly visible” [i.e. at the upper and both distal anastomotic sites].

No verification or description of any presence or signs of tissue or epithelial ingrowth in the scaffold, which was of main interest when performing this bronchoscopy. Clearly visible sutures verify no tissue ingrowth from the anastomosis sites.

- d. Biopsy report at 8 weeks, Jan. 10, 2012 states (Appendix 10):

“The material consists mainly of graft parts surrounded with egg white precipitation [N.B. pathological non-vascular finding not equivalent to any tissue ingrowth or cellular lining] *focally containing large amounts of leucocytes. No coherent tissue can be detected. Graft material with admixture of inflammatory cells and minimal flakes of squamous epithelium type.”*

- e. Bronchoscopy film at 8 weeks, Jan. 10, 2012 (separately attached):

The absence of any tissue ingrowth or vascularization (dysfunctional and non-viable synthetic scaffold) is verified by the performed bronchoscopy (Bronchoscopic images: pp. 32-37 and bronchoscopy film Jan. 10, 2012).

It needs to be emphasized that PM partook in this examination (Appendix 9) and thereby was fully aware of the pathological findings when he signed the protocol 4 weeks later on Feb. 5, 2012.

The claim that a plastic tube of several centimetres in length could be vascularized and develop a functional airway epithelium (which necessitates the formation of a submucosa and basal membrane) in one week as stated in protocol is bizarre and beyond ridiculous. We have in previous petitions repeatedly criticized PM because he made similarly surreal claims that this process could transpire (reusing the same fabricated patient data over and over again as reference) within 1, 3 or 7 days after implantation of a synthetic trachea (27, 32). This is an impossible scenario that even PM in earlier publications has described as unfeasible even in much smaller grafts than a plastic tube equivalent in the size to a human trachea (33):

“...It is well known that a tissue-engineered cellular graft of larger than 0.8 mm in diameter needs vascularization to maintain viability after implantation into the host. However, the revascularization process usually begins within the first 2 weeks and flourishes within the eighth week of implantation. One might therefore speculate that an implantation time of 1

week is almost certainly too short for sufficient revascularization of small-diameter grafts."

3. ***"Fig 2 A. Bronchoscopy of the PET-nanocomposite trachea one week after implantation (November 2011), showing presence of a normal mucosa on the bioscaffold."***

This claim is false and based on falsification of data from the patient's medical records.

As already commented earlier it is biologically impossible for a plastic tube of several centimetres in length to develop a fully functional respiratory epithelium after only one week.

Furthermore and as previously reported (27) PM has in the protocol not supplied any biopsy data from the tracheal scaffold before implantation in patient 2. This would have shown if the plastic scaffold surface was covered with any cellular layer that after implantation could have possibly prevented immediate colonisation by pathogens found in ambient air. This is analogous to the pre-operative biopsies which were acquired at the time of the first tracheal transplantation on June 9, 2011, immediately before the actual implantation of the synthetic trachea graft in patient 1. Seven out of seven biopsy samples taken from different parts of the synthetic scaffold showed that ***"no developed cell layer could be detected"*** and ***"no detectable cell components or matrix structures can be found"*** (Appendices 1, 2). This means that patient nr. 1 received a naked plastic trachea without any cell layer covering it and thereby immediately was exposed and colonised by normally inhaled ambient air (32) resulting in chronic infection and subsequently death.

This implies that it must be suspected that the plastic scaffold which was implanted in patient 2 and which PM specifically refers to as a success in the protocol in all likelihood also was immediately contaminated and colonised (27). Such a (chronic) life threatening infection can only be treated by removal of all the foreign material.

PM's statement also implies that a *"normal mucosa"* and *"respiratory epithelium"* would have appeared on a cell-free (*"naked"*) plastic tube at one week after implantation and then suddenly and completely have disappeared 4 days later (at the day 11 bronchoscopy on Nov. 22, as described above under point 2a) without reappearing on day 19 or 8 weeks after implantation, a scenario which is bizarre and won't be discussed further.

Even though PM was not unaware of this *"naked scaffold"* situation in the first patient (32), PM still went on to implant the new synthetic scaffold in the second patient without in the protocol mentioning or reflecting over this extremely serious findings. It must thereby be construed that PM consciously concealed this from the ethical committee and subsequently put new patients in a dire predicament with deadly consequences.

4. ***B. Ciliated respiratory epithelial cells (white arrow) obtained from a brush biopsy from the center of the transplanted trachea one week after implantation."***

This claim by PM is false. No biopsies are registered from *"one week"* after implantation:

A bronchoscopy was performed on **day 5** (Nov. 22, 2011) were the following samples were taken:

- a. Brush biopsy. Biopsy location: **“Nr 1: Proximal suture line”** and **“Nr 2: Distal suture line”**.

The report describes: *“The material consists of mostly mucus and granulocytes. Furthermore some benign squamous epithelial cells, **probably contamination from the upper airway**. Single benign bronchus epithelial cells of typical phenotype. Also found a good deal of degenerated or necrotic cylinder cells, probably bronchus epithelia, **but far too degenerated changes in order to allow for analysis.**”* (Appendix 6).

- b. Biopsy from the main carina [scaffold’s synthetic carina]. Description of the findings: **“non-representative material.”** (Appendix 7).

The brush biopsy was thereby evidently not taken from *“from the center of the transplanted trachea”* [i.e. plastic scaffold] as postulated by PM but instead from the anastomotic sites. This cannot be a case of a mix-up since the other biopsies (point 4b above) were not brush biopsies and concluded to show non-representative material.

5. *“The fact that this biopsy was done almost immediately after transplantation, allows us to assume that the cells derive from the differentiated stem cells, **and not from the spread of normal epithelial cells from the proximal or distal end of the transplant.**”*

This claim by PM is false and misleading, since in the pathologist report it is stated that in all likelihood the sample is **“probably contamination from the upper airway”** (point 4a above).

The evidence above shows that PM’s statements of an established normal mucosa with respiratory epithelial cells in the synthetic scaffold are fabricated and misleading.

Text section on p. 8:

6.0 Обоснование отсутствия отказа

В ходе предыдущих исследований не было зарегистрировано каких-либо негативных последствий, которые обусловили бы отказ от предлагаемого плана исследования (протокола).

Exhibit 4, p. 8: **“6.0 Rationale for not cancelling.**

In the previous research there have not been any negative effects or complications which would cause rejection of the proposed research plan (protocol).”

Comments to exhibit 4:

1. **“In the previous research...”**

This statement adds to previous evidence that despite PM though he later denied that that was the case that the two transplantations performed at Karolinska in June and Nov. 2011 were research on humans (6, 7, 8, 9, 10, 11, 12, 14, 15) which is further supported by the fact that the protocol is signed by PM stating himself as the “leading scientist” on p. 40 (34).

2. "... not been any negative effects or complications..."

This is fabrication and omission of crucial data. Both patients developed life-threatening complications (35, table 3) which PM was well aware of at the time of signing the protocol on February 5, 2012.

Patient 1:

- a. Biopsy evidence from the synthetic implants that showed that there was no cell layer covering the plastic was omitted by PM which led to exposure to ambient air and consequently chronic infection in patient 1.
- b. Life-threatening thromboembolic complications (right pulmonary arterial occlusion, thrombosis of the left brachiocephalic, jugular and subclavian veins and multiple distal pulmonary embolies) during administration of off-label supra-therapeutic doses of the growth factors erythropoietin (EPO,) and granulocyte-colony stimulating factor (G-CSF, Filgrastim, Neupogen®), (see further comments under exhibit 5).
- c. Bilateral distal anastomosis fistulation with the need for bilateral stenting of the scaffold.
- d. Obstruction of ventilation to the right lung secondary to pathological granuloma formation due to chronic inflammation at the site of attachment to the native right bronchi.
- e. No establishment of normal respiratory lining, vascularization or tissue growth in the synthetic scaffold.

Bronchoscopic images (pp. 18-24, 27-31) and CT images (pp. 25-26) verify the severe pathology.

The pathological radiological findings of fistulation, obstructive granuloma, stents, scaffold size mismatch which was documented from Case 1 (July 6, 2011 and Nov. 22, 2011) before PM signed the protocol (Feb. 5, 2012) have been previously been described by us in a previous petition for an investigation of scientific misconduct (36).

Patient 2:

- a. Despite biopsy evidence from the synthetic trachea implanted into patient 1 which demonstrated that there was no cell layer covering the graft PM proceeded to implant a synthetic trachea into patient 2 with the same protocol.
- b. Life-threatening thromboembolic complications (venous thrombosis in the left jugular, subclavian and axillary vein systems, pulmonary embolus in the left underlobe) during high dose administration of the growth factors (EPO, G-CSF, TGF- β 3) (further comments under exhibit 5 comments below).

- c. No establishment of normal respiratory lining, vascularization or tissue growth in the synthetic scaffold.

Bronchoscopic images (pp. 27-31) as well as CT images (p. 38) verifying severe pathology secondary to the scaffold implantation.

It should be pointed that PM when having been confronted with findings such as presented above in previous claims, among others to the independent investigator Prof. Gerdin, purported that he had not been given access to these patients' medical files and that due to language barriers was unaware of the suffering and morbidity that they have endured (37, p. 2, section 4-5):

"I had not (and indeed could not due to the language barrier)", "I and my research team had no routine access to the clinical healthcare records.", "The original written evidence documenting the patients' condition and results of tests at every stage are not only written in Swedish or Icelandic (two languages I have no knowledge of)."

This is an absurd attempt to avoid responsibility. In the case of the two patients referred to in the protocol, PM was present and in charge of decision making in the clinic and therefore was fully informed of all the crucial clinical circumstances and findings.

According to the medical files PM's presence was documented on the following dates:

- a. Karolinska Case 1: Besides during the postoperative period in June 2011, PM was present during the clinical evaluations and exams in November 21 and 22, 2011 when serious pathology in the airway (fistulation, severe obstructive granuloma, need for stenting etc.) as well as lack of any respiratory lining, vascularisation or tissue ingrowth in the synthetic scaffold was clearly demonstrated.
- b. Karolinska Case 2: October 21, November 17, 18, 19, 20, 21, 23, 27, 28, December 1, 2, 6, 9, 16, 2011 and January 6, 7, 10, 2012 when a non-viable scaffold and lack of any respiratory lining, vascularisation or tissue ingrowth in the synthetic scaffold was clearly demonstrated.

Text section on p. 21:

Послеоперационные процедуры

Для стимулирования процесса регенерации в послеоперационный период пациент будет получать фармакологические средства посредством следующих системных инъекций:

- а) рекомбинантные аналоги G-CSF (филграстин, 10 мкг/кг/день, не более 30 мкг/кг/день)
- б) синтетические аналоги эритропоэтина (эритропоэтин альфа или бета, не более 40000 МЕ).

Оба этих фактора будут вводиться в соответствующих концентрациях (в восстановительной дозах, не связанных с какими-либо побочными эффектами) для стимуляции мобилизации / трансформации клеток-предшественников / стволовых клеток костного мозга.^{3,4,5,15,16} Каждый день будут контролироваться плазменный уровень эритропоэтина и подсчёт форменных элементов крови (в том числе лейкоцитарная формула крови). Уровни выше 50 000 - 60 000 лейкоцитов в крови будут считаться проявлением токсичности и, как следствие, будут снижены дозы / прекращена терапия. Лечение будет проводиться через день в течение 2 недель после трансплантации.

Exhibit 5, p. 21:

"Postoperative procedures

To stimulate the process of regeneration in the postoperative period, the patient will receive pharmacological agents with following systemic injections:

- a) Recombinant analogues of G-CSF (Filgrastim, 10mcg/kg/day, no more than 30 mcg/kg/day)*
- b) Synthetic analogues of erythropoietin (EPO alpha or beta, max 40000 IU).*

Both of these factors will be administered in adequate concentrations (in reduced doses not associated with any side effects) for stimulating mobilization and transformation of progenitor stem^{3,4,5,15,16} and bone marrow cells [...] day automatic controlled plasma erythropoietin level and calculation of whole blood (including leukocyte blood count). Levels above 50000-60000 cells in the blood will be considered a manifestation of toxicity and as a result will be reduced dose or discontinued. The treatment is carried out every other day for two weeks after transplantation."

Comments to exhibit 5:

"... (in reduced doses not associated with any side effects)..."

This is extensively misleading:

- a) Both growth factors G-CSF (Granulocyte-Colony Stimulating Factor, Filgrastim, Neupogen®) and EPO (synthetic analogue of Erythropoietin, NeoRecormon®) have side-effects independently of dose and especially in patients with malignant disease (both patient 1 and 2 had cancer of the trachea).

- b) Synergistic effects and potential risks have not been studied for this experimental off-label combination therapy given in high-dose and not for Erythropoietin (NeoRecormon®) at high-doses as mono-therapy.
- c) G-CSF and Erythropoietin have been administered without ethical approval and without permission from the Swedish MPA for an off-label indication and in high doses (multiple times greater than recommended maximum doses) to two patients with malignant disease.
- d) The producers of the substances (Amgen, Europe BV Breda Netherlands and Roche, Grenzach-Wyhlen, Germany) have no knowledge of this off label use and do not recommend their usage (38).
- e) PM did not inform the Swedish MPA of the life-threatening complications associated with the administration of these substances which had afflicted both of the two Karolinska patients. PM did not report to the Swedish MPA the complications related directly to the implanted medical device (plastic scaffold).

It should be pointed out that the substance TGF-β3 (Recombinant Human Transforming Growth Factor β-3) which is not mentioned in the text section of specifically exhibit 5 on p. 21 in the reviewed protocol however is clearly described on p. 18 (point 9), p. 39 ("Appendix 3: Characteristics of biological agents and factors TGF-β3", table presenting growth factors used preoperatively in the present protocol to accelerate tissue regeneration) and p. 40 ("TGF-β3: calculation of the necessary dose of TGF-β3...") was used even though the substance is not permitted to be used in humans or animals because of the risk for viral transfer between species with potentially unforeseen consequences (39, 40). Both patient 1 and 2 were exposed to this substance without prior ethical approval and without permission from the Swedish MPA.

Text sections on pp. 25-26:

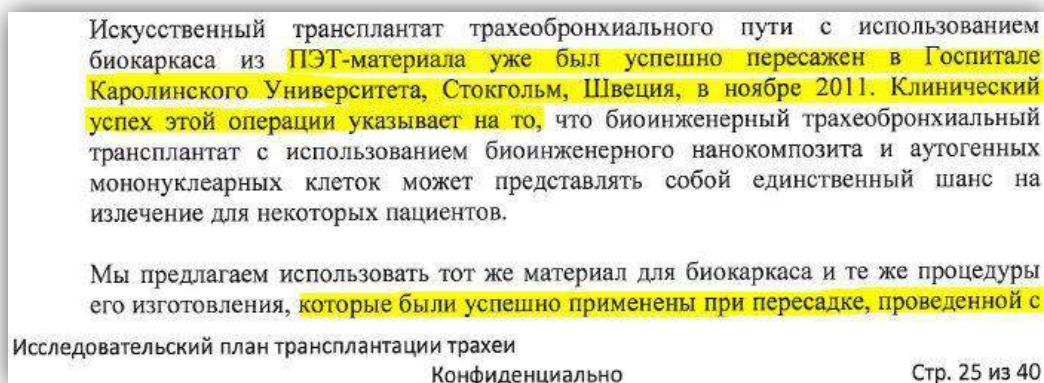


Exhibit 6A, p. 25: ***"An artificial tracheobronchial graft using bioscaffold from PET-material has already been successfully transplanted at Karolinska University Hospital, Stockholm, Sweden, in November 2011. The clinical success of this operation indicates that the tracheobronchial graft of bioengineered nanocomposite and autologous mononuclear cells may be the only chance of cure for some patients.***

*We propose to use the same material for the bioscaffold and the same procedure for its production, **which has been successfully used for the tracheal transplantation in November...**"* [Text continues on p. 26].

использованием данного протокола трансплантации трахеи в ноябре 2011 г. Полимерные нанокompозиты из ПЭТ тщательно изучались на клеточную совместимость, и недавняя операция, проведенная в Госпитале Каролинского Университета, продемонстрировала их способность обеспечивать приживляемость и пролиферацию аутологических моноклеарных клеток и раннюю (7 дней) реэпителизацию клетками дыхательного эпителия.

Exhibit 6B: "...2011, using this Protocol. The polymer nanocomposite PET has carefully been studied on cell compatibility, and recent surgery, performed at Karolinska University Hospital, **demonstrated its acceptability, ability to allow for proliferation of autologous mononuclear cells and early (7 days) re-epithelialization with respiratory epithelium.**"

Comments to exhibits 6A, B:

1. **"...has already been successfully transplanted at Karolinska University Hospital, Stockholm, Sweden, in November 2011. The clinical success of this operation..."**

Postulation is misleading as described above.

2. **"...and early (7 days) re-epithelialization with respiratory epithelium."**

Postulation as shown above is fabrication.

Text section on p. 26:

Заключение: Информация о биосовместимости имплантируемых протезов спинного мозга, пищевода и сердечных клапанов, изготовленных из подобного ПЭТ-материала, приведена ниже в таблице. Все данные подтверждают отличную биосовместимость потиэтилентерефталата при его использовании в качестве материала для медицинских имплантатов жизненно важных органов. Эти данные, а также успешная пересадка трахейного трансплантата пациенту в ноябре 2011 г., продемонстрировавшая отличную биосовместимость, позволяют заключить, что предлагаемый материал биокаркаса удовлетворяет требованиям биосовместимости и является безопасным для использования.

Exhibit 7, p. 26. **"Conclusion:** information on the biocompatibility of implantable prostheses made of PET-material such as spinal cord, esophagus and cardiac valves is provided in the table below. All data confirm excellent biocompatibility when using the material for medical implants for vital organs. **These data, and also the successful tracheal transplantation in a patient in November 2011, have shown excellent biocompatibility, allow concluding that the proposed bioscaffold material meets the requirements of biocompatibility and is safe for use."**

Comments to exhibit 7:

"These data, and also the successful tracheal transplantation in a patient in November 2011, have shown excellent biocompatibility, allow concluding that the proposed bioscaffold material meets the requirements of biocompatibility and is safe for use."

This is a fabricated and misleading conclusion that does not truthfully present the actual medical data which has been documented in the two Karolinska patient's medical records who have undergone synthetic scaffold implantation.

Conclusion

Based on the above presented evidence the following conclusion can be reached:

Data from the medical records of the patients who underwent synthetic trachea implantation at Karolinska without ethical approval and without permission from the Swedish MPA have been systematically falsified, omitted or glorified by PM with the purpose to describe these experiments on humans as more successful than they actually were. This is one further example of a multitude of examples where PM has misled the research community by falsifying data to glorify the results of his research (9, 10, 27, 32, 35, 36, 41, 42, 43, 44, 45).

The serial falsification and glorification of crucial data imply that the responsible authorities, funding bodies and ethical committees in Russia who approved these applications have been consciously misled. The gross transgression of manipulating an ethical committee in order to attain approval to perform high risk procedures on human beings obviously necessitates criminal investigation under the jurisdiction of the country where those transgressions transpired.

The results of these high-risk procedures were well known at the time that PM signed the protocol and should be of great concern to those regulatory bodies. If these allegations are verified then it can be concluded that multiple patients in Russia have been subjected to deadly experiments on the basis of conscious manipulation of the above-mentioned regulatory bodies and that criminal proceedings should be initiated against the responsible parties and prosecuted according to Russian law.

We implore Karolinska Institutet without further delay to inform the involved Russian authorities and ethical committees¹²³ who have judged, approved and financed this multi-million dollar research which lead to disastrous results for these Russian patients of the allegations contained in this petition.

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The embassy is kindly invited to update any of the above if needed.

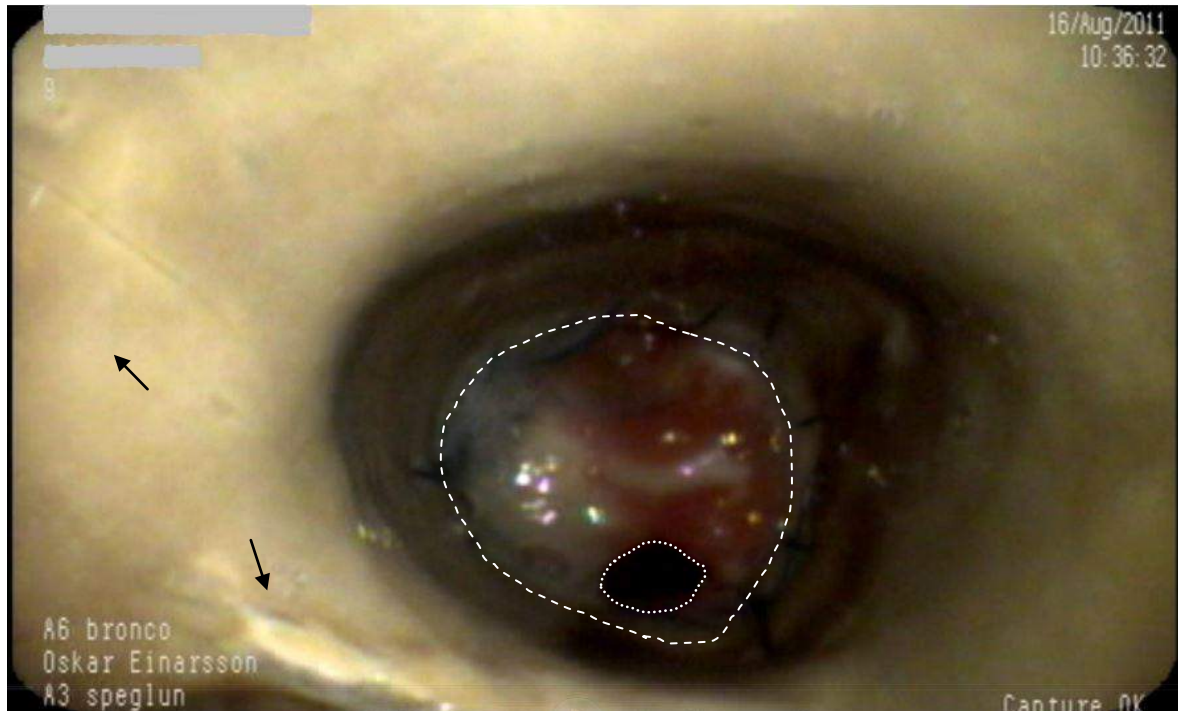


Figure 1. **Bronchoscopy 2011-08-16, 10 weeks after implantation** (performed on Island). The synthetic scaffold's right "leg". The distal right main bronchus anastomosis (connection) between the synthetic scaffold and the right main bronchus opening. Left arrow: inner wall of the synthetic scaffold without any covering epithelium, vascularization or tissue ingrowth. Right arrow: synthetic carina (separating ridge between the synthetic right and left main bronchus departures, the scaffold's "legs"). Large dotted line: right distal anastomosis, small dotted line: obstructed native right main bronchus opening (should have the same area as the large dotted line) blocking the right lung from being normal ventilated due to the extensive and pathological formation of granulation tissue (chronic inflammation). Pathological airway, compare to figure 6 on p. 20.

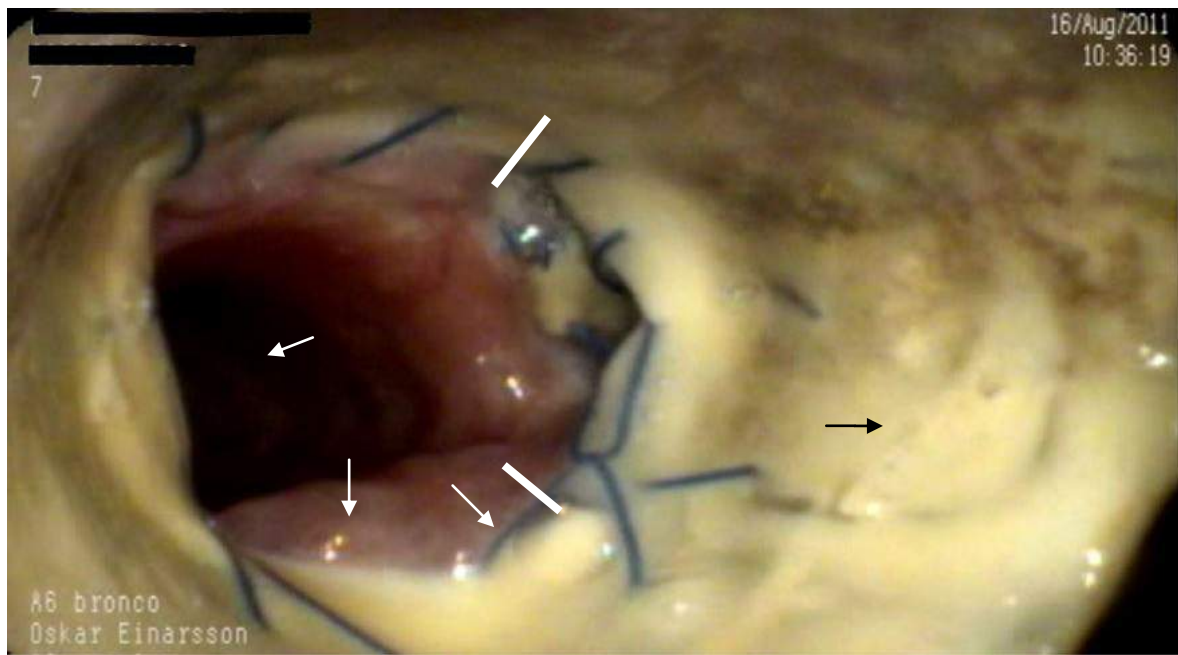


Figure 2. View advanced in distal direction. Distal left main bronchus anastomosis (the synthetic scaffold's left "leg"). Arrows from left to right: left main bronchus opening, granulation tissue, nude sutures, thick white lines marks fistula opening (covering ca. 20% of the anastomotic circumference), "nude" synthetic scaffold without any covering epithelium or tissue ingrowth.

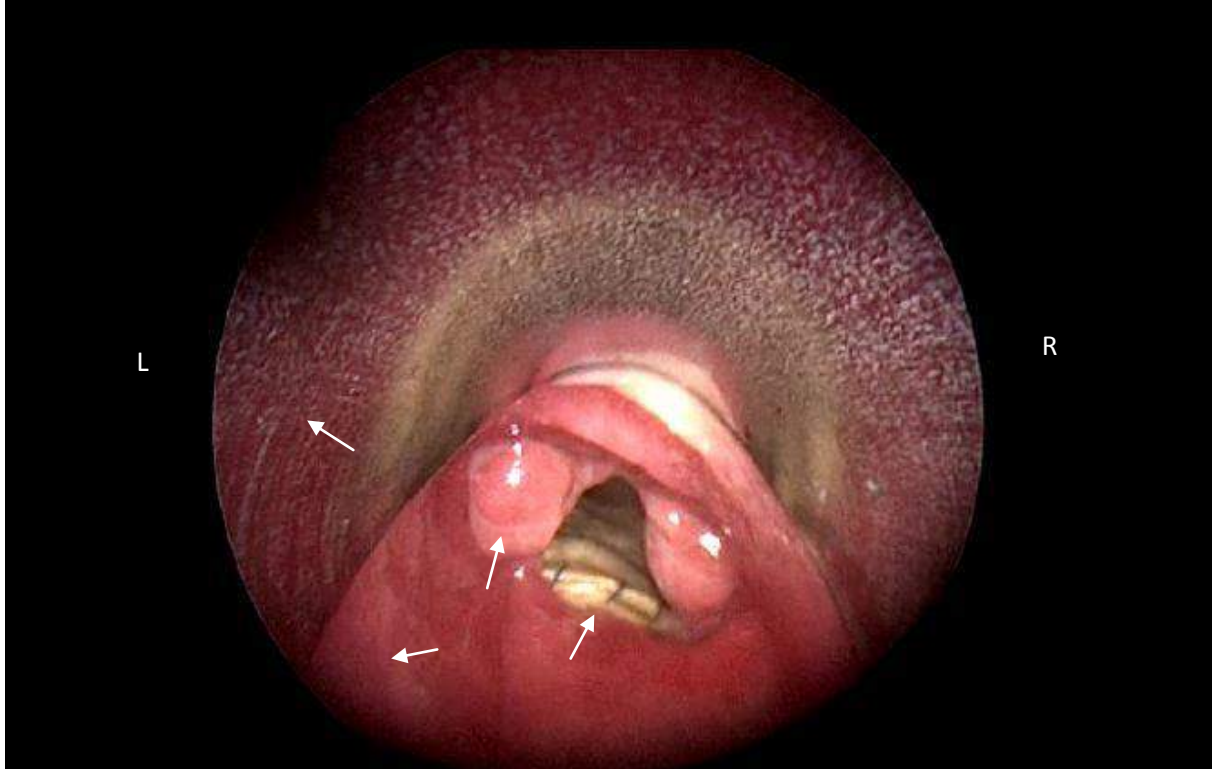


Figure 3. **Bronchoscopy 2011-11-21, 5½ months after implantation.** View from the upper (proximal) part of the native trachea down towards the synthetic scaffold (white-yellowish). Arrows from left to right: inner wall of the bronchoscope, native trachea with normal vascularization, granulation tissue obstructing the upper connection to the synthetic scaffold (as sign of chronic pathological inflammation).

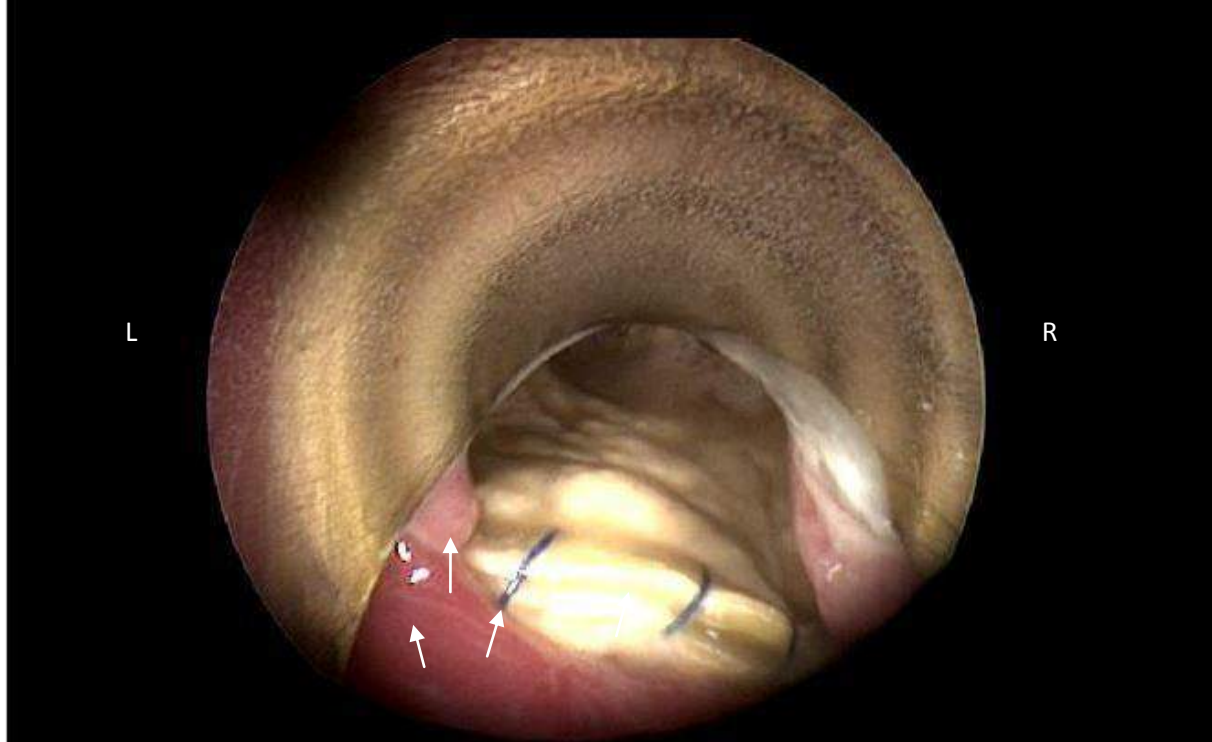


Figure 4. View advanced in distal direction. Arrows from left to right: normal native tracheal vascularized tissue, granulation tissue, tissue uncovered sutures, proximal (upper) connection between native trachea and nude synthetic scaffold (white-yellowish) without any covering epithelium, vascularization or tissue ingrowth.

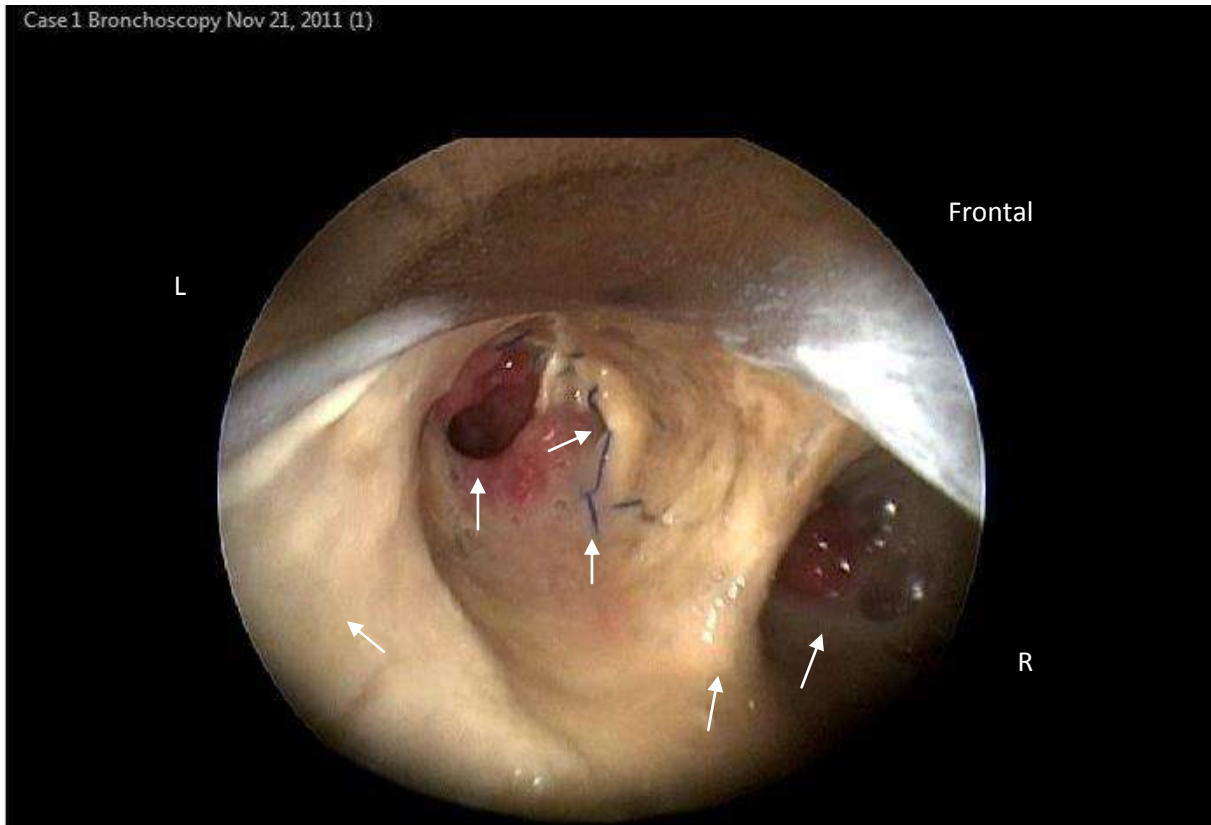


Figure 5. View into the nonviable and dysfunctional synthetic scaffold. Arrows from left to right: inner wall of synthetic scaffold (yellowish-white) without any covering epithelium, vascularization or tissue ingrowth, pathological obstruction of left main bronchus opening by granulation tissue, fistulation, tissue uncovered sutures, synthetic scaffold's carina and the scaffold's "right leg" with complete obstruction of the native right main bronchus opening. Compare the non-vascularized and non-tissue covered (nonviable) scaffold with next figure 6 showing a normal vascularized inner wall of a normal healthy and viable trachea.

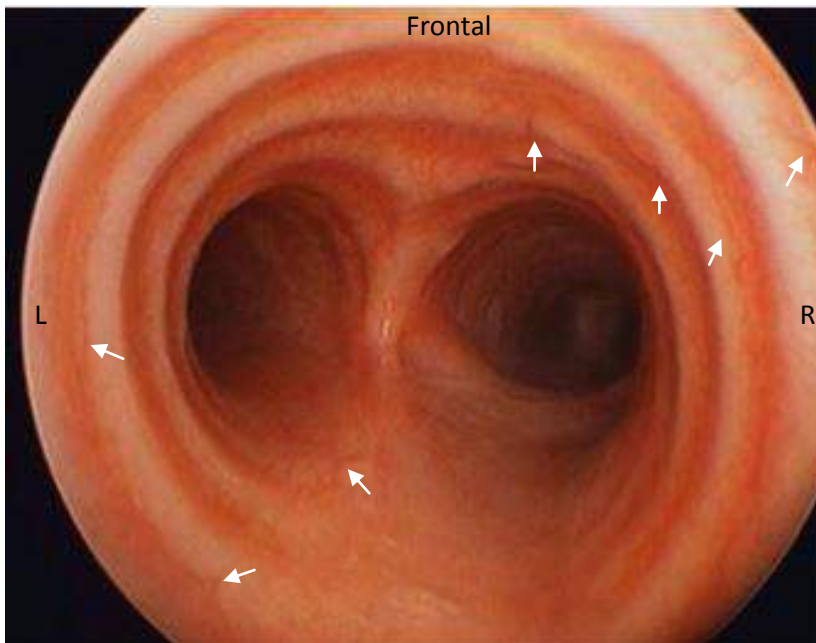


Figure 6. Normal (non-synthetic) trachea (N.B. not the same patient) covered with a well vascularized and functional airway tissue. Arrows: examples of vessels.

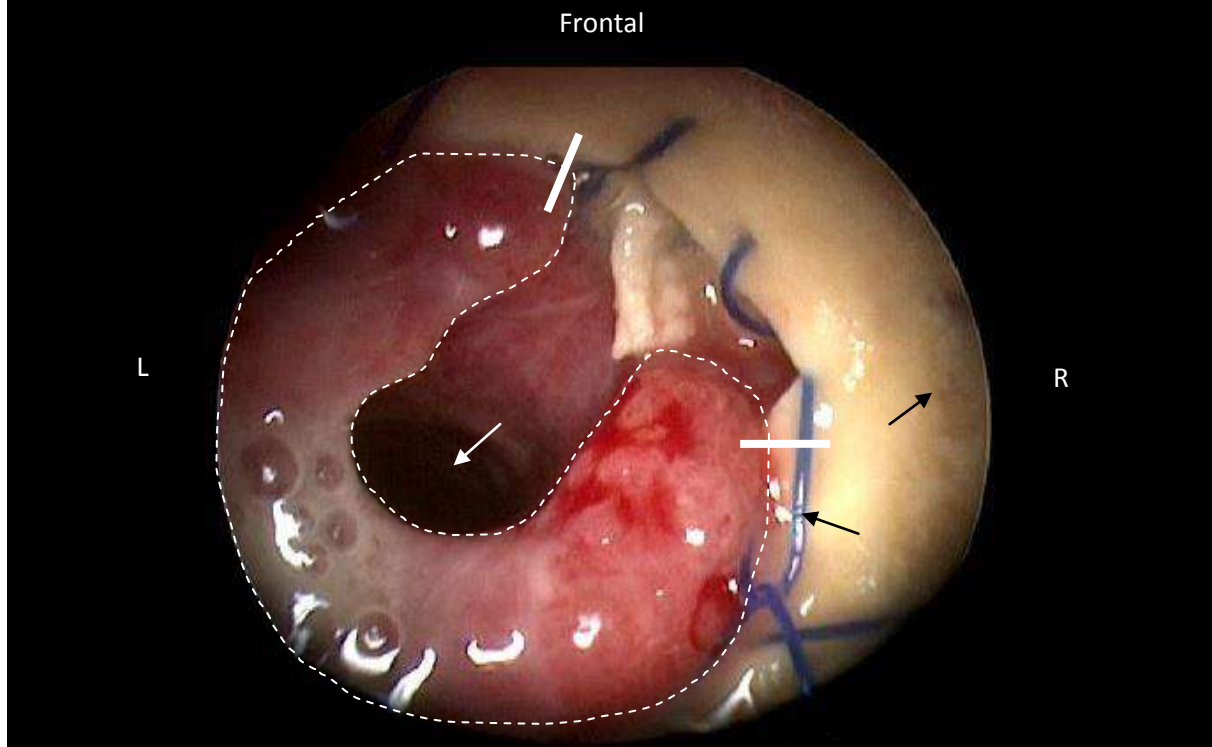


Figure 7. Left distal anastomosis (connection) between the synthetic scaffold's "left leg" and rest of native left main bronchus. Dotted line: area of excessive granuloma formation (inflammatory tissue) obstructing the left main bronchus opening. Arrows from left to right: native left main bronchus opening, white lines marks fistula opening (covering ca. 20% of the anastomotic circumference), tissue uncovered sutures, synthetic scaffold's inner wall without any covering epithelium or tissue ingrowth.

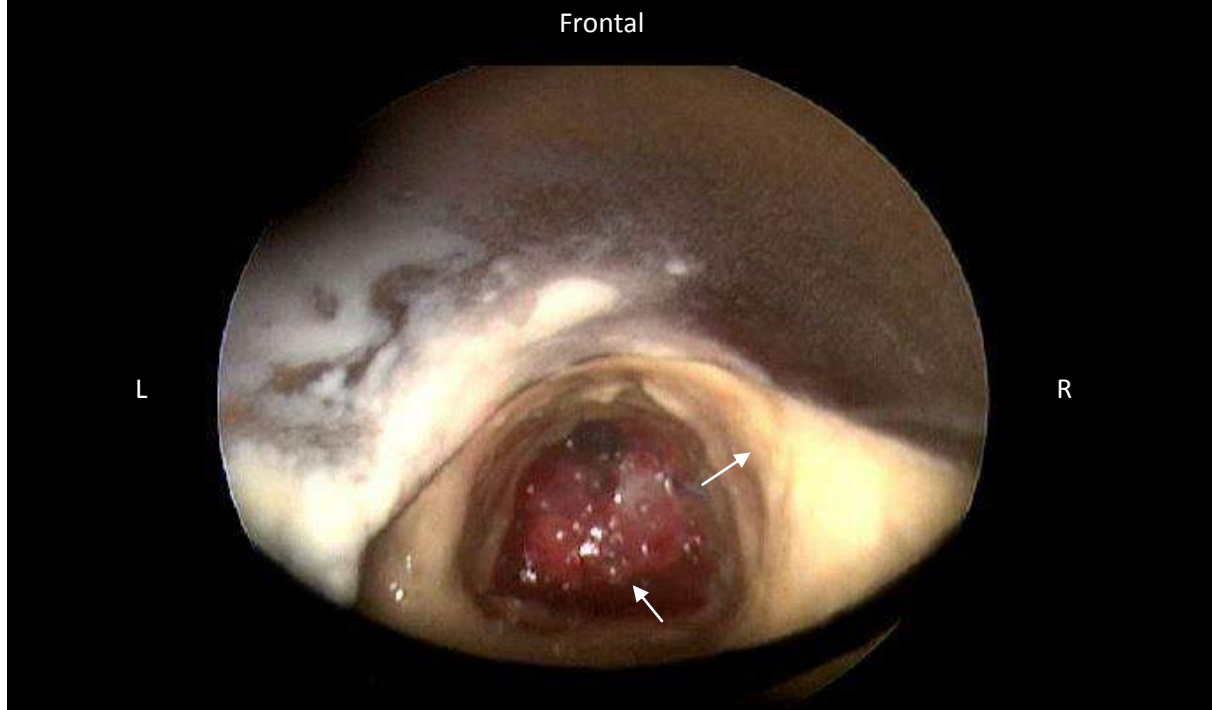


Figure 8. View into the synthetic scaffold's "right leg". Right main bronchus opening completely obstructed by granulation tissue growth (left white arrow) blocking the right lung from ventilation. Inner wall of the synthetic scaffold without any covering epithelium or vascularization (right arrow).

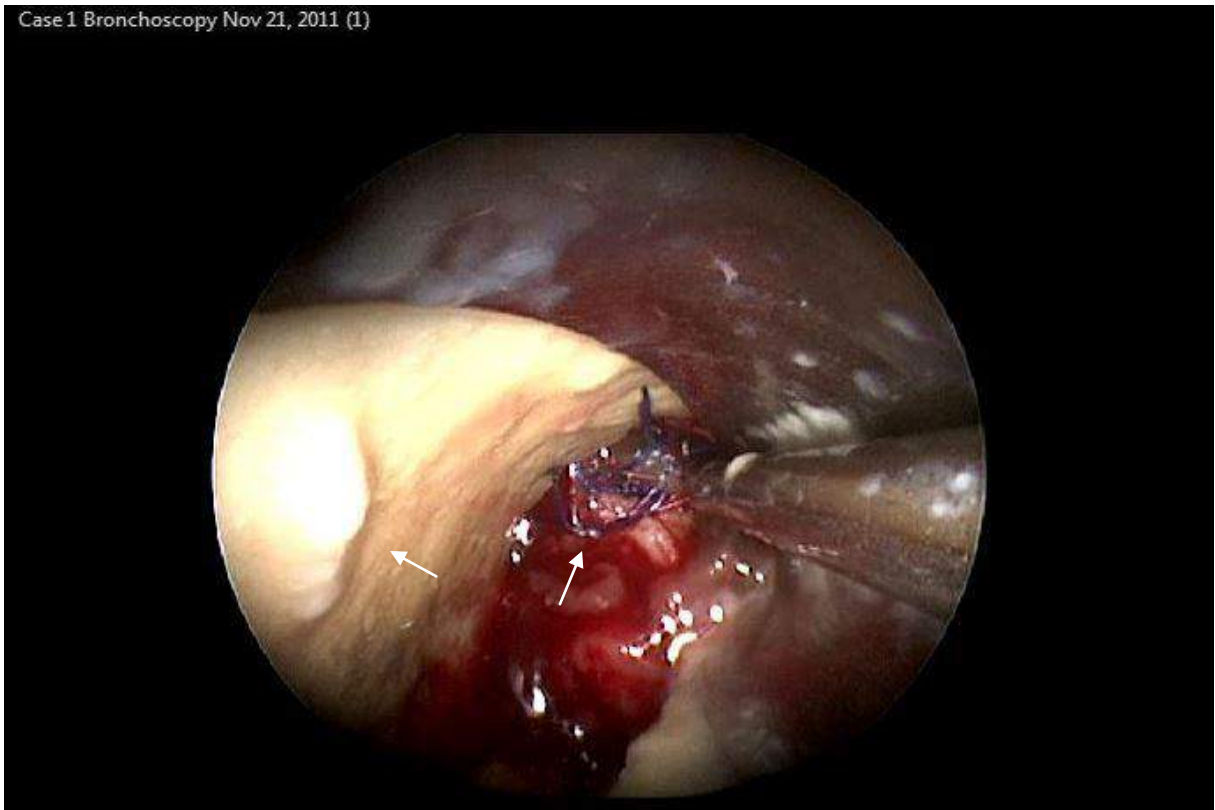


Figure 9. View into the nonviable synthetic scaffold's "right leg" down towards right main bronchus opening. Completely blocked right bronchus opening. Left arrow: synthetic scaffold without any covering epithelium, vascularization or tissue ingrowth. Right arrow: loose tissue uncovered anastomotic sutures.

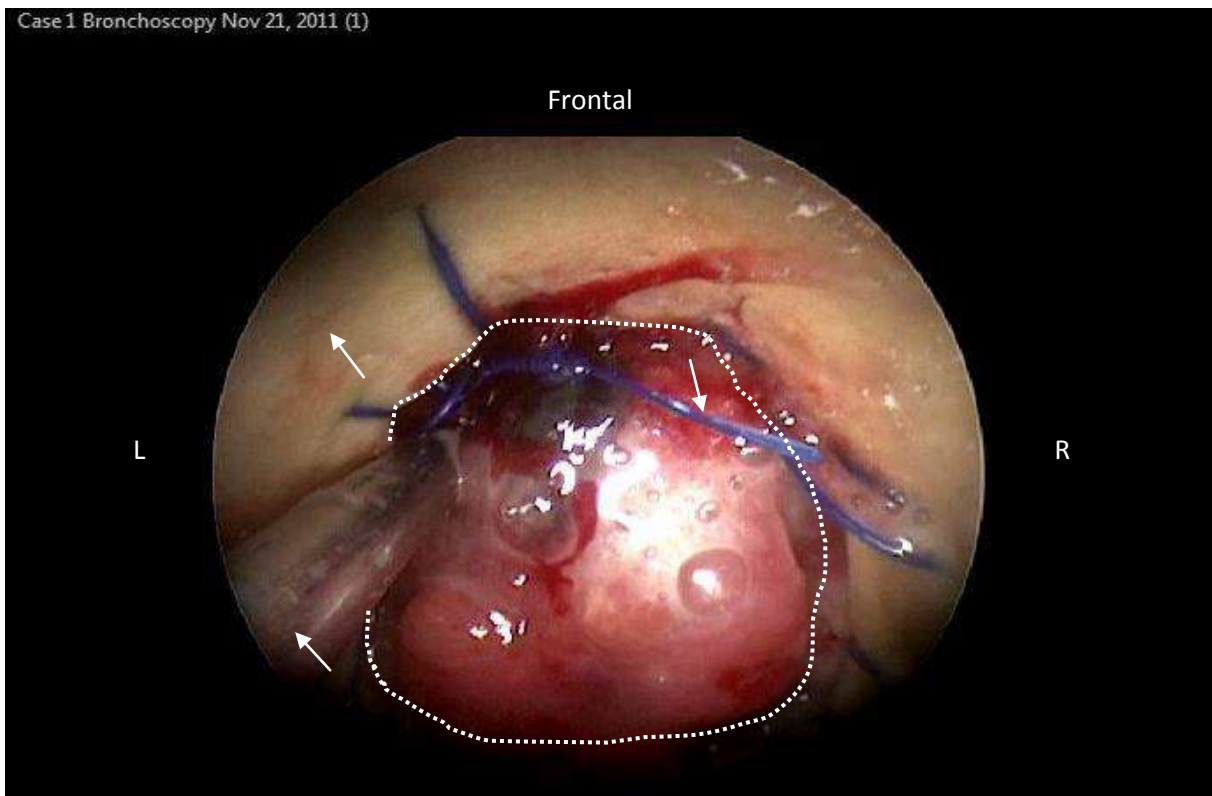


Figure 10. View further advanced showing excessive granulation (inflammatory) tissue completely obstructing the right main bronchus opening which prevents the right lung from being ventilated. Arrows from left to right: bronchoscopic instrument (searching for bronchus opening), scaffold's inner wall without any covering epithelium or tissue ingrowth, loose anastomotic sutures. Dotted line marks the distal right anastomosis area which should have been open but here is filled with granulation tissue,

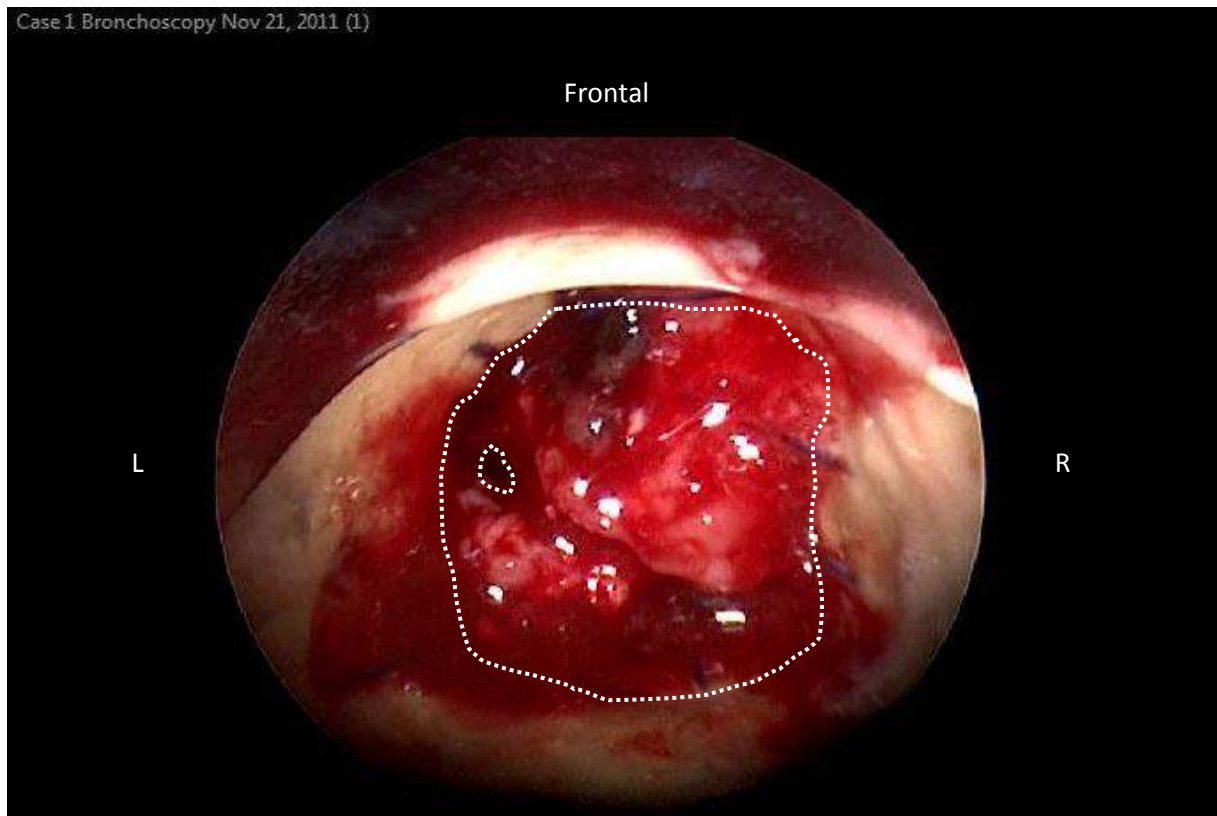


Figure 11. Completely blocked right main bronchus opening. Small dotted line marks the minor opening to the native right main bronchus after starting resection of granulation tissue (the right main bronchus opening should have had the same area as the large dotted line).



Figure 12. **Bronchoscopy at the following day Nov. 22, 2011.** View into the nonviable synthetic scaffold without any covering epithelium, vascularization or tissue ingrowth. Compare scaffold's inner wall to the normal vascularized functional airway in figure 6 above. Airway stents in the left and right main bronchus openings (green colored endings), completely fluid filled right main bronchus opening, right lung not being normally ventilated. Proof of a dysfunctional synthetic scaffold and severely pathological airway.

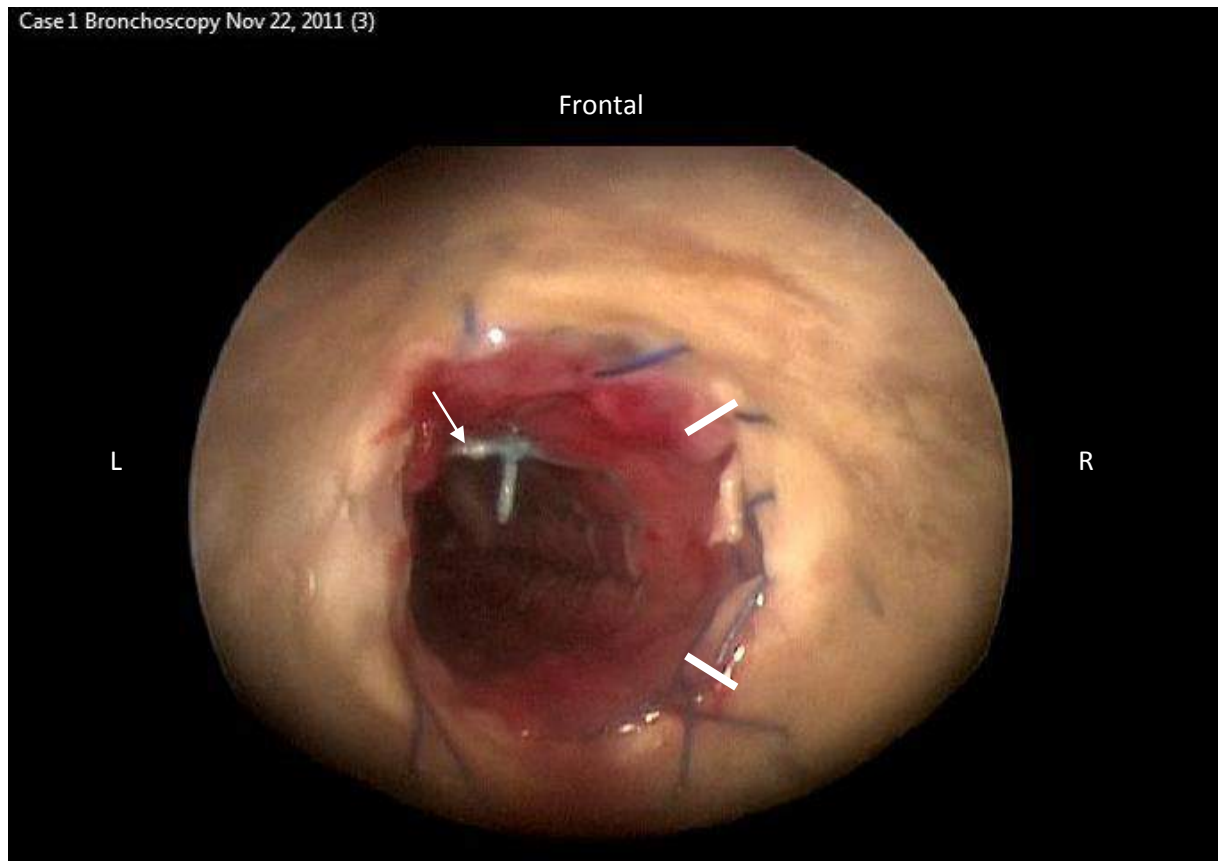


Figure 13. View further advanced into the left main bronchus opening. Note the color difference between vascularized (red) airway tissue and the synthetic scaffold's inner wall without any epithelialization, vascularization or tissue ingrowth. Arrow: airway stent in native left main bronchus (green stent ending), white lines marks fistula opening (covering ca. 20% of the anastomotic circumference).

Radiological examination performed on **Nov. 22, 2011, 5½ months after implantation on June 9, 2011** (figures 12a-c, 13), verifies the bronchoscopic findings of severe airway pathology consisting of bilateral fistulations, obstruction of airway and air surrounding the implant. Airway stents have been placed in an attempt to obliterate fistulation. The presence of fistulation is indicative of chronic infection and inability of the synthetic implant to heal into the surrounding native tissue, as is the continuous ingrowth of obstructive granulomatous tissue (threatening ventilation) is indicative of chronic inflammation.

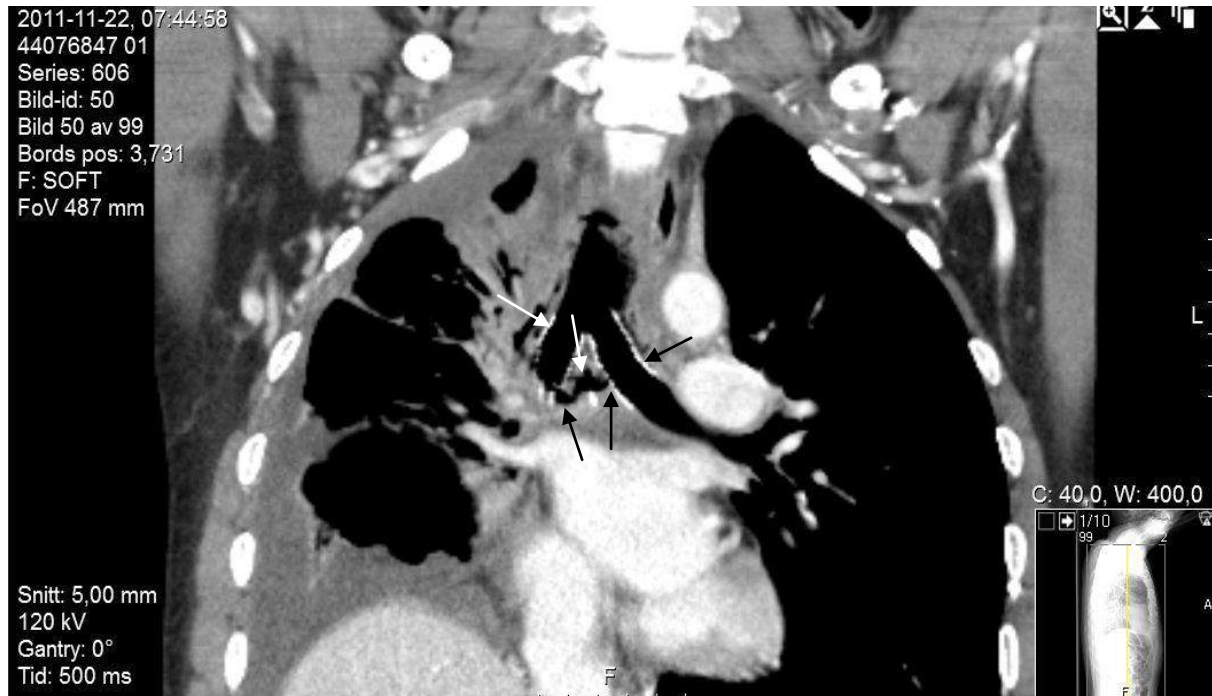


Figure 14a. Frontal view. Arrows from left to right: stent in the right main bronchus, fistula at the distal right main bronchus anastomosis, air outside the synthetic scaffold, fistula at the distal left main bronchus anastomosis, stent in the left main bronchus.



Figure 14b. Frontal view, different slice compared to figure 14a. Arrows from left to right: stent in the right main bronchus, circumferential fistula at the distal right main bronchus anastomosis (detached right scaffold's "leg"), fistula at the distal left main bronchus anastomosis, stent in the left main bronchus.

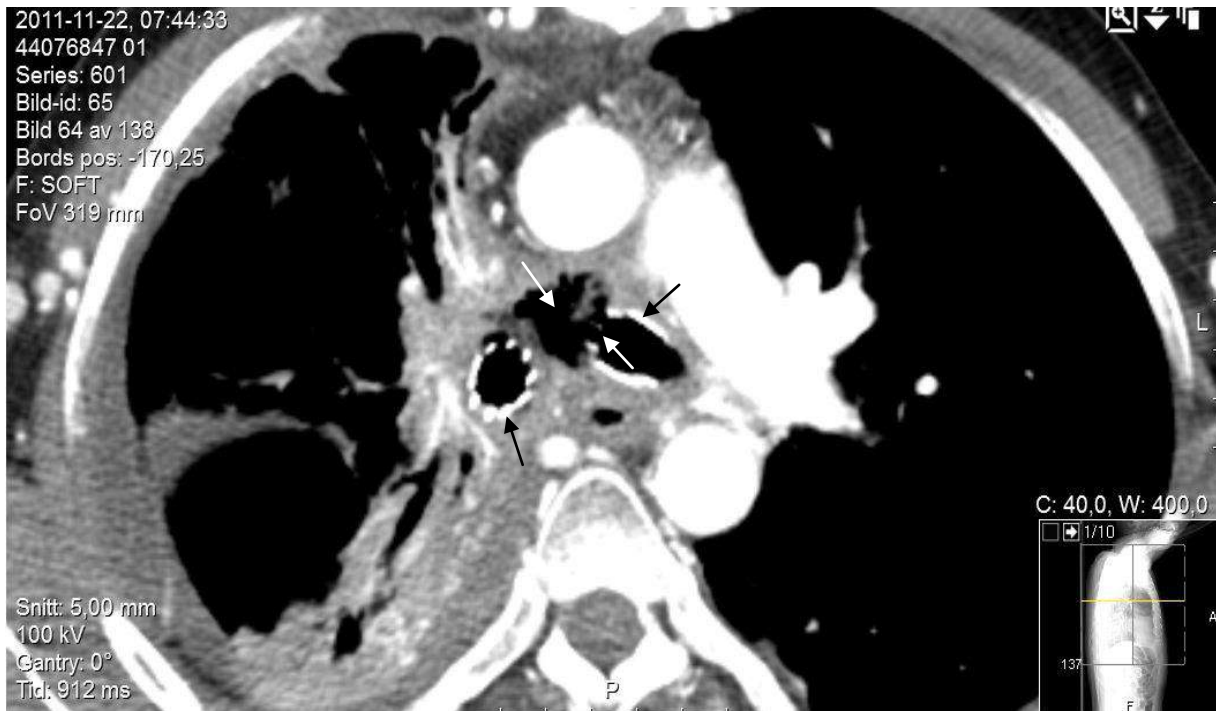


Figure 15. Transversal view. Arrows from left to right: stent in the right main bronchus, air outside the synthetic scaffold, large fistula at the distal left main bronchus anastomosis, stent in the left main bronchus,

A radiological examination showing 3-D volume rendered images was performed on Nov. 22, 2011 *after* stent implantation on the day before (Nov. 21, 2011) due to severe airway pathology (obstruction, bilateral fistulations between synthetic trachea and left and right bronchi).

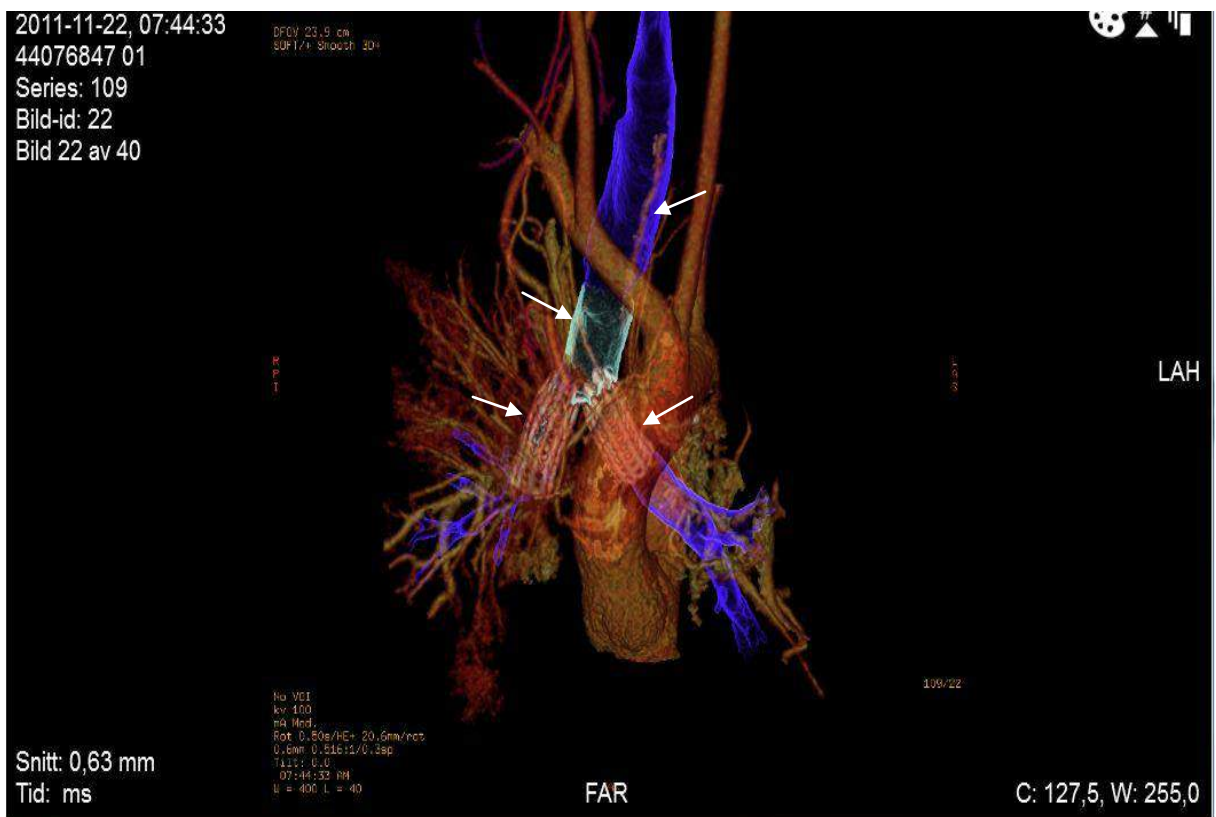


Figure 16. Frontal view. Arrows from left to right: stent in the right main bronchus, synthetic trachea, tracheal "blue air tube" (air filled native trachea), stent in the left main bronchus.

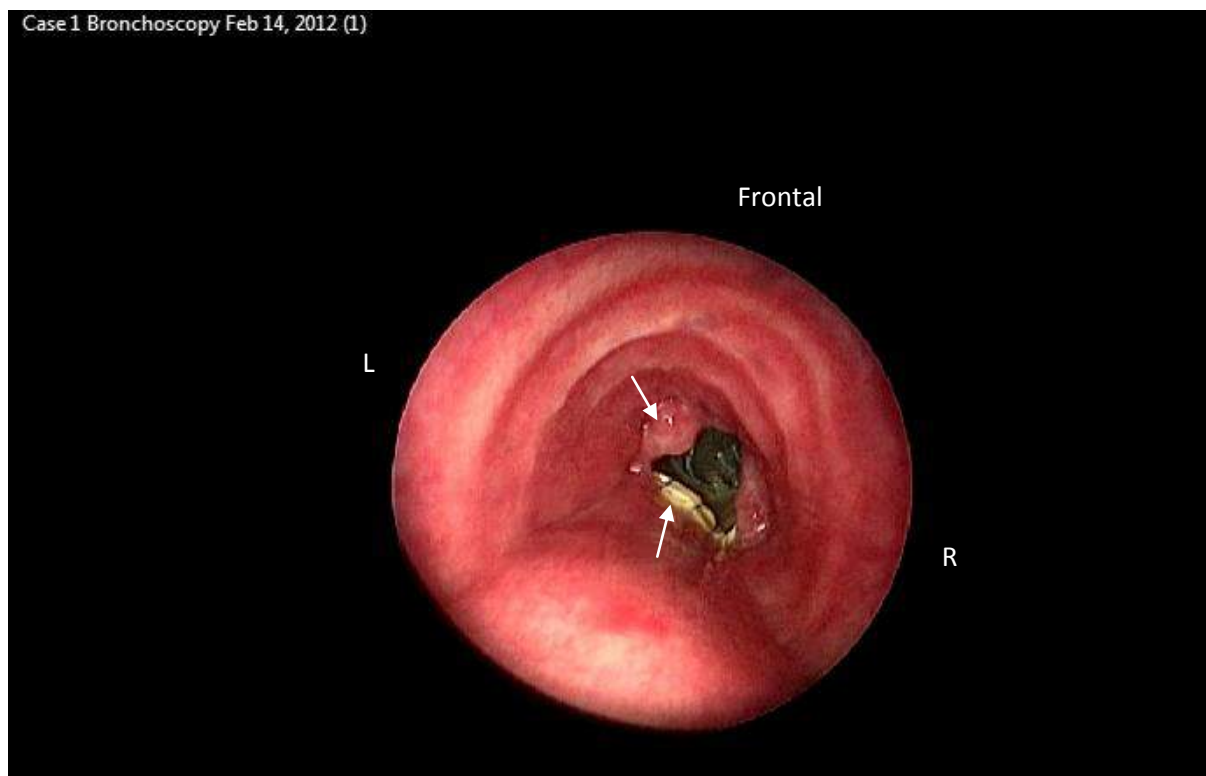


Figure 17. View from the proximal (upper) part of the native trachea down towards the synthetic scaffold (white-yellowish). Note the normal vascularization and color of the native airway tissue. Arrows from left to right: granulation tissue at the upper connection (anastomosis) between the synthetic scaffold and native trachea, upper edge of tissue unversed synthetic scaffold.

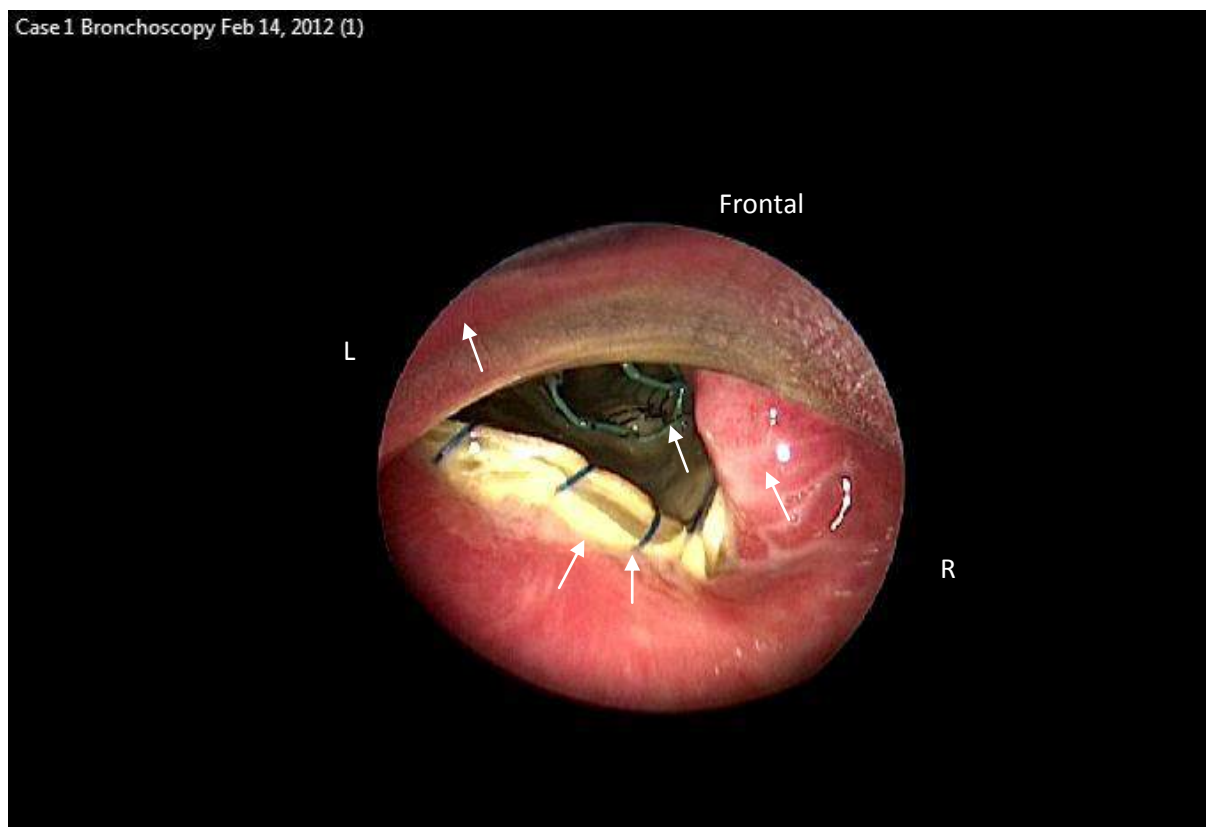


Figure 18. View advanced in distal direction. Arrows from left to right: Inner wall of bronchoscope, Upper edge of the tissue uncovered synthetic scaffold, sutures, airway stent, obstructing granulation tissue.



Figure 19. View into the nonviable synthetic scaffold (posterior wall) without any signs of vascularization or tissue ingrowth, dislocated airway stent (arrow).

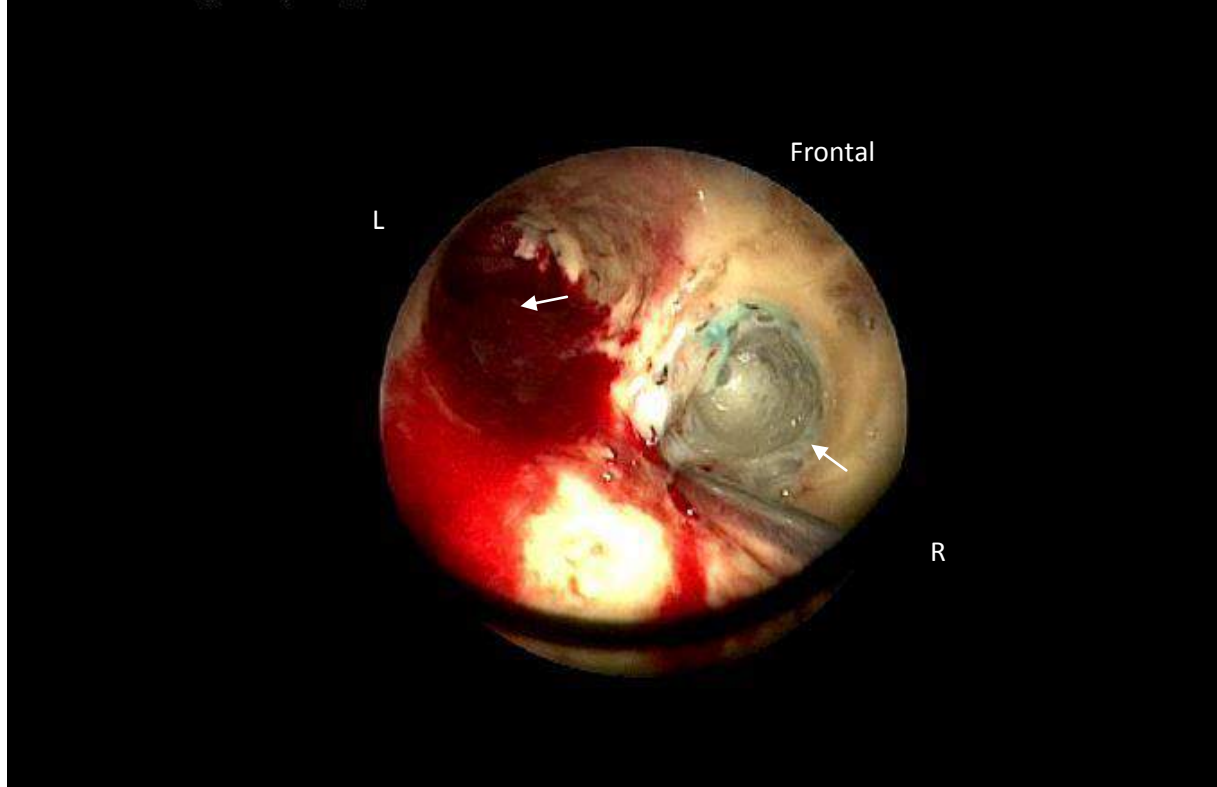


Figure 20. View advanced into the nonviable synthetic scaffold without any covering epithelium, vascularization or tissue ingrowth. Bleeding into the left main bronchus opening (N.B. originating from resection of granulation tissue at the upper connection between native trachea and the scaffold and not from the scaffold itself which has no living tissue on the inside). Arrows from left to right: left main bronchus opening, airway stent in the right main bronchus opening. Severely pathological airway.

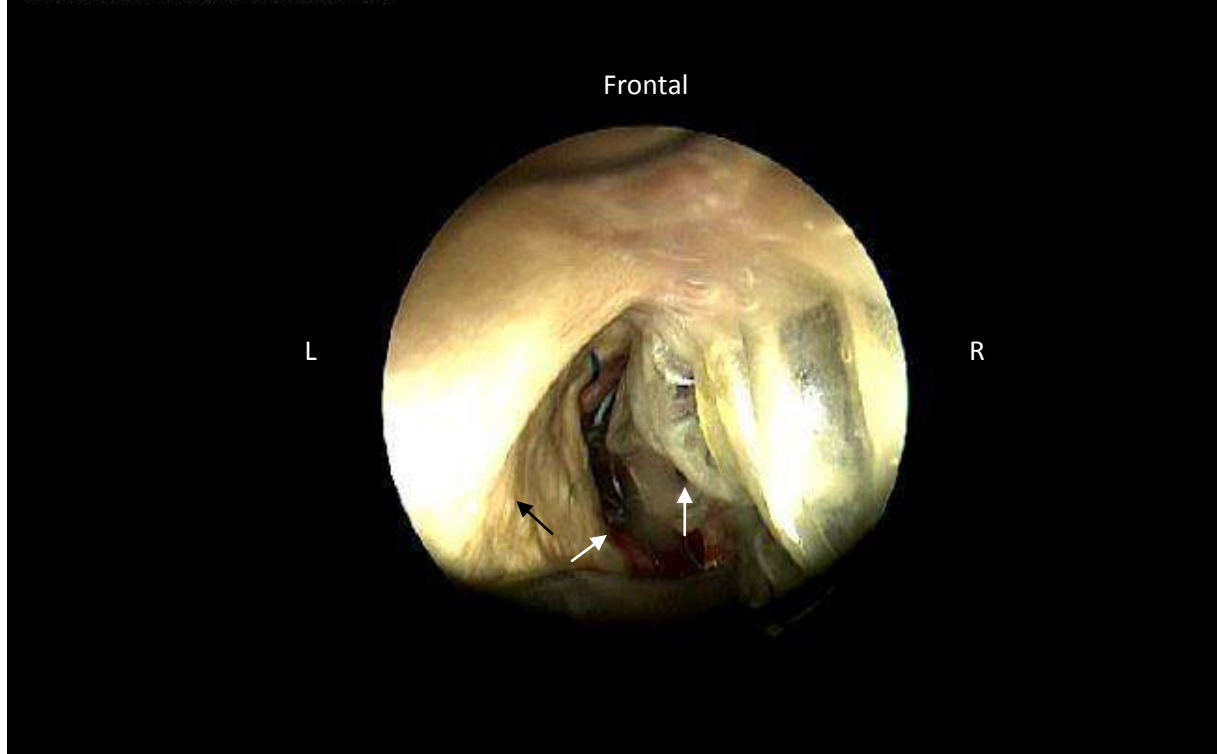


Figure 21. View into the synthetic scaffold's "left leg" down towards the left main bronchus opening. Arrows from left to right: inner wall of synthetic scaffold without any epithelialization, vascularization or tissue ingrowth, distal connection between scaffold and native left main bronchus, outside of airway stent which is about to be pulled out and exchanged.

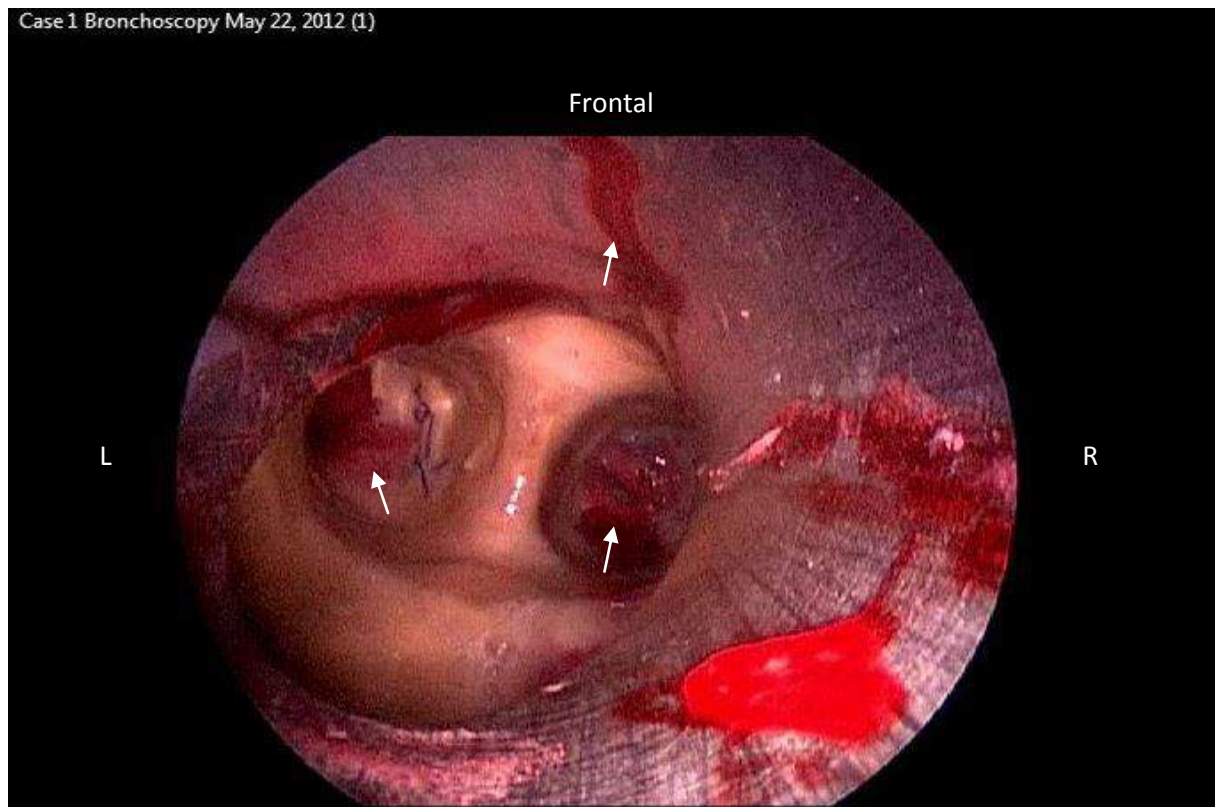


Figure 22. View into nonviable synthetic scaffold without any covering epithelium, vascularization or tissue ingrowth. Arrows from left to right: Left main bronchus opening significantly obstructed by granulation tissue, inner wall of bronchoscope, obstructed right main bronchus opening.

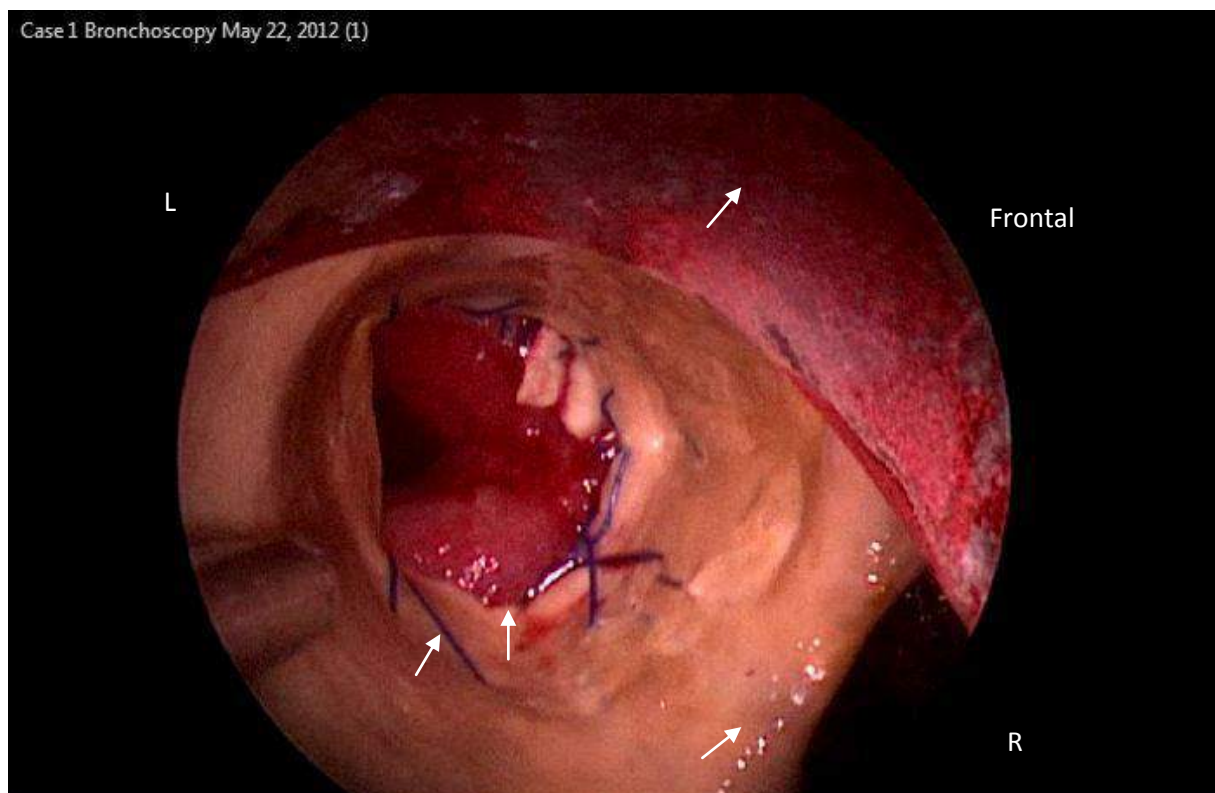


Figure 23. View into left main bronchus opening. Nonviable synthetic scaffold's inner wall without any covering epithelium, vascularization or tissue ingrowth (compare to figure 6 on p. 20). Arrows from left to right: tissue uncovered sutures (left arrow), inner wall of bronchoscope, synthetic carina.

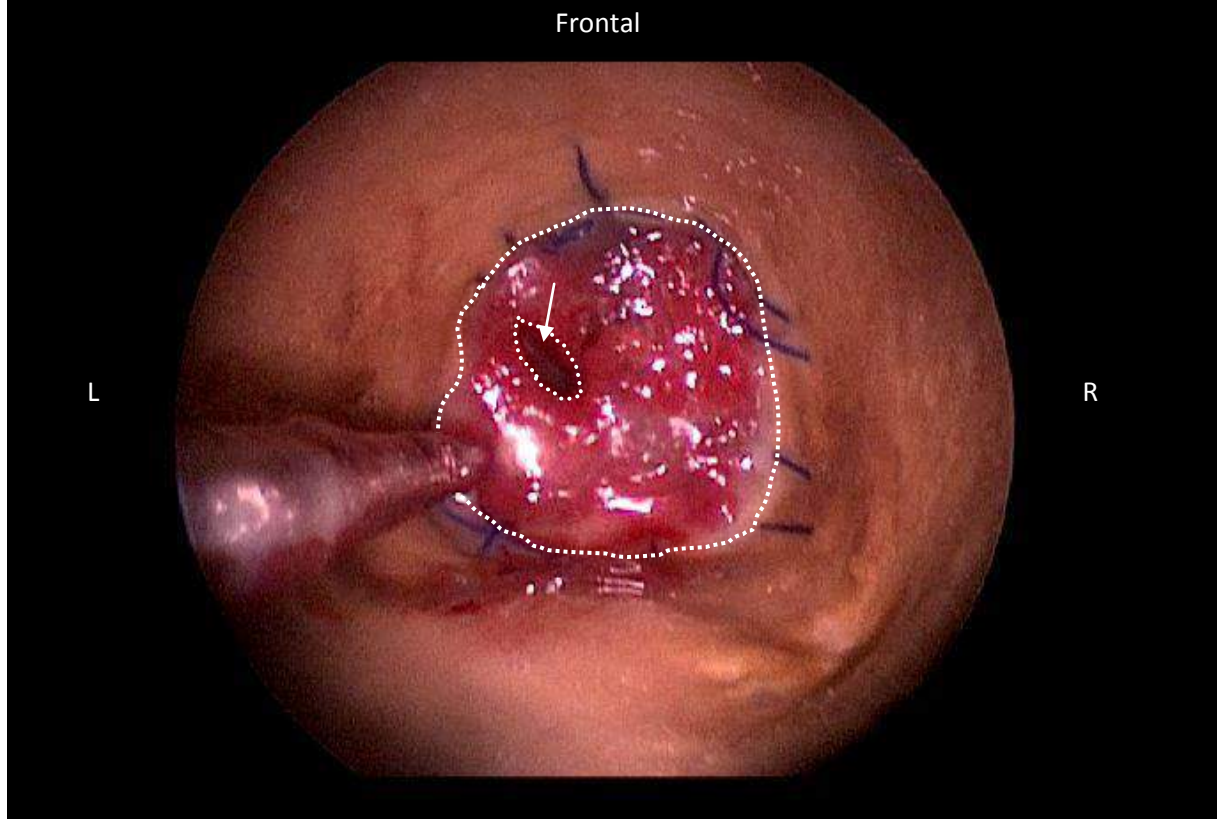


Figure 24. Nearly completely obstructed right main bronchus opening (small dotted area) blocking the right lung from being normally ventilated. Large dotted line the scaffold's distal edge. Note synthetic scaffold's inner wall without any covering epithelium, vascularization or tissue ingrowth 1 year after implantation, anastomotic (tissue uncovered) sutures. Severely pathological and dysfunctional airway.

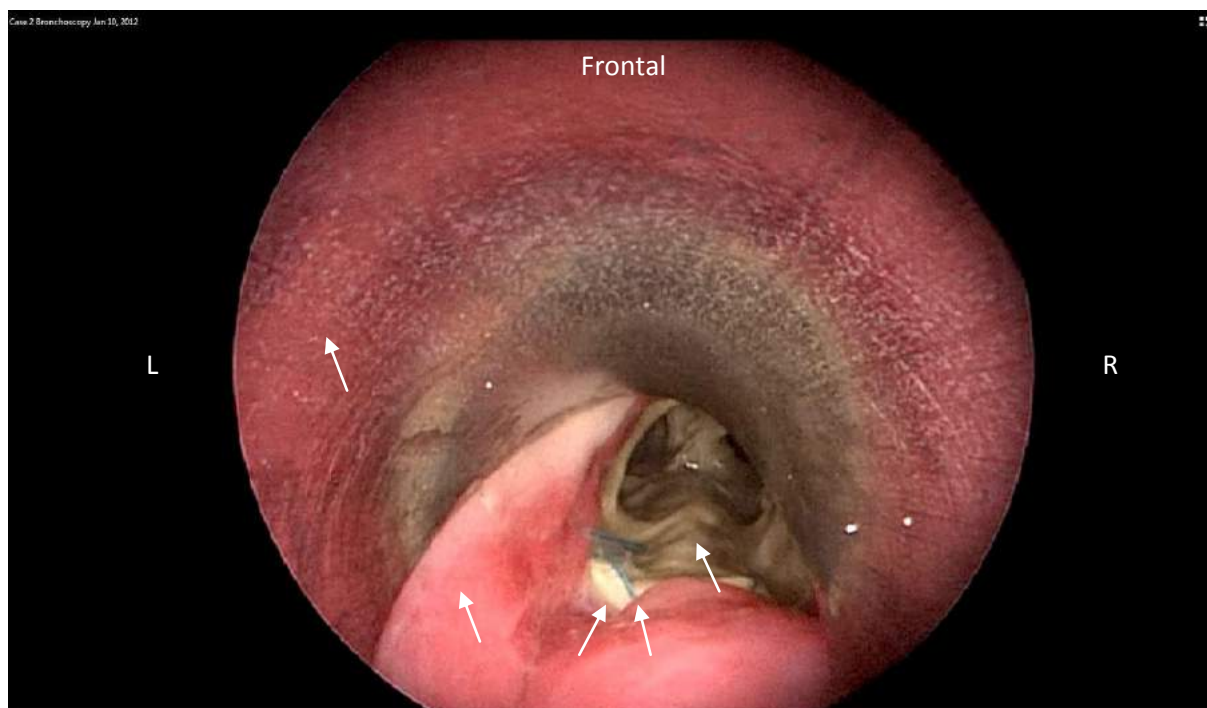


Figure 25. View from the upper (proximal) part of the native trachea (pink colored) down towards the synthetic scaffold (white-yellowish). Arrows from left to right: Inner wall of the bronchoscope, native normal tracheal (pink) vascularized tissue, upper edge of the synthetic scaffold, nude (tissue uncovered) blue sutures, upper part of nude synthetic scaffold without any covering epithelium, vascularization or tissue ingrowth.

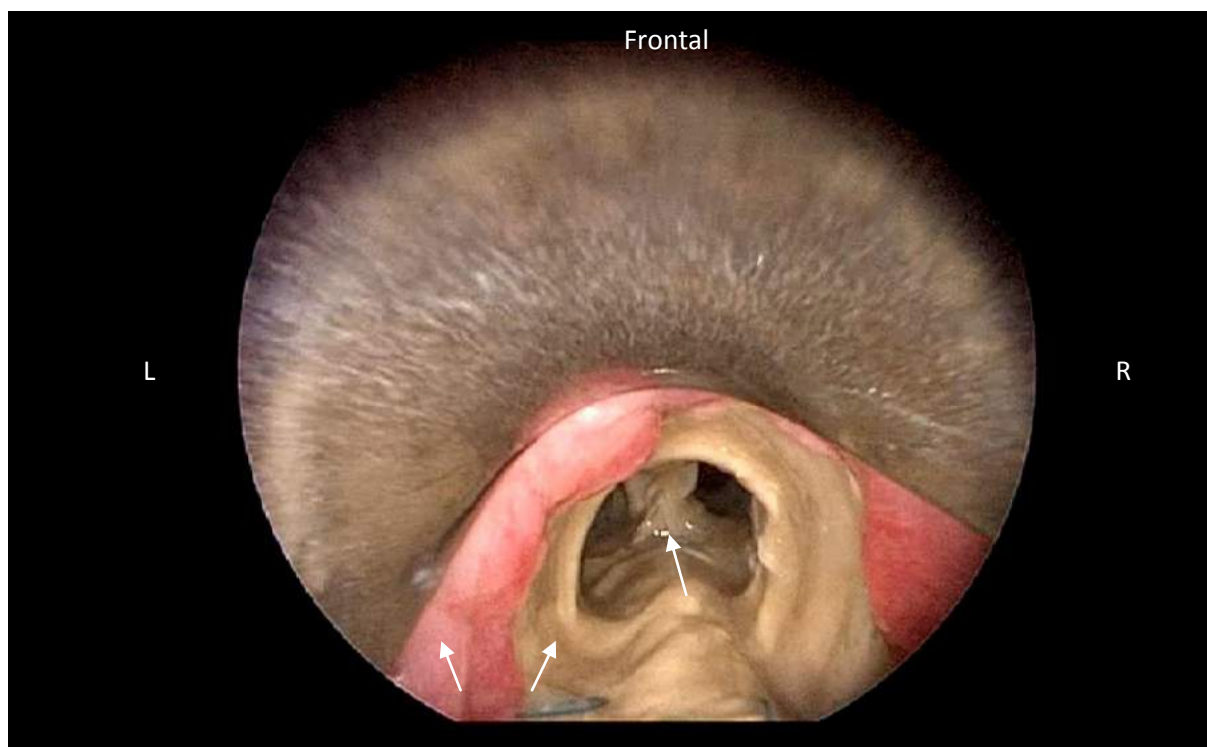


Figure 26. View advanced in distal direction. Arrows from left to right: native tracheal (pink) vascularized tissue, nude synthetic scaffold (white-yellowish) without any covering epithelium, vascularization or tissue ingrowth, synthetic carina with left and right synthetic main bronchus departures.

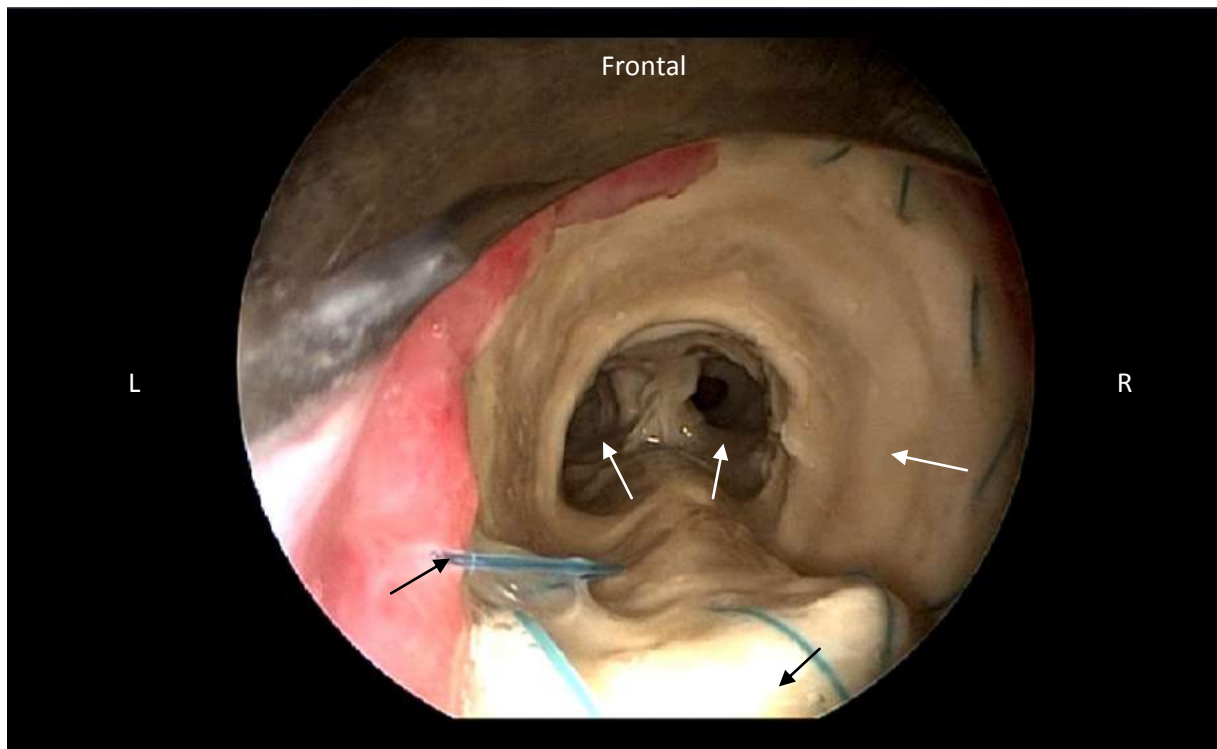


Figure 27. View into the nonviable synthetic scaffold. Arrows from left to right: nude (tissue uncovered) blue sutures, left and right synthetic main bronchus departures (white arrows), proximal (upper) edge of the synthetic scaffold, inner wall of synthetic scaffold (yellowish-white) without any covering epithelium, vascularization or tissue ingrowth.

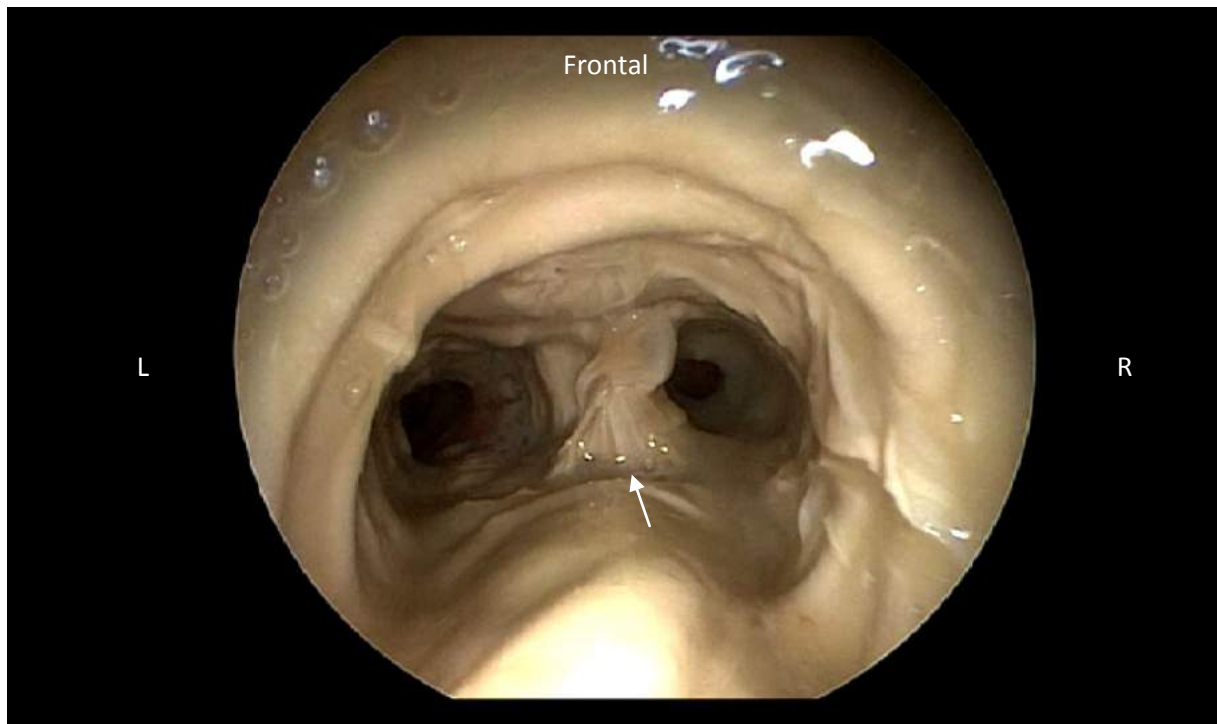


Figure 28. View into the nonviable synthetic scaffold without any covering epithelium, vascularization or tissue ingrowth. The exfoliation (arrow) on the inner scaffold wall is an "egg white precipitation" resulting from protein leakage into the synthetic airway and contains of proteins who lost its solubility due to environmental changes in the non-biological (synthetic) environment, precipitating forming a "paper towel" like structure, a pathological (even if principally a normal chemical reaction) in this location and has nothing to do with establishment of a normal airway epithelium and is not a type of cellular layer (see Biopsy report Jan. 10, 2012). Compare the non-vascularized and non-tissue covered (nonviable) scaffold with figure 6 above showing the inner wall of a normal viable trachea.

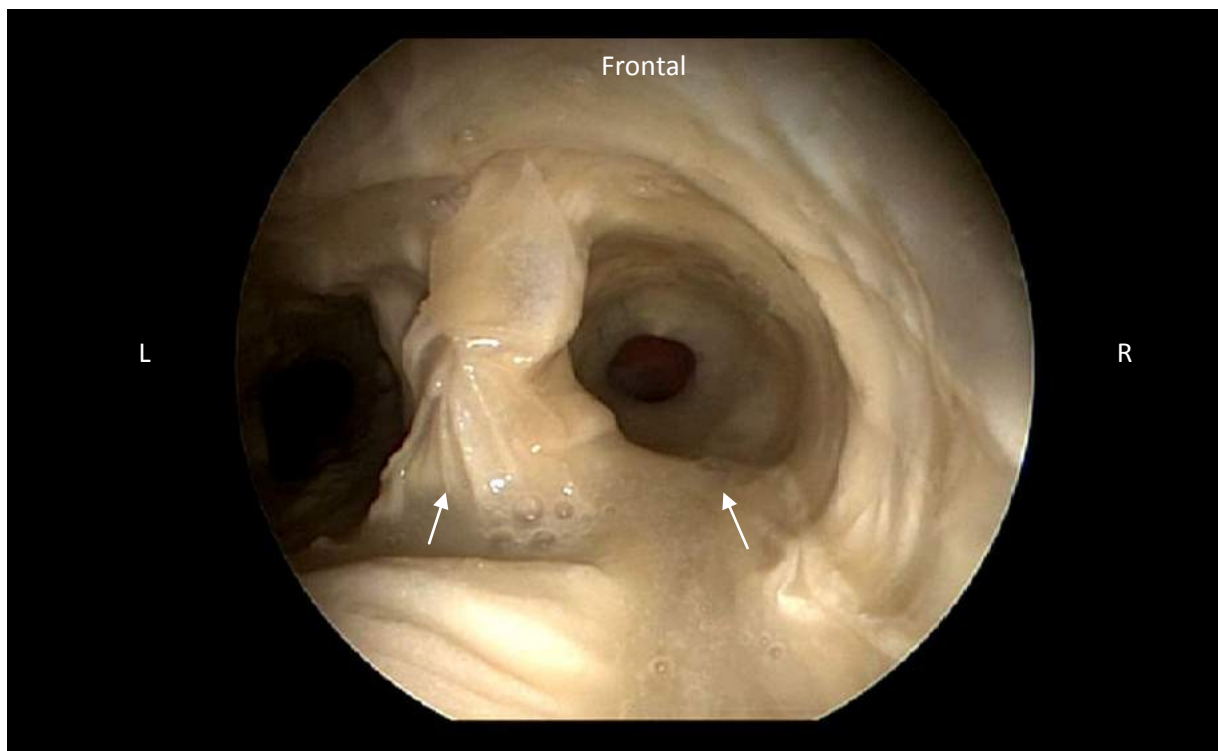


Figure 29. View into the synthetic scaffold without any covering epithelium, vascularization or tissue ingrowth. Arrows from left to right: Exfoliation on the inner wall of the scaffold, right synthetic main bronchus departure.

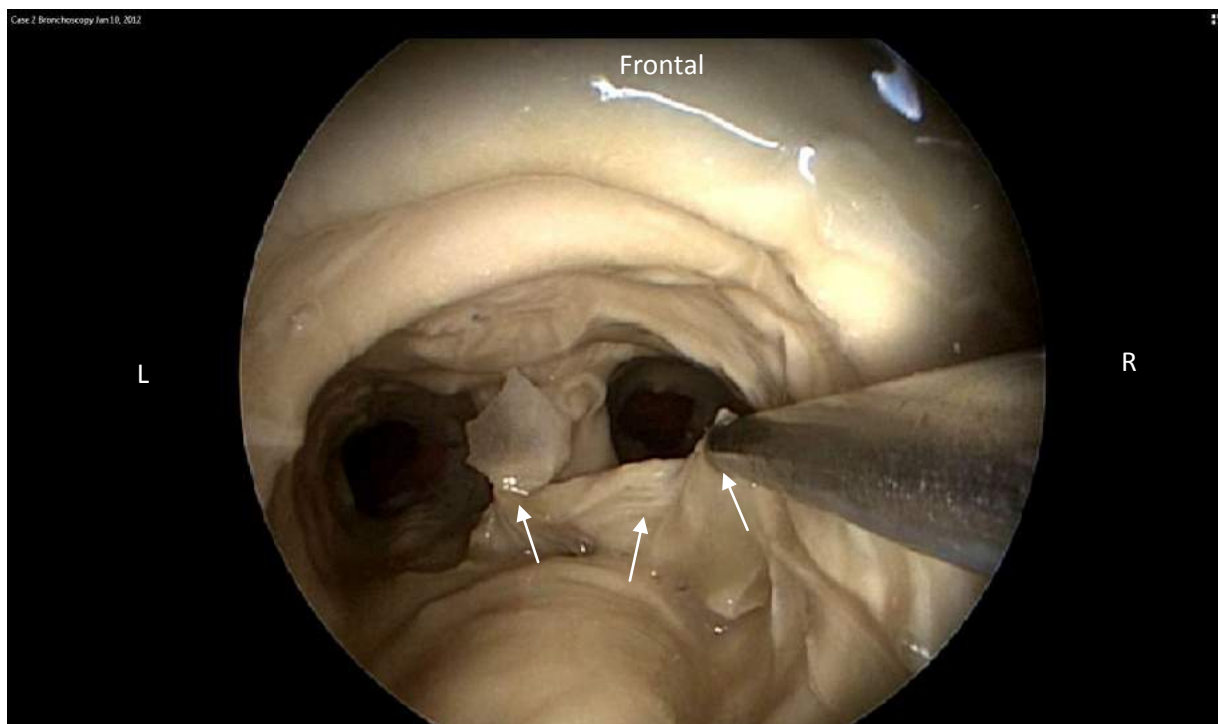


Figure 30. View into synthetic scaffold without any covering epithelium, vascularization or tissue ingrowth. Arrows from left to right: pathological exfoliation of the inner scaffold wall, bronchoscopy pincers gripping the exfoliation (precipitation) layer.

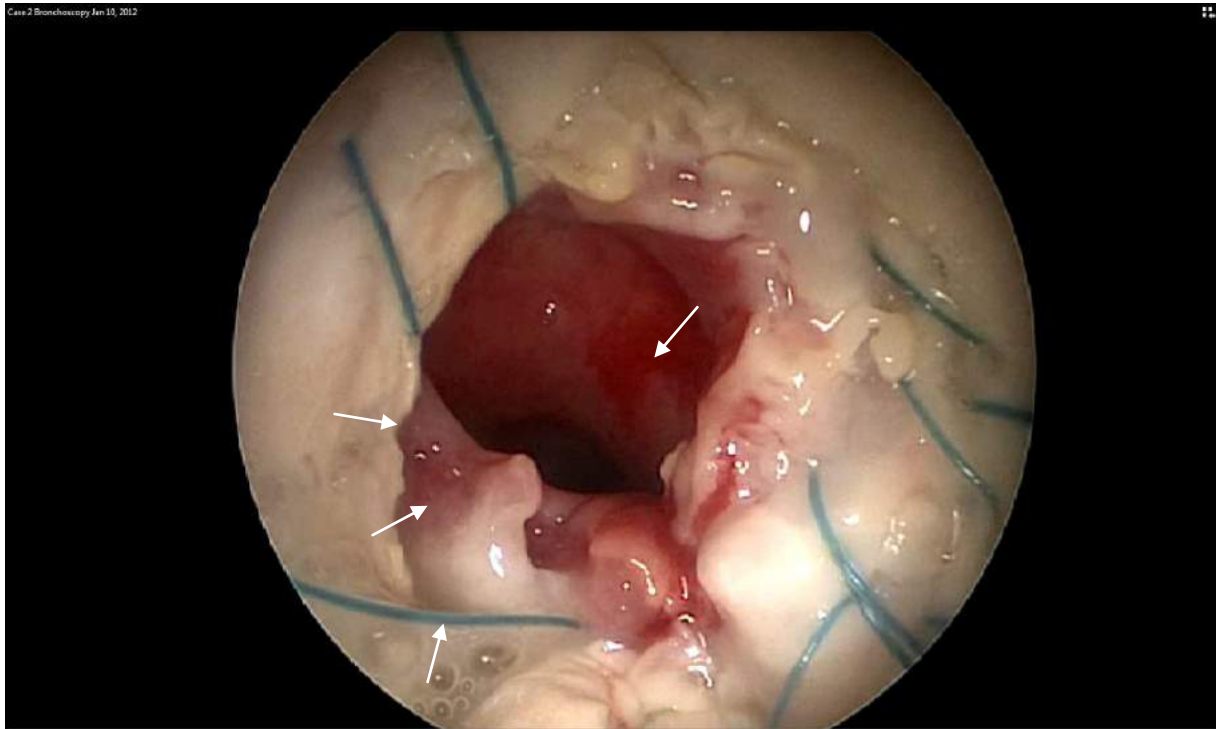


Figure 31. Right distal anastomosis (connection) between the synthetic scaffold's "right leg" and the rest of native right main bronchus (partly folded at 8 o'clock). Arrows from left to right: nude edge of synthetic scaffold without any tissue coverage or ingrowth, partly obstructing anastomotic granulation tissue (as sign of chronic pathological inflammation), loose blue nude (tissue uncovered) suture, native right main bronchus opening (white arrow) partly obstructed by anastomotic granulations from 4 to 9 o'clock.

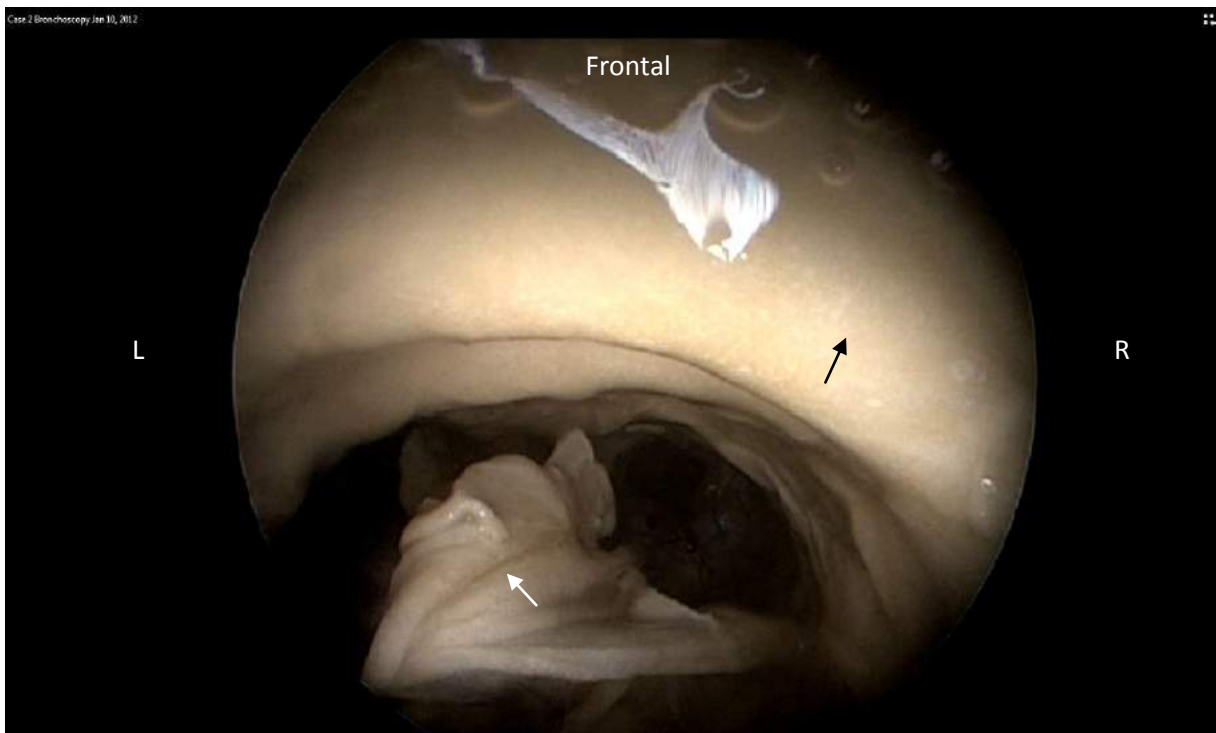


Figure 32. View from the upper part down into the synthetic scaffold. Bronchoscope pulled back from the right main bronchus up into the mid part of the synthetic trachea. Arrows from left to right: bronchoscopy pincers starting to remove the exfoliated inner layer of the synthetic scaffold, nude synthetic implant wall without any covering epithelium, vascularization (no visible vessels compare to figure 6 on p. 20) or tissue ingrowth.

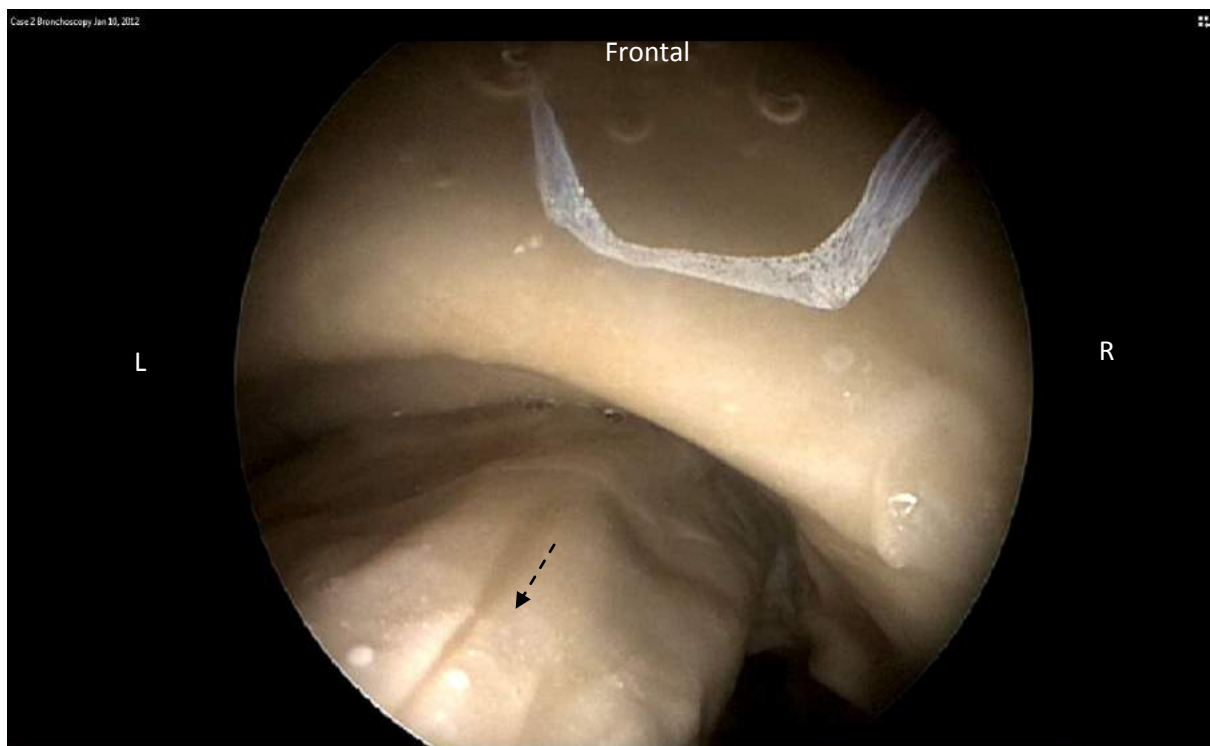


Figure 33. View into the synthetic scaffold. The whole frontal part of the scaffold's inner surface comes off when the exfoliation layer detaches as it is pulled further up to be removed. The dotted arrow shows the direction of the exfoliation detaching (being pulled out) from the inner wall.

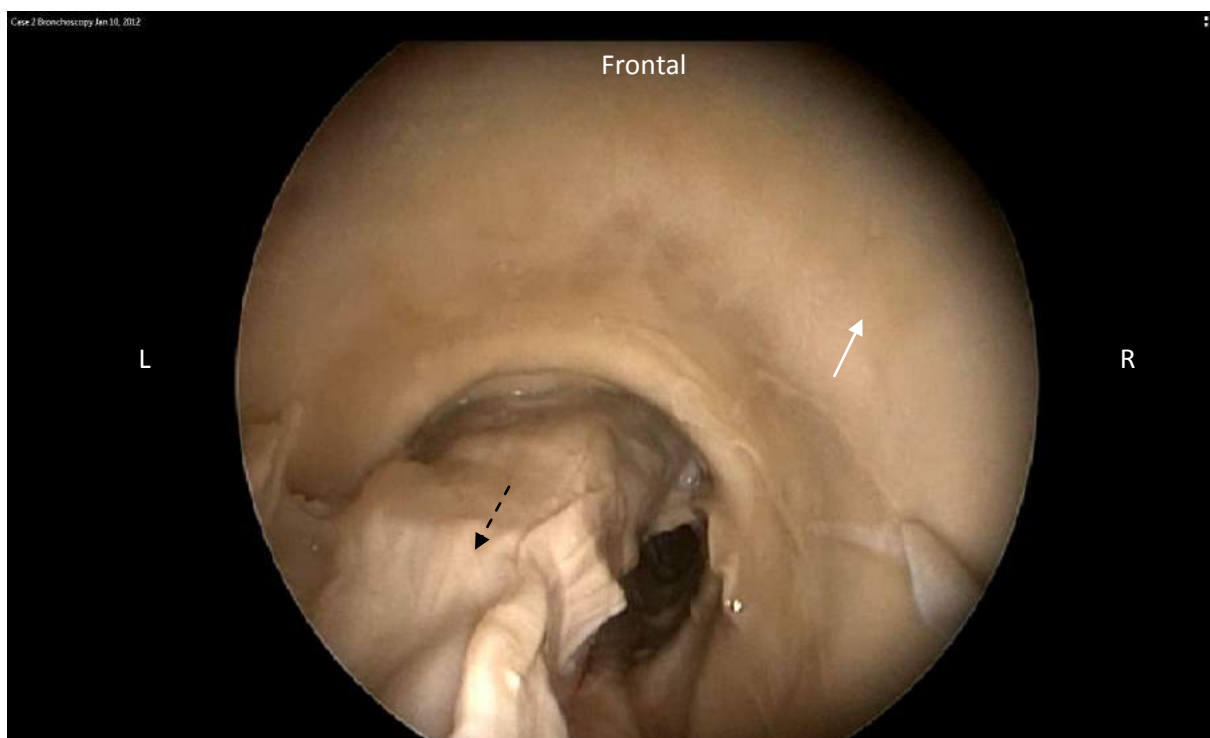


Figure 34. View into the synthetic scaffold. The whole scaffold's inner surface comes off when the exfoliation layer detaches as it is pulled further up to be removed. The dotted arrow shows the direction of the inner scaffold surface (exfoliation) detaching from the inner wall. Note the nude synthetic inner wall (white arrow) without any covering epithelium, vascularization or tissue ingrowth.

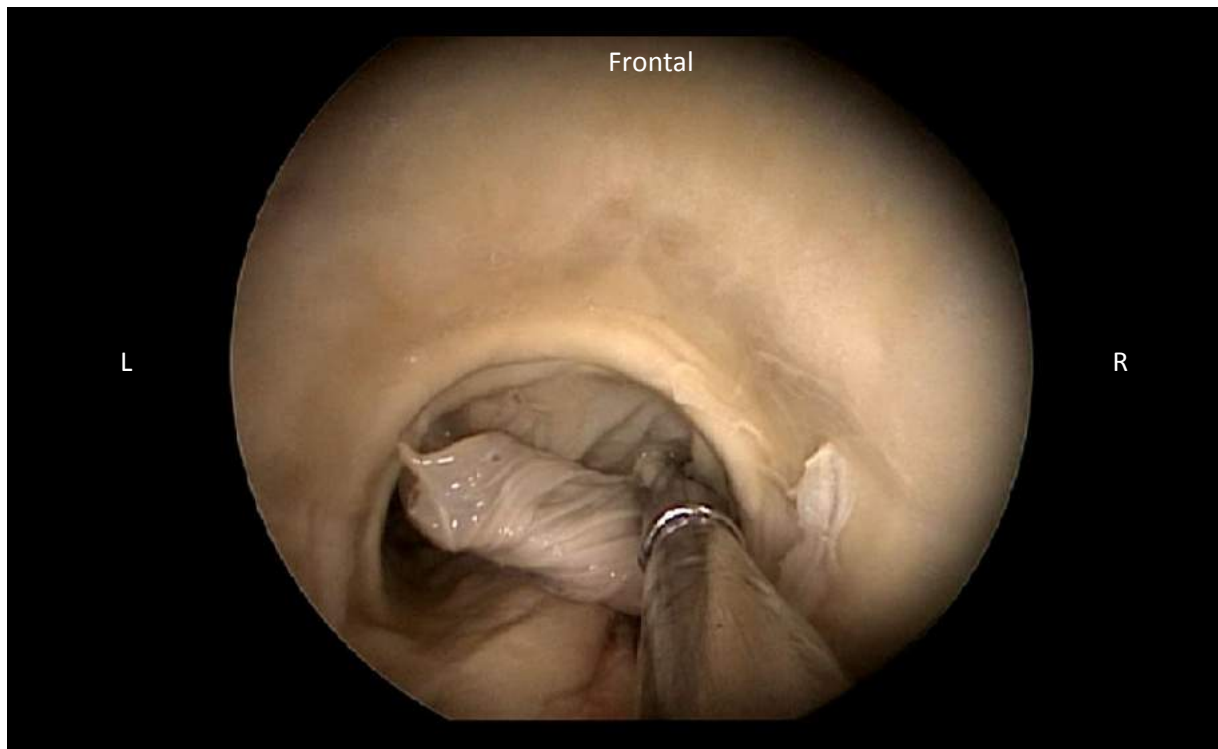


Figure 35. View into the synthetic scaffold. Bronchoscopy pincers further removing the inner surface layer of the synthetic scaffold. **A nonviable and completely dysfunctional synthetic tracheal scaffold (no tracheal regeneration, covering epithelium, vascularization or tissue ingrowth) is verified 8 weeks after implantation** (compare to the normal tracheal wall in figure 6 on p. 20).



Figure 36A. CT examination 2012-01-10, 8 weeks after implantation. Frontal view. Arrows: constriction of both distal connection sites between synthetic scaffold and native main bronchus openings (size mismatch between scaffold and connecting native right and left main bronchus openings).

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3. Protocol № 9, Resolution of the ethical commission, Ethical Commission, State Budgetary Educational Institution for Higher Education “Kuban State Medical University” of the Ministry of Health Care and Social Development of the Russian Federation, February 15, 2012, section “Russian Mega Grant Trachea Transplant Trial”,
<http://www.circare.org/info/pm/protocol9.pdf>
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Full English version: <http://www.circare.org/info/pm/fallet-macch-google-20160903.pdf>
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In Swedish: <http://www.svt.se/dokument-inifran-experimenten/>
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<http://www.svt.se/dokument-inifran/did-paolo-macchiarini-describe-his-experiments-truthfully-in-his-scientific-articles>
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 - b. Example # 2-the 2-month sample
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 - c. Example # 3 the 8-month sample
<http://www.svtplay.se/klipp/6465765/do-the-articles-of-paolo-macchiarini-reflect-reality-example-3-the-8-month-sample>
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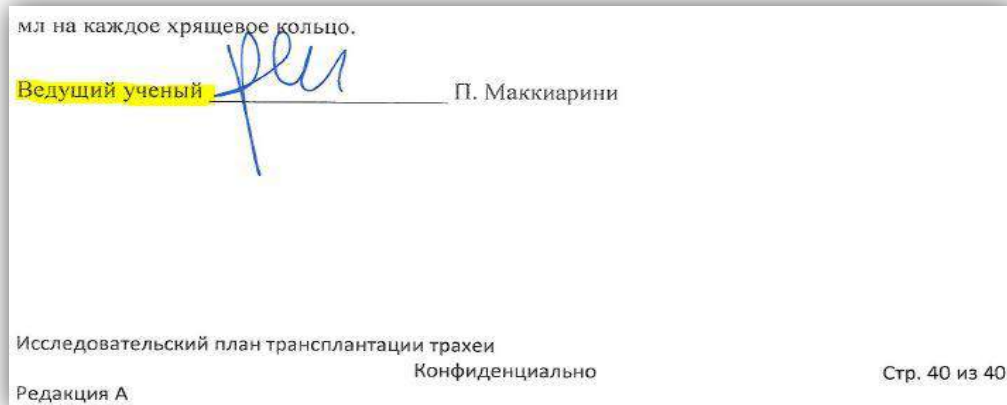
1.0 Клинические врачи-исследователи

1.1 Ведущий исследователь: д-р Паоло Маккиарини, Каролинский Институт, Стокгольм, Швеция

“1.0 Clinical doctors – researches”

1.1 Leading researcher: Dr Paolo Macchiarini, Karolinska Institutet, Stockholm, Sweden”

PM signing the protocol on p. 40:



“Leading scientist ____ [PM:s signature] ____ P. Macchiarini”

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<http://www.circare.org/info/pm/web-amendment-to-formal-appeal-24sep2014-2.pdf>

- Table 3: <http://www.circare.org/info/pm/web-amendment-tables-1-3-24sep2014.pdf>

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37. Dr. Macchiarini’s response to the external review, “Re: Statement of opinion on assignment ref. 2-2184/2014” June 26, 2015, p. 2, sections 4-5.

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41. **The fraudulent 6 trachea articles by PM:** “Formal Appeal for an Investigation of Scientific Misconduct. To the President of Karolinska Institutet, Stockholm Aug. 18, 2014.”
<http://retractionwatch.com/wp-content/uploads/2014/12/Letter-to-Prof-Hamsten.pdf>
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<http://retractionwatch.com/wp-content/uploads/2014/12/Analysis-of-Clinical-Outcome-of-Synthetic-Tracheal-Transplantation.pdf>
 - **The fraudulent “proof-of-concept article”:** Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study. **Jungebluth P**, Alici E, Baiguera S, Blomberg P, Bozóky B, Crowley C, Einarsson O, Gudbjartsson T, Le Guyader S, Henriksson G, Hermanson O, Juto JE, Leidner B, Lilja T, Liska J, Luedde T, Lundin V, Moll G, Roderburg C, Strömblad S, Sutlu T, Watz E, Seifalian A, **Macchiarini P**. *Lancet*. 2011 Dec 10; 378(9808):1997-2004.
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| FRÅN | STOCKHOLMS LÄNS LANDSTING Karolinska Universitetssjukhuset B: 11001-341-306 Karolinska Universitetslaboratoriet S: 11001-341-306 Klin Pat/Cyt lab F: 11001-341-306 Tfn R: 1026-7510367-9 L: T12760-11 | SVAR PATOLOGI/CYTOLOGI Sida 1 (1) |
| TILL | Karolinska Universitetssjukhuset Thoraxkliniken, Solna N 13/23 Thorax 171 76 Stockholm | Regnr T12760-11 |
| | Provtagningstid: 2011-08-04 10:00 Ankomstid lab: 2011-08-04 | Remittent: Karl-Henrik Grinnemo SNABBSVAR: Tfn: 0700568440 |
| | Preparatets natur: Syntetisk trachea med inodlade autologa celler Frågeställning: Strukturell översikt av det syntetiska graftet, extracellulära matrix proteiner? engraftade celler? Anamnes: Det vi skickar för undersökning är samma graft (syntetisk trachea) som implanterades i pat i juni i år. Det här graftet är syntetiskt och har samodlats med autologa stamceller. Vi är därför intresserade att studera ur strukturen på graftet ser ut när det samodlats med celler och vill därför ha följande analyser: 1) HTX 2) Giemsa 3) Mason Trichrome 4) Verhoeffs elastic staining. Materialet består av 3 olika olika delar: vä bronk, hö bronk samt trachea. Preparaten ska paraffinbäddas Strålbehandlad: Nej | |
| | SVAR UTLÅTANDE 2011-09-06 T12760/2011 2011-442098 I snitten från de insända tre rör syntetisk trachea som representerar vänster bronch, höger bronch samt trachea ses likartad bild av ej färgbart poröst material med dubbelbrytande karaktär. På ytan av detta syntetiska material kan endast ett fåtal smala mesenkymala celler förmodas. Något välutvecklat cellager kunde ej identifieras. Tillägg: Vid specialfärgning och i ytterligare utskurna bitar framkomer ej mer detekterbart material som vid ovan. DIAGNOS Se ovan. BIOBANKSINFORMATION Patienten vill inte att provet lagras, men svarstalong saknas eller har ännu ej registrerats. Provet lagras tills vidare i avvaktan på att svarstalong inkommer/registreras. Bela Bozoky 2011-12-01 -----slut----- | |

Biopsy from the synthetic scaffold immediately before implantation on June 9, 2011. The report describes: *"In the sections from the three samples of the synthetic trachea which represent the left bronchus, right bronchus and trachea a similar picture of non-stainable porous material with double refractory characteristics. On the surface of this synthetic material only a few thin mesenchymal cells can be suspected. No well-developed cell layer could be identified."*

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| TILL | Karolinska Universitetssjukhuset Thoraxkliniken, Solna N 13/23 Thorax 171 76 Stockholm | Regnr T13678-11 | |
| Provtagningsstid: | 2011-08-24 08:00 | Remittent: | Karl-Henrik Grinnemo |
| Ankomststid lab: | 2011-08-25 | SNABBSVAR: | Tfn: 0858582443 |
| Preparatets natur: | Syntetisk trachea graft | | |
| Frageställning: | Cellinväxt? Extracellulärmatrix struktur? | | |
| Anamnes: | Pat som op med trachea graft i juni. Detta är ett syntetiskt graft coatat med mesenchymala stamceller. Vi har tagit provbitar före implantation som vi vill få analyserade angående cellinväxt, matrix struktur? Jag hänvisar till telefonkontakt med Överläkare Bela Bozoky. Var snäll och meddela läkaren att proverna har anlänt. Strålbehandlad: Nej | | |
| <hr/> | | | |
| SVAR | | | |
| UTLÅTANDE | | | |
| 2011-08-26 T13678/2011 | | | |
| 2011-442098 | | | |
| I snitten från de inslädda fyra små vävnadsbitarna kan ett poröst främmande material av syntetisk graft identifieras. Några detekterbara cellkomponenter eller matrixstruktur ses ej. | | | |
| DIAGNOS | | | |
| Se ovan. | | | |
| BIOBANKSINFORMATION | | | |
| Patienten vill inte att provet lagras, men svarstalong saknas eller har ännu ej registrerats. Provet lagras tills vidare i avvaktan på att svarstalong inkommer/registreras. | | | |
| Bela Bozoky 2011-09-02 | | | |
| -----slut----- | | | |

Biopsy from the synthetic scaffold immediately before implantation on June 9, 2011. The report describes: *"In the sections from the four delivered small tissue samples a porous foreign material of synthetic graft can be identified. Any detectable cellular components or matrix structures are not seen."*

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| FRÅN | Karolinska Universitetssjukhuset Karolinska Universitetslaboratoriet Klin Pat/Cyt lab Tfn | B: 11002-521-SV1 S: 11002-521-SV1 F: 11002-521-S03 R: 1026-8518486-7 L: A1006-12 | | |
| TILL | Karolinska Universitetssjukhuset Öron-,näs- och halskliniken, Huddinge Avdelning B82 141 86 STOCKHOLM | Regnr A1006-12 | | |
| Provtagningsstid: 2012-02-14 13:37 Ankomststid lab: 2012-02-14 | | Remittent: Jan-Erik Juto Tfn: | | |
| Preparatets natur: Borstprov från lumen mitt i graft i trachea. Frageställning: epitelfynd? luftvägsepitel?? annat?? Anamnes: Op kliniskt radikalt för ett recidiv av mucoepidermoid cancer i distala trachea och proximala bronker. Har ett "stamcells-preparerat" graft av ngn slags plast inopererat som ersättning för defekten. Nu kontrollskopi. Borstprov taget ifrån graften ngt ovan carinahöjd i bakväggen ovan avgången för graften ned i hö huvudbronk. Strålbehandlad: Ja, år 2010 | | | | |
| SVAR | | | | |
| UTLÅTANDE 2012-02-15 A1006/2012 2011-442098 | | | | |
| I centrifugat av insänd sköljvätska ses inget nämnbart epitelialt material. | | | | |
| DIAGNOS Se ovan. | | | | |
| BIOBANKSINFORMATION Provet får användas för samtliga, enligt biobankslagen, godkända ändamål. | | | | |
| Anders Hjerpe 2012-02-21 | | | | |
| -----slut----- | | | | |

Brush biopsy at Feb. 14, 2012, 8 months after implantation. The report describes: "Brush biopsy from the lumen in the middle of the graft in trachea. In the centrifuged fluid of delivered brush biopsy fluid, **no significant epithelial material can be found.**"

This finding contradicts any presence of a healthy mucosa 8 months after transplantation. A normal mucosa should yield normal (airway) epithelial cells upon brush sampling.

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| STOCKHOLMS LÄNS LANDSTING | | SVAR PATOLOGI/CYTOLOGI | | Sida 1 (1) | | | | |
| FRÅN | Karolinska Universitetssjukhuset Karolinska Universitetslaboratoriet Klin Pat/Cyt lab Tfn | B: 11002-521-SV1 S: 11002-521-SV1 F: 11002-521-S03 R: 1026-8518380-2 L: T1851-12 | | | | | | |
| TILL | Karolinska Universitetssjukhuset Öron-, näs- och halskliniken, Huddinge Avdelning B82 141 86 STOCKHOLM | Regnr: T1851-12 | | | | | | |
| Provtagningsstid: 2012-02-14 13:30 Ankomststid lab: 2012-02-15 | | Remittent: | Jan-Erik Juto Tfn: | | | | | |
| Preparatets natur: | biopsier från vä huvudbronker samt från trachea. | | | | | | | |
| Frageställning: | granulationsvävnad? mucoepidermoid cancer??? | | | | | | | |
| Anamnes: | Op kliniskt radikalt för ett recidiv av mucoepidermoid cancer. Nu kontrollskopi med borttagande av granulationsvävnad i trachea och vä huvudbronk. Burk nr 2 granulationsvävnad vä huvudbronsanastomos Burk nr 4 granulationsvävnad från anastomos upptill i trachea. Strålbehandlad: Ja, år 2010 | | | | | | | |
| SVAR | | | | | | | | |
| UTLÅTANDE | | | | | | | | |
| 2012-02-17 T1851/2012 | | | | | | | | |
| 2011-442098 | | | | | | | | |
| Biopsier från vänster huvudbronk samt trakea. I bägge fraktionerna ses rikligt med granulationsvävnad med måttlig plasmocytär infiltration. Ytepitelet utgörs av skivepitel som ställvis är eroderat med granulocytangrepp, ställvis är den helt avstött med sårbildning, och fokalt ses enstaka atypiska skivepitelceller, dessa bedöms dock snarast vara reaktivt betingade. Inga hållpunkter för recidiv av patientens tidigare opererade mucoepidermoida cancer. | | | | | | | | |
| DIAGNOS | | | | | | | | |
| Se ovan. | | | | | | | | |
| BIOBANKSINFORMATION | | | | | | | | |
| Provet får användas för samtliga, enligt biobankslagen, godkända ändamål. | | | | | | | | |
| Katalin Dobra 2012-02-17 | | | | | | | | |
| -----slut----- | | | | | | | | |

Biopsy at Feb. 14, 2012, 8 months after implantation. The report describes: "Biopsies from the left main bronchus and from the trachea. "Biopsies from left main bronchus as well as trachea. In both fractions one can see a lot of granulation tissue with some plasmocyte infiltration. The surface epithelium consists **partially of squamous epithelium which is eroded by granulocytic attack, partially completely rejected with scab formation, and focally single atypical squamous epithelial cells are seen but these seem to be mostly of a reactive character.**"

N.B. these biopsies were *not* taken from the synthetic scaffold's inside but at the border zone between native trachea and scaffold thereby not verifying any tissue ingrowth or epithelialization in the scaffold, however verifying chronic inflammation as sign of the plastic scaffold not healing into the patients native tracheal tissue.

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| FRÅN | STOCKHOLMS LÄNS LANDSTING Karolinska Universitetssjukhuset B: 11002-521-SV1 Karolinska Universitetslaboratoriet S: 11002-521-SV1 Klin Pat/Cyt lab P: 11002-521-S03 Tfn R: 1026-9099262-7 L: T5723-12 | SVAR PATOLOGI/CYTOLOGI | Sida 1 (1) |
| TILL | Karolinska Universitetssjukhuset Öron-,näs- och Halskliniken, Huddinge Avdelning B82 141 86 STOCKHOLM | Regnr T5723-12 | |
| Provtagningsstid: 2012-05-22 13:45 Ankomststid lab: 2012-05-23 | | Remittent: Jan-Erik Juto Tfn: | |
| Preparatets natur: biopsier från granulationer höger huvudbronk och trachea samt från graft i trachea Frågeställning: granulationer? malignitetstecken? bronkial-epitel i graft? Anamnes: Op 1 år sedan för malignitet. Kontroll efter 1 år Burk 2; granulationer från anastomos i hö huvudbronk samt anastomos i trachea. Burk 3 biopsi från vänster sida ovan carinaområdet mitt i graft. Strålbehandlad: Ja, år 2010 | | | |
| SVAR UTLÅTANDE 2012-06-01 T5723/2012 2011-442098 | | | |
| Inkommer material i två fraktioner här markerat II respektive III. II: Vävnadsbitar bestående av skivepitelklädd slemhinna med uttalad ospecifik inflammation i stromat. Betydande eosinofili. Intet malignt. III: Av allt att döma helt acellulära strukturer, rester av själva graftet? DIAGNOS Se ovan. BIOBANKSINFORMATION Provet får användas för samtliga, enligt biobankslagen, godkända ändamål. Anders Hjerpe 2012-06-05 -----slut----- | | | |

Biopsy at May 22, 2012, 1 year after implantation. The report describes: "Sample containing biopsies from granulations right main bronchus and from **tracheal graft in trachea. Box 3; biopsy from the left side above the area of carina in the middle of the graft.**" Having judged everything, nothing but an acellular structure is seen, residual components of the graft itself?"

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| STOCKHOLMS LÄNS LANDSTING | | SVAR PATOLOGI/CYTOLOGI | | Sida 1 (1) |
| FRÅN | Karolinska Universitetssjukhuset Karolinska Universitetslaboratoriet Klin Pat/Cyt lab | B: 11001-111-M01 S: 11001-111-M01 F: 11001-341-306 R: 1026-8042610-7 L: EX3560-11 | | |
| Tfn | Stockholm Care Ab 113 82 Stockholm | | | |
| TILL | Karolinska Universitetssjukhuset Lung Allergi kliniken, Solna Lungdagvård Thorax N1:02 171 76 Stockholm | Tel: Regnr EX3560-11 | | |
| Provtagningsstid: | 2011-11-22 08:55 | Remittent: | Stephanie Mindus | |
| Ankomststid lab: | 2011-11-22 | SNABBSVAR: | Tfn: 73344 | |
| Preparatets natur: | Skyddade borstprov OBS! Till Johan Veide innan infärgning | | | |
| Frageställning: | Typ av celler? Viabla bronkialepitelceller? Tacksam för Immunohistokemi | | | |
| Anamnes: | Adenocystisk cancer men direktinväxt i trachea. Artificiell trachea. Op för 6 dygn sedan. Endobronchiellt tillfredställande slihinnbild och suturstatus. | | | |
| | Skyddade borstprov | | | |
| | Nr 1: Proximala suturranden | | | |
| | Nr 2: Distala suturranden | | | |
| | OBS! Till Johan Veide innan infärgning | | | |
| | Strålbehandlad: Nej | | | |
| SVAR | | | | |
| UTLÅTANDE | | | | |
| 2011-12-07 EX3560/2011 L 2011-62 | | | | |
| BORSTPROV: | | | | |
| Fyra insända utstryk utan särskild märkning förutom namn och reservnummer. Samtliga utstryk rutinfärgades i omgångar. Materialet består till större delen av slem och slemklumpar samt granulocyter. Därutöver förekommer en del benigna skivepitelceller, troligen kontamination från övre luftvägar. Enstaka benigna bronkepitelceller av ordinarie utseende förekommer. Man finner även en hel del degenererade eller nekrotiska cylindelformade celler, sannolikt bronkepitel, vilka dock är alltför degenerativt förändrade för bedömning. Inga maligna celler identifierade. | | | | |
| DIAGNOS | | | | |
| Benign cytologi enligt ovan, med sparsam förekomst av benigna viabla bronkepitelceller. | | | | |
| BIOBANKSINFORMATION | | | | |
| Patienten är vid provtagningsstillfället oförmögen att ta ställning till lagring av prov. Provet lagras tills vidare i avvaktan på uppgift om samtycke. | | | | |
| Johan Wejde, Överläkare 2011-12-08 | | | | |
| -----slut----- | | | | |

Brush biopsy at day 5, Nov. 22, 2011. Biopsy location: **"Nr 1: Proximal suture line"** and **"Nr 2: Distal suture line"**. The report describes: *"The material consists of mostly mucus and granulocytes. Furthermore some benign squamous epithelial cells, **probably contamination from the upper airway**. Single benign bronchus epithelial cells of typical phenotype. Also found a good deal of degenerated or necrotic cylinder cells, probably bronchus epithelia, **but far too degenerated changes in order to allow for analysis.**"*

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| FRÅN | STOCKHOLMS LÄNS LANDSTING Karolinska Universitetssjukhuset B: 11001-111-M01 Karolinska Universitetslaboratoriet S: 11001-111-M01 Klin Pat/Cyt lab F: 11001-341-306 Tfn R: 1026-8042598-4 L: K18486-11 | | SVAR PATOLOGI/CYTOLOGI Sida 1 (1) | |
| TILL | Karolinska Universitetssjukhuset Lung Allergi kliniken, Solna Lungdagvård Thorax N1:02 171 76 Stockholm | | Stockholm Care Ab 113 82 Stockholm Tel: Regnr K18486-11 | |
| Provtagningsid: 2011-11-22 08:54 Ankomstid lab: 2011-11-22 | | | Remittent: Stephanie Mindus SNABBSVAR: Tfn: 73344 | |
| Preparatets natur: PX huvudcarina OBS! Till Johan Veide inna infärgning! Frågeställning: Typ av celler? Viabla bronkialepitelceller? Tacksam för Immunohistokemisk bed. | | | | |
| Anamnes: Adenocystisk cancer men direktinväxt i trachea. Artificiell trachea. Op för 6 dygn sedan. Endobronchiellt tillfredställande slihinnbild och suturstatus. PX huvudcarina OBS! Till Johan Veide inna infärgning enligt telök. Strålbehandlad: Nej | | | | |
| <hr/> | | | | |
| SVAR | | | | |
| UTLÅTANDE 2011-11-24 K18486/2011 L 2011-62 | | | | |
| Px huvudcarina. Materialet representeras av minimala px-fragment som utgöres av små koagler med enstaka inbakade celler. Otillräckligt material. | | | | |
| DIAGNOS Icke-representativt material. | | | | |
| BIOBANKSINFORMATION Patienten är vid provtagningsstillfället oförmögen att ta ställning till lagring av prov. Provet lagras tills vidare i avvaktan på uppgift om samtycke. | | | | |
| Georg Jaremko, Överläkare 2011-11-24slut..... | | | | |

Biopsy at day 5, Nov. 22, 2011. Biopsy from the main carina [scaffold's synthetic carina].
 Description of the findings: ***"non-representative material."***

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| Karolinska Universitetssjukhuset Öron-, näs- och halskliniken, Solna Mottagning 171 76 Stockholm tel: 08-517 768 60 fax:08-517 742 65 | 11001521M02 | JOURNALBLAD | Utskrifts-id: | Sida 1 av 1 |
| | | 2011-62 | KOPIA | |
| | | Stockholm Care Ab 113 82 Stockholm Tel: | | |
| * 2011-11-28 18:37 Richard Kuylensstierna, Läk S - ÖNH mott (signerad) | | | | |
| Rättelse: 2012-01-10 10:19 Jan-Erik Juto, Läk | | | | |
| Rättelse: 2012-01-10 10:17 Jan-Erik Juto, Läk | | | | |
| OPERATION | | | | |
| Preop. bedömn. | Pat har blivit successivt sämre. Högfebril och infiltrat på lungorna. Finns även lite luft omkring den nedre anastomoserna och i mediastinum. Syrgasberoende. Juto har varit i kontakt med prof Macchiarini. Man rekommenderar re-trakeostomi. Pat lättsederad med Fentanyl. | | | |
| Operations- åtgärds kod | GBB00 Trakeostomi UGC12 Flexibel bronkoskopi ZXD00 Akut operation | | | |
| Operatör | Richard Kuylensstierna[ny text >>]Jan-Erik Juto[<< ny text] (läk) /1mwj/[ny text >>] /1f3x/[<< ny text] | | | |
| Operatör 2 | [ny text >>]Richard Kuylensstierna (läk) /1mwj/ [<< ny text] | | | |
| Operationsberättelse | Trakeostomisåret står öppet och är infekterat. Rengör i och omkring såret. Med Carléns hakar visualiseras kanalen ner till trakea som ligger djupt. Man kan se den övre anastomosraden genom stomat. En 8:ans portex med kuff lirkas ner i trakea. Kan därefter suga rent. Övergår så till bronkoskopi. Med fiberteknik går ner via den nyinsatta kanylen. Måttligt med sekret i anastomoserna men desto mer längre ner i framförallt hö lunga. Suger rent där till odling. Sekretet är blodtillblandat purulent. På vä sida ser det något bättre ut. Det förefaller endoskopiskt ganska tätt i de nedre anastomoserna. Själva transplantalet står öppet och några tecken på slemhinneinväxt etc finns inte än. Ingreppet avslutas. Förband. Lite syrgas på kanylen har pat 100% saturation. | | | |
| ----- slut utskrift ----- | | | | |

Bronchoscopy at day 11, Nov. 28, 2011, by senior ENT-physician with full report stating:
"...and there are no signs of tissue ingrowth yet."

| | | | | |
|--|--|---|--------------|-------------|
| Karolinska Universitetssjukhuset Öron-, näs- och halskliniken, Huddinge Avdelning B82 141 86 STOCKHOLM tel: 08-585 877 91 fax: 08-585 873 25 | 11002521SV1 | JOURNALBLAD | Utskr.id: v | Sida 1 av 1 |
| | | 2011-62 | KOPIA | |
| | | Stockholm Care Ab 113 82 Stockholm Tel: | | |
| 2012-01-10 11:55 Jan-Erik Juto, Läk H - ÖNH-avd B82 (läst) | | | | |
| OPERATIONSBERÄTTELSE | | | | |
| Patientansvarig läkare | Jan-Erik Juto (läk) /1f3x/ | | | |
| Operatör | Jan-Erik Juto (läk) /1f3x/ | | | |
| Operatör 2 | Paolo Macchiarini. | | | |
| Diagnos enl ICD-10 | C339 Malign tumör i luftstrupen | | | |
| Operations- åtgärds kod | UGC05 Rigid bronkoskopi med biopsi från bronk eller trakea | | | |
| Operationsförlopp | <p>Jetventilation. Går ner med ett stelt 7,5 bronkoskop och optikkamera till stapel. Hela op-proceduren dokumenteras. Kommer ner till övre anastomosranden mellan graft och trakea. Suturer är väl synliga relativt och det var egentligen ingen granulationsväxt här. Man ser i carinaområdet på graften en exfoliering av ytlager i graften. Detta borttages med tång och sändes separat för undersökning. Jag tittar ner på vä sida och det finns en del sekret distalt i vä bronken som suges rent. Det finns lite granulationer i anastomosen vä bronk medialt, dessa lämnas, de är lättblödande, dock ej speciellt lumeninskränkande.</p> <p>Går över på hö sida och här finns en viss stenosering av granulationsvävnad i anastomosnivån. Suturer synliga. Man kan se avgången för ovanlobsbanken framåt och något åt hö och det finns en del någorlunda klart sekret som suges distalt i bronkträdet. Går sedan upp och på professor Macchiarinis önskemål togs dels biopsier mitt i graften på vä sida snett bakåt och även borstprov togs från graften. Härfter görs borstprov från hö och vä underlob. Prover skickas för svampodling, bakterieodling och cytologi på celler PAD. Efter rensugning avslutas op.</p> | | | |
| ----- slut utskrift ----- | | | | |

Bronchoscopy at 8 weeks, Jan. 10, 2012. The report describes: ***“Exfoliation of the outer layer of the graft. Sutures are clearly visible”*** [at the upper and both distal anastomotic sites]. A detailed report (written by a senior ENT-physician) containing no description of any signs or presence of tissue ingrowth in the synthetic scaffold. Clearly visible sutures verify no tissue ingrowth from the anastomosis sites. The absence of any tissue ingrowth and vascularization (completely dysfunctional synthetic scaffold) is also clearly verified by the full bronchoscopic recording of the very same procedure. PM (registered as the surgeon nr 2 in the report) was participating in the procedure deciding the biopsy locations from the middle inner part of the graft.

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| FRÅN | STOCKHOLMS LÄNS LANDSTING Karolinska Universitetssjukhuset B: 11002-521-SV1 Karolinska Universitetslaboratoriet S: 11002-521-SV1 Klin Pat/Cyt lab F: 11002-521-S03 Tfn R: 1026-8303945-1 L: T344-12 | SVAR PATOLOGI/CYTOLOGI | Sida 1 (2) |
| TILL | Karolinska Universitetssjukhuset Öron-, näs- och halskliniken, Huddinge Avdelning B82 141 86 STOCKHOLM | Stockholm Care Ab 113 82 Stockholm Tel: Regnr T344-12 | |
| Provtagningsstid: Ankomststid lab: | 2012-01-10 11:41 2012-01-11 | Remittent: Jan-Erik Juto Tfn: | |
| Preparatets natur: Frågeställning: | biopsier från tracheo-bronkialgraft cellväxt? Anamnes: prep märkt 1: exfoliat från insidan i carinaområdet av graft. Finns cellväxt här? Typ?? prep märkt 2: Biopsier från intraluminalt område till vänster i tracheala delen av graft. Strålbehandlad: Nej | | |
| SVAR | | | |
| Tidigare utlåtande | 2012-01-27 T344/2012 L 2011-62 | | |
| 1: Materialet består huvudsakligen av graftdelar omgivna av äggviteprecipitat innehållande fokalt stor mängd leukocyter. På ett par ställen enstaka grupper av kärnförande celler, som immunhistokemiskt är av epitelial typ och utan nämnvärd atypi (närmast förefaller det röra sig om skivepitelceller). | | | |
| 2: Minimalt material av samma karaktär som i fraktion 1. | | | |
| 1+2 Ingen sammanhängande bedömbar vävnad påträffad. | | | |
| Tidigare diagnos | | | |
| 1+2: Graftmaterial med inflammatorisk celltillblandning och minimala epitelflagor av skivepiteltyp. | | | |
| BIOBANKSINFORMATION | | | |
| Provet får användas för samtliga, enligt biobankslagen, godkända ändamål. | | | |
| KOMPLETTERANDE UTLÅTANDE | | | |
| 2012-02-10 T344/2012 LYLES, CHRISTOPER 2011-621857 | | | |
| Specialfärgning för mikroorganismer (gram och Grocott) visar svamplika och bakterielika mikroorganismer. | | | |
| DIAGNOS | | | |
| 1+2: Graftmaterial med inflammatorisk celltillblandning och minimala epitelflagor av skivepiteltyp. (se ovan). | | | |
| BIOBANKSINFORMATION | | | |
| Provet får användas för samtliga, enligt biobankslagen, godkända ändamål. | | | |
| Nada Majeed 2012-02-10 | | | |

Biopsy from synthetic scaffold at 8 weeks, Jan. 10, 2012. The report describes: ***"The material contains mainly of graft parts surrounded with egg white precipitation [N.B. completely pathological non-vascular finding not equivalent to tissue ingrowth, or cellular lining] focally containing large amounts of leucocytes."***, ***"No coherent tissue can be detected."***, ***"Graft material with admixture of inflammatory cells and minimal flakes of squamous epithelium type."***, ***"Special stain for micro-organisms (gram and Grocott) shows fungi and bacteria like microorganisms."*** PM was participating in the procedure deciding the biopsy locations from the middle inner part of the graft (Appendix 9).