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Expérience française sur la prise en charge des infections de prothèses synthétiques de veine cave supérieure après exérèses tumorales intra-thoraciques

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UNIVERSITÉ CLERMONT AUVERGNE
UFR DE MÉDECINE ET DES PROFESSIONS PARAMÉDICALES

THÈSE D'EXERCICE
pour le
DIPLOME D'ÉTAT DE DOCTEUR EN MÉDECINE
par

FILAIRE, Laura

Présentée et soutenue publiquement le 18 octobre 2019

Expérience française sur la prise en charge des infections de prothèses synthétiques de veine cave supérieure après exérèses tumorales intra-thoraciques

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Listes des abréviations

BPF: Bronchopleural fistula

COPD: Chronic obstructive pulmonary disease

CoNS: Coagulase negative staphylococcus

FEV1: Forced expiratory volume in one second

LA: Left atrium

ML: Middle lobe

MSSA: Methicillin-Sensible Staphylococcus Aureus

MRSA: Methicillin-Resistant Staphylococcus Aureus

MT: Mediastinal tumor

NPWT: Negative pressure wound therapy

NSCLC: Non-small cell lung cancer

NSGCT: Non-seminomatous germinal cell tumor

OWT: Open Window Thoracostomy

PTFE: Polytetrafluoroethylene

RUL: Right upper lobe

SCC: Squamous cell carcinoma

SVC: Superior vena cava

PVGI: Prosthetic vascular graft infection

Introduction

Prosthesis vascular graft infection (PVGI) secondary to intrathoracic tumors resection is rare with a potential delayed or cancellation of oncological treatment.

Resection of non-small cell lung cancer (NSCLC) or mediastinal tumors (MT) enlarged to superior vena cava (SVC) is admitted with a proven benefit in overall survival. 5-years survival is around 15 (1) to 36% (2) for lung cancer and from 50 (3) to 62,5% (4) for mediastinal tumors. Initial SVC resection/reconstruction by prosthesis is advised when more than 30% of the circumferential is invaded (5) without extensive thrombosis and no bulky N2 (6). Many different materials are available for initial reconstruction either biological (venous graft, pericardial graft, arterial allograft) or synthetic (Dacron, polytetrafluoroethylene PTFE) with preferential use for PTFE and heterologous bovine pericardial graft. Although operative and surgical management are well described (6–8), SVC graft replacement is associated with an increased risk of death (1,9) and surgical complication (9,10). Secondary graft infection is reported in few cases or briefly mentioned in retrospective studies focusing on long-term survival or patency after NSCLC or MT resection (11–14). Incidence ranges from 7 to 10% which represents only two patients on each study (7,9). Recently Maurizi and colleagues did not find any differences in terms of major complications or survival between PTFE and pericardial graft for surgical thymus tumors invaded SVC. Moreover, they do not report any case of graft infection (5). Thus, management of such infection remains not very well-known without consensus.

Consequently, we report the French experience of SVC graft infection management after intrathoracic tumors resection enlarged to SVC.

1. Methods and Patients

Institutional Review Board of the French Society of Thoracic and Cardiovascular Surgery (FSTCS) approved the prospective database used for this study on the 11th of November 2018 (approval number 2018-10-20-7-52-3-FILa).

1.1. French Database EPITHOR

The database EPITHOR was created by the FSTCS in 2002. To date, this registry includes more than 160 000 procedures and is daily implemented by 114 public or private institutions. Epithor process has been previously described (15,16). The database is daily implemented by each surgeon identified with a login and password. Each medical record contains 50 variables, concerning patient's characteristics and medical history, preoperative assessment, surgical procedure, cancer staging and outcomes (17). All the data are automatically anonymized when sent to the database. Patient's consent was obtained, and patients were aware of the use of their medical records for potential clinical research purposes. Since 2010, an external audit regularly checked the accuracy of the data (15).

1.2. Patient selection

Data from 2001 to 2018, prospectively entered in EPITHOR and database from participating center, were retrospectively reviewed. Patient data were first screened on the coding act and surgical procedure. After eliminating all patients with inconsistent or missing values, patients with unknown information on mandatory variables for study, 249 patients were mentioned to have SVC resection. All participating thoracic centers were asked to review each medical record in order to check the type of SVC reconstruction (direct repair, patch enlargement or graft reconstruction) and collect follow-up information. Among the 127 patients with SVC

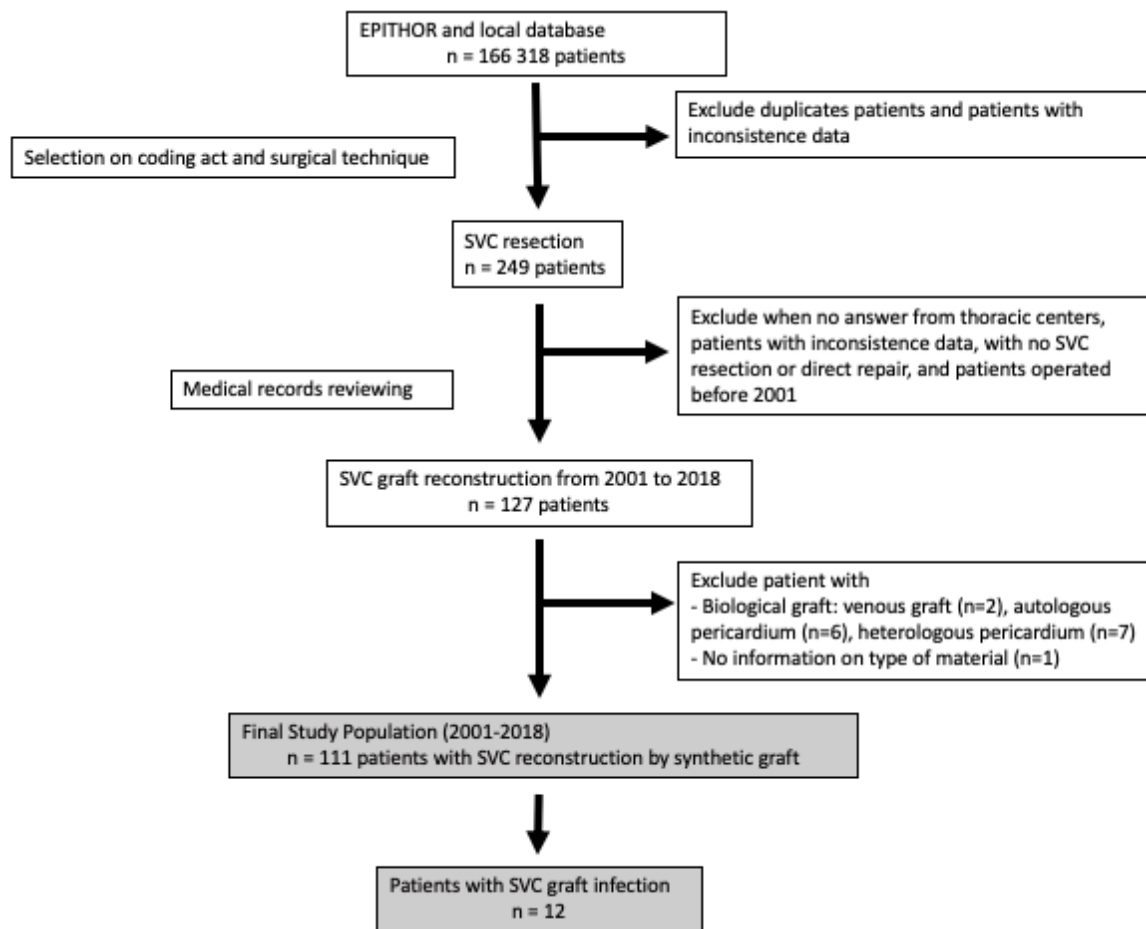
graft reconstruction, replacement was performed with venous graft (n=2), autologous pericardium patch (n=6) or heterologous bovine (n=4) or equine pericardium patch (n=3). Patient who underwent a direct repair of SVC, autologous or heterologous pericardial patch were not included. Finally, we selected 111 patients with a synthetic SVC graft replacement (Fig.1). Ninety-eight patients were operated for malignant thoracic diseases (NSCLC, MT, neuroendocrine carcinoma, mesothelioma, metastasis of breast or rectal cancer, thyroid cancer) and thirteen for benign superior vena cava obstruction (secondary to indwelling catheter, fibrosis mediastinitis, hemangioendothelioma of SVC).

Baseline characteristics, comorbidities, treatment-related variables (neoadjuvant chemo or radiotherapy, type of lung or mediastinal resection, extended resection, lymph node dissection, partial or total SVC reconstruction, SVC clamping time, use of hemostatic or surgical glue), disease-related variables (histological finding, stage, tumors margin), and follow-up variables (adjuvant therapy, infectious complications and their management) were recorded.

The number of comorbidities were used as a categorial variable, since recent data from EPITHOR suggested the superiority of this variable in a predictive model of in-hospital mortality. The comorbidities selected for analysis were chronic bronchitis, smoking, pulmonary hypertension, pulmonary embolism, diabetes mellitus, coronary artery disease, valvular heart disease, cardiac arrhythmia, congestive heart failure, peripheral vascular disease, alcoholism, cirrhosis, cerebral vascular event, renal insufficiency, coagulopathy, history of malignant disease, prior thoracic surgery, preoperative chemotherapy and steroids (16). Force expiratory volume in 1 second (FEV1) were recorded as a percentage of predictive value. Patients were classified as having chronic obstructive pulmonary disease if FEV1/forced vital capacity were under 70% or if mentioned in medical record. The Fitzgerald criteria were

used for the diagnosis of graft infection (18,19). Diagnosis was made if two of the following three criteria were present: (i) clinical finding with either general signs (fever, sepsis, chills) or local signs (wound infection, bronchopleural fistula with pyothorax, mediastinitis); (ii) biological signs (C-reactive protein > 100mg/L, white blood count > 10 000/mm³) or morphological signs of infection (perigraft air, abscess corresponding to pyothorax, perigraft fluid collection persisting more than 8 weeks after surgery, false aneurysm); (iii) positive bacterial culture of intraoperative samples or blood samples. SVC graft infection were classified as early-onset infection when occurring within 4 months postoperatively, and as late-onset when occurring after 4 months postoperatively (20). SVC graft in a pyothorax or mediastinitis were considered as graft infection.

Figure 1: Study flow chart of patients with SVC reconstruction after non-small cell lung cancer resection, mediastinal tumor resection or benign superior vena cava obstruction.



SVC, superior vena cava

1.3. Outcome definition

Primary outcome was the incidence and management of SVC graft infection. Secondary outcomes were overall survival, operative and overall mortality, complications and risk factor of graft infection. Overall survival was defined as any patient alive at the moment of the study or alive at 10 years follow-up. Operative mortality was defined as any death within the 30-days after operation or later if patient was still in hospital. Complications are classified as pulmonary, cardiovascular, infectious, iatrogenic or surgical complications (15). Pulmonary complications were defined as atelectasis, need for bronchial aspiration, pneumonia,

respiratory failure requiring invasive (acute respiratory distress syndrome) or non-invasive ventilation. Arrhythmia, cardiac failure, coronary events, deep venous thrombosis, pulmonary embolism, stroke, acute limb ischemia were considered as cardiovascular complications. Surgical complications were prolonged air leak, hemothorax, bronchopleural fistula, empyema, nerve palsy (vocal cord and phrenic), wound abscess, cardiac luxation and mediastinitis. Infectious complications were urinary tract infection, septicemia or fever unrelated to pneumonia or surgical complications. Iatrogenic complications were defined as any allergy (to antibiotic therapy, low-weight heparin) or drug overdose (oral anticoagulation).

1.4. Statistical analysis

All statistical analyses were performed with R software (R-Project, version 3.6.1). The tests were two-sided with $p < 0.05$ considered statistical significance. The assumption of normality was assessed with the Shapiro-Wilk test and homogeneity of the variance with a Bartlett test. Continuous variables are expressed as mean \pm standard deviation and compared by a Student's t-test or a Wilcoxon-Mann-Whitney test if non-compliance with normality. Categorical data were compared by a Chi-square test or a Fisher exact test if needed. Differences between the SVC graft infected patients and others were considered as significant for variables yielding a p-value ≤ 0.05 . Preoperative and operative variables with a $p < 0.05$ were included in the univariate analysis. A logistic regression analysis was performed to determine independent risk factors of graft infection. Odd ratios were calculated and presented with a 95% confidence interval. Analysis of actuarial survival was performed by means of Kaplan-Meier method. The log-rank test was performed to compare survival between NSCLC and MT.

2. Results:

2.1. Baseline characteristics

Characteristics of the 111 selected patients are shown in Table I.

Table I. Patient Characteristics

Characteristics	All patients (n = 111)	Patients with no SVC graft infection (n = 99)	Patients with SVC infection (n = 12)	p-value
Sex				0.75
Men	76 (68.5)	67 (67.7)	9 (75)	
Females	35 (31.5)	32 (32.3)	3 (25)	
Age	53 ± 15	53 ± 15	52 ± 17	0.966
BMI	25 ± 4.9	25 ± 4.9	23 ± 5.1	0.272
Number of comorbidities ≥ 3	35 (31.5)	30 (30.3)	5 (41.7)	0.513
FEV1 %	77 ± 19	79 ± 19	64 ± 17	0.014
COPD	37 (39.4)	27 (32.9)	10 (83.3)	0.001
Induction Therapy (%)	53 (47.7)	45 (45.5)	8 (66.7)	0.279
Type of resection n (%)				
Pneumonectomy	32 (28.8)	26 (26.3)	6 (50)	0.101
Lobectomy	35 (31.5)	34 (34.3)	1 (8.3)	0.099
Mediastinal tumor resection	41 (36.9)	37 (37.4)	4 (33.3)	0.99
Extend of resection				
Atypical lung resection	24 (21.6)	20 (20.2)	4 (33.3)	
Lobectomy	13 (11.7)	12 (12.1)	1 (8.3)	
Carina	21 (18.9)	18 (18.2)	3 (25)	
Left Atrium	4 (3.6)	4 (4)	0	
Right Atrium	6 (5.4)	6 (6.1)	0	
Esophagus	1 (0.9)	0	1 (8.3)	
Chest Wall	16 (14.4)	12 (12.1)	4 (33.3)	
Brachio-cephalic artery	8 (7.2)	8 (8.1)	0	
Manual bronchial closure	30 (28)	25 (26)	5 (45.5)	0.285
Lymph node dissection	53 (50.5)	46 (49.5)	7 (58.3)	0.786
Graft replacement				0.99
PTFE	109 (98.2)	97 (98)	12 (100)	
Dacron	2 (1.8)	2 (2)		
Flap coverage	26 (25.7)	20 (22.5)	6 (50)	0.092

Glue	28 (27.2)	23 (25.3)	5 (41.7)	0.3
Histology				
NSCLC	48 (43.2)	41 (41.4)	7 (58.3)	
Thymoma	17 (15.3)	16 (16.2)	1 (8.3)	
Thymic carcinoma	8 (7.2)	7 (7.1)	1(8.3)	
NSGCT	13 (11.7)	12 (12.1)	1 (8.3)	
Others	22 (19.8)	20 (20.2)	2 (16.7)	
Length of hospitalization (n)	19 ± 16	17 ± 13	36 ± 26	0.007

Numbers in parentheses are percentages (%). Others histology type included benign superior vena obstruction, metastasis of breast or rectal cancer, sarcoma, mesothelioma, lymphoma and thyroid cancer.

SVC, superior vena cava; BMI, body mass index; PTFE, polytetrafluorethylene; NSGCT, non-seminomatous germinal cell tumors

SVC reconstruction consisted in a patch enlargement in 3 patients (2.7%) and total graft replacement in 108 patients. Initial SVC replacement was made with PTFE graft in 109 patients (98.2%) and with Dacron in 2 (1.8%) patients. SVC reconstruction was truncal in 41 patients (36.9%), single left or right brachiocephalic vein in 61 patients (57%), and a Y-graft reconstruction in 3 patients (2.7%). Mean clamping time was 33 ± 19 minutes.

A total of twelve patients (10.8%) were diagnosis with SVC graft infection. Graft infected patients were more likely to be COPD (83.3% vs 32.9%; p=0.001), have a lower FEV1 (64 ± 17 vs 79 ± 19; p=0.014), a longer hospital stay (36 ± 26 days vs 17 ± 13 days; p=0.007). A significantly increased number of patients with graft infection received transfusion (100% vs 46.5%; p=0.003). There was no other statistical difference concerning induction therapy and operative characteristics (manual closure of bronchial stump, lymph node dissection, use of flap coverage and additional glue or hemostatic material) between the two groups.

Cardiovascular complications occurred in 33.3% in SVC graft infected patients and 29.3% in non-graft infected patients. There was significantly more surgical (100% vs 32.3% p < 0.001), and iatrogenic complications (25% vs 5.1%, p = 0.04) in patients with SVC graft infection than

in patients with no-graft infection. Empyema, mediastinitis and BPF occur only in SVC graft infected patients, in 7 patients (58.3%), 5 patients (41.7%) and 4 patients (33.3%) respectively ($p < 0.001$).

2.2. SVC graft infection

Eleven patients underwent a single graft reconstruction and one patient a patch enlargement. Early-onset graft infection occurred in 11 patients (ten in the first month and one in the third month). Late-onset graft infection occurred in one patient at six years after initial surgery. All SVC graft infection was either due to pyothorax or mediastinitis. We report no case of graft infection secondary to hematogenous dissemination.

In early-onset graft infection, sepsis (including fever and hyperleukocytosis) was present in 6 patients (50%), purulent discharge in 4 patients (33.3%), sternal instability in one patient. Altered general status with chronic cough was present in one patient with late pyothorax. Computed tomography was available only in seven patient (58.3%) and revealed perigraft collection, retrosternal abscess, perigraft air bubbles, pleural fluid with bronchial stump dehiscence and sternal disjunction.

Identification of causative microorganism was achieved in 11 (91.6%) patients. Bacteriological finding and SVC graft infection management are listed in Table II. *Staphylococcus* species were identified in five patients, MRSA in two patients, *Streptococcus* species in two patients, *Pseudomonas Aeruginosa* in three patients, *Candida albicans* in two patients. Microbiological samples were negatives in one patient. Seven SVC graft infection were secondary to empyema. Bronchopleural fistula (BPF) was present in four patients. In two patients, medical management (adapted antibiotic therapy with closed chest tube drainage) with or without irrigation succeeded to eradicate all SVC graft infection. In 4 patients, the control of infection

of the infection was obtained after a surgical debridement with bronchial stump closure alone (patient 7) or in association with flap coverage and surgical techniques decreasing pleural space (open window thoracotomy and/ or thoracoplasty). Among the two patients with *Candida albicans* graft infection, one had later-onset graft infection. (patient 6). The patient had several operations including epiplooplasty, open window thoracostomy, muscle flap coverage, thoracoplasty and partial removal of PTFE graft. Because of the recurrence of the sepsis, the two extremities of the PTFE graft were removed by sterno-thoracotomy (Annexe I). The patient is still alive with a chronic mild SVC syndrome without recurrence of disease and infection two years after the complete remove of the graft. The other one had early graft infection (patient 5). He was treated with BPF exclusion, omental flap wrapping around the SVC graft without infection recurrence at follow-up (Annexe II).

Five SVC graft infection were secondary to mediastinitis, all surgically managed with a large cleaning and debridement in association with adapted antibiotic therapy. In three patients, infection recurrence appeared, successfully managed either medically (long-life suppressive antibiotic) or surgically in case of virulent microorganism (*Pseudomonas aeruginosa* or MRSA): one omental flap and one graft excision. No SVC syndrome was present in the last patient before discharge.

Table II: Outcomes for patients with SVC graft infection

Case	Patient	Primary surgery	Infection	Management of infection	Follow -up	Graft Management
1	M/58	Pneumonectomy enlarged to carina, SVC, esophagus, chest wall Adenocarcinoma, Stage IIIA Adjuvant Chemotherapy	Early pyothorax, no BPF <i>Streptococcus oralis from pleural fluid</i>	Chest tube drainage 4 Weeks Antibiotics therapy	No recurrence of graft infection Died 6 Months later due to pneumopathy	Conservation
2	F/ 55	Neoadjuvant Chemotherapy Pneumonectomy enlarged to carina, chest wall, SVC Large Cell lung carcinoma, Stage IIIA	Early Pyothorax, no BPF <i>P. Aeruginosa from pleural fluid streptococcus, CoNS from pleural fluid and bronchial sampling</i>	Chest tube drainage with Irrigation of vancomycin 6 Weeks Antibiotics therapy	No recurrence of graft infection Died 6 Months later due to cancer evolution	Conservation
3	F/ 56	Neoadjuvant Chemotherapy Right upper lobectomy enlarged to chest wall, SVC Adenocarcinoma, Stage IIIB	Early pyothorax No BPF <i>CoNS, Lugdunensis staphylococcus from pleural sampling</i>	Surgical lavage-debridement + OWT + NPW therapy + removal of osteosynthesis material. 6 Weeks Antibiotics therapy Recurrence septicemia - Suppressive antibiotherapy	Persistence graft infection Alive 2 years later	Conservation
4	M/55	Neoadjuvant RadioChemotherapy Pneumonectomy enlarged to carina, SVC Large-cell lung cancer, Stage IIIA	Early pyothorax with BPF <i>MRSA, multiresistant P. Aeruginosa from bronchial sampling</i>	Surgical lavage-debridement + Omental flap + OWT	Died 15 days later due to Multivisceral failure	Conservation
5	M/65	Neoadjuvant Chemotherapy Pneumonectomy enlarged to carina, SVC SCC	Early pyothorax with BPF <i>Candida albicans from bronchial and pleural sampling</i>	Chest tube drainage Surgical lavage-debridement + thoracoplasty + OWT + serratus anterior flap + NPW therapy 6 Weeks Antibiotics therapy Recurrence infection: - Endobronchial stenting to exclude BPF + omental flap around the SVC graft in pleural space	No recurrence of graft infection 1-year Graft thrombosis Died to 2 years later due cancer evolution	Conservation
6	M/61	Pneumonectomy enlarged to SVC Adjuvant chemotherapy Adenocarcinoma, Stage IIIA	Late pyothorax with BPF (6 years later) <i>Candida albicans from per operative sampling</i>	Thoracostomy + NPW Therapy Omental Flap 9 Months later: Recurrence infection to <i>Prevotella melaninogenica</i> - Pectoralis major flap - 1 months later: Partial graft thrombosis + persistence BPF and septicemia - Thoracoplasty + partial graft excision (body of the graft) + serratus muscle flap Recurrence septicemia involving SVC stump graft:	No recurrence of infection Alive 3 years later	Removal

				- Total excision of the graft. No revascularization		
7	M/ 64	Pneumonectomy enlarged to SVC Adjuvant radio-chemotherapy SCC, Stage IIIA	Early pyothorax with BPF Microbiological sample negative	Surgical lavage-debridement + Closure of Bronchial stump Recurrence infection and BPF: - OWT	Died due to respiratory failure 1 month later	Conservation
8	M/ 20	Induction chemotherapy Mediastinal germ cell mass excision enlarged to SVC, LA, ML RUL Teratoma	Early mediastinitis <i>Methicillin-resistant Staphylococcus epidermidis from per operative sampling</i>	Surgical lavage-debridement + irrigation with antiseptic solution Persistence infection with collection in contact with SVC patch - Patch excision	Lost to follow up at discharge	Removal
9	F/ 17	Neoadjuvant chemotherapy Thymectomy enlarged to RUL, pericardium, SVC Thymic carcinoma, Masaoka IIIB	Early mediastinitis <i>MSSA from purulent discharge Peroperative sampling: negative</i>	Surgical lavage-debridement 6 Weeks Antibiotics therapy	Lost to follow-up at discharge	Conservation
10	M/ 49	Thymectomy enlarged to SVC and RUL Adjuvant Radiotherapy Thymoma B2, Masaoka IIIB	Early mediastinitis <i>MSSA from peroperative sampling</i>	Surgical lavage-debridement 6 Weeks Antibiotics therapy	Lost to follow-up at discharge	Conservation
11	M/ 73	Tumor resection enlarged to SVC, RUL, diaphragm Sarcomatoid mesothelioma	Early mediastinitis <i>P. Aeruginosa from peroperative sampling</i>	Surgical lavage-debridement Antibiotics therapy Persistence mediastinitis: - Omental flap	No recurrence of infection Alive 4 months later	Conservation
12	M/ 55	SVC replacement SVC obstruction due to indwelling catheter	Early mediastinitis <i>MSSA from blood cultures</i>	Surgical lavage-debridement 6 Weeks Antibiotics therapy Recurrence - Suppressive antibiotherapy	No recurrence of infection Alive 3 years later	Conservation

BPF, bronchopleural fistula; MSSA, methicillin-sensible staphylococcus aureus; MRSA, methicillin-resistant staphylococcus aureus; CoNS, Coagulase-negative staphylococcus;

P.Aeruginosa, Pseudomonas Aeruginosa; PTFE, polytetrafluoroethylene; OWT, open window thoracostomy; NPWT, negative pressure wound therapy; SCC, squamous cell

carcinoma; SVC, superior vena cava; LA, left atrium; ML, middle lobe; RUL, right upper lung

2.3. Risk factors

Risk factor of graft infection in univariate analyses are listed in Table III. The multivariate analysis demonstrates that risk factors of graft infection included COPD (OR 20.97, 95%CI 3.35-212.70; p=0.003) and iatrogenic complications (OR 9.09, 95%CI 1.12 - 88.66; p= 0.0038). The number of comorbidities ≥ 3 , age ≥ 55 years and pneumonectomy were not significant.

Table III: Risk factors of graft infection in univariate analysis

	Odd ratio	p-value	95% CI
COPD	10.19	0.004	2.47 - 69.36
Pneumonectomy	2.81	0.096	0.81 - 9.74
Iatrogenic complication	6.27	0.023	1.14 - 30.25
Number of complications ≥ 3	11.20	<0.001	3.13 - 46.56

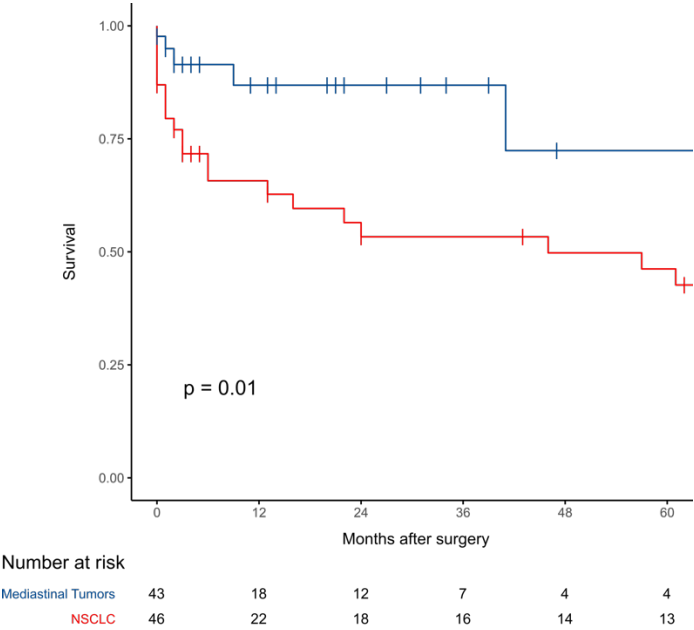
CI, confidence interval

2.4. Long-term results

Mean follow-up was 24 ± 35 months. 61 patients (49.6%) were lost-to follow-up with a median follow-up of two months. At the completion of the study, 17 patients (14.5%) were still alive among them one having SVC graft infection. Overall survival is shown in Figure 2. The overall mortality rate was 26.1% (n=29). The operative death rate is about 10.8% (n=12).

In patients with SVC graft infection, overall mortality and operative death rate are 41.6% and 16.7 % respectively.

Figure 2: Survival curve: SVC replacement after NSCLC resection (red line) versus mediastinal tumors (blue line). Five-year survival was 40% (n=13) after NSCLC resection and 70% after mediastinal tumors resection (NSGCT, thymoma, thymic carcinoma, sarcoma, and lymphoma). Log rank test p=0.01.



NSCLC, non-small cell lung cancer

3. Discussion

Main results

Our study is the first gathering as many patients with prosthetic SVC graft reconstruction and focusing on graft infection, its risk factors, bacteriological aspect, outcome and management. It confirms the scarcity and potential life-threatening condition of SVC graft infection as in other series mentioning this complication (7,9). Caused by contiguous infection (empyema or mediastinitis), favored by surgical and iatrogenic complications, graft conservation was always attempted at first reoperation whatever bacteriological finding.

Primary Outcome

Different classification of prosthesis vascular graft infection (PVGI) are described. Fitzgerald criteria are the most commonly used for diagnosis (18) and Samson classification for the deepness of infection (21). SVC graft infection can either be intracavitary if associated to empyema or extracavitary in case of mediastinitis. We did not use the Samson classification as all infections in our series involved at least the body of the graft with septicemia or fistula, mentioned as major graft infection(21). Recently, the MAGIC consensus proposed major and minor diagnosis criteria divided in three categories (clinical, radiological, laboratory) as for endocarditis diagnosis (22). The added value of this consensus relies on the adjunction of positron emission tomography (PET/CT), radiolabeled leukocyte imaging and the ranking of laboratory finding (23). It seems more precise and helpful in case of high suspicion of graft infection or for chronic or late graft infection. However, in our series, only one patient presented a late SVC graft infection and PET/CT as radiolabeled leukocyte imaging was never used at diagnosis.

Traditionally, PTFE is thought to be the best material for prosthetic SVC replacement. Known for its low thrombogenicity potential, long-term patency has been reported due to fast reendothelization of the inner lumen of the graft by a thin layer of neointima (7). Furthermore, rigidity associated with ringed PTFE (10) might prevent compression from surrounding structures or secondary to mediastinal fibrosis. However, our nation study confirmed a 10,8% risk of prosthetic SVC graft infection, in accordance with the 7% (1) (and 10% (7) rate reported in the literature. Meanwhile, no case of infection has been reported with bovine pericardial conduit (5,24–26) nor cryopreserved aortic allograft suggesting a better tolerance in infected condition. This latter has been used for benign pathologies (mediastinal fibrosis, chronic SVC obstruction) or malignant tumors resection without infection after a median follow-up ranging from 18 months to 4 years (27–29).

Our study shows a large majority of early-onset infection in 91.6% (n=11). All, but one, were treated with conservation of the prosthesis. Late-onset infection occurred only in 8.3% (fungal graft infection in patient 6) and need prosthesis removal. One persistence of graft infection was observed among the 7 survival patients with 19 months mean follow-up (4 - 36 months). Among the 5 other patients, 2 died postoperatively (patients 4 and 7) and 3 were lost to follow up after discharge (patients 8, 9 et 10).

Beside our series, the literature is scarce. To the best of our knowledge, six papers collecting eight cases are reported in literature. Spaggiari and colleagues reported two SVC prosthesis graft infection on 28 SVC graft reconstruction. One patient had a lung abscess and the other one a BPF (1,9) They also reported a case after an early empyema due to tracheal fistula following right upper lobectomy enlarged to carina and esophagus (30). All were treated with a surgical debridement and latissimus dorsi muscle flap. They do not report any case of

recurrence. Alifano and colleagues reported a case of SVC graft infection to Gram-negative bacteria after an early empyema without BPF. Surgical debridement and latissimus dorsi flap were also performed (31). Bacha and colleagues successfully treated a mediastinitis with SVC graft infection with omentopexy and tracheostomy after a third recurrence of thyroid cancer. The association of antibiotics, omental flap and tracheostomy allowed a successful control of prosthesis infection due to mediastinitis after tracheal necrosis (7,32). Darteville and colleagues successfully treated a PTFE graft infection secondary to empyema with BPF. After failure of a Clagett procedure, the progressive graft clamping followed by graft removal allowed the control of infection although patient died of lung pneumonia (7). Itoda and colleagues reported a successful SVC graft excision after an early mediastinitis to MRSA following a thymectomy enlarged to the right upper lobe and SVC. That strategy was complicated by a pseudoaneurysm of the ascending aorta and redo surgery was needed (33). Okubo and colleagues reported a late chronic mediastinitis to *Pseudomonas Aeruginosa* complicated with mycotic aneurysm of the brachiocephalic artery and a septic SVC graft thrombosis after thymectomy in the treatment of a Masaoka stage III B3 thymoma. PTFE graft excision without reconstruction was performed, in association with brachiocephalic artery replacement using a Dacron graft and omental flap (34).

No surgical guidelines handle with SVC graft infection. The results of literature taken together with ours give us useful information about the management of SVC graft infection.

Medical conservative approach are not recommended showing an increased in-hospital mortality rate in peripheral graft infection (35). Moreover, due to the associated mediastinitis or empyema to SVC graft infection, a conservative surgical approach should at least be attempt.

Surgical irrigation strategy (irrigation, chest tube drainage and antibiotic therapy) should be reserved to high risk patients due to a higher in-hospital mortality rate contrary to other options (36). Umminger and colleagues treated 14 patients according to this protocol. Among them 2 died postoperatively, and 2 patients were reoperated on due to graft infection recurrence (37).

The graft-sparing strategy (surgical debridement, muscle or omental flap, NPWT, and antibiotic therapy) in association with surgical technique to treat empyema (OWT, thoracoplasty) (38,39) appears to be the preferential option. In fact, this approach shows the lowest mortality and recurrence of infection rate (36,37). Furthermore, the use of muscle or omental flap to cover the graft is an independent protective factor in-hospital mortality in multivariate analysis (HR 0.24, 95% CI 0.10 - 0.56; $p = 0.001$) (36). In case of post pneumonectomy BPF, the control of the SVC graft infection is conditioned by the early treatment of BPF. The use of bronchial stenting should improve the outcome of these patients (40–42).

Graft removal was used in case of late-onset graft infection (37), fungal (43,44) and multiresistant microorganism graft infection (33). MRSA infection was found to be a risk factors of death with a significant lower one-year survival than non-MRSA graft infection (47.1% vs 78.6%, $p = 0.016$) (36). Moreover, according to last guidelines on thoracic graft infection, graft removal still remains the better option for major graft infection (Type III to V of Samson classification) (45). Revascularization may not be always mandatory and will depend on clinical signs of superior vena cava syndrome.

Suppressive antibiotic therapy is admitted when dealing with PVGI medically treated or with graft-sparing surgery in case of documented microorganism (46). Recently Oda and colleague found a higher 1-year survival rate in patient with continued use of antibiotics after discharge

(96.8%) than patient without antibiotic therapy (76.2%) (36). Thus, the administration of a suppressive antibiotic therapy might be discussed after SVC graft infection treated with a graft-sparing surgery on a case-by-case basis after a multidisciplinary meeting.

Secondary outcomes

In our series, surgical complications including a majority of mediastinitis, empyema with or without BPF were found as a major local risk factor of SVC graft infection confirming the results of previous study (7). We think that early diagnosis of these complications may improve the control of infection and the prognosis.

We also found that patients with SVC graft infection had more severe COPD status and a lower FEV1 compared to non-graft infected patients. Our results differ of those from series including abdominal aortic graft or peripheral graft (19). General status of our patients is mainly dependent of COPD status while patients with aneurysmal or occlusive arterial pathologies have a higher trend to have obesity, diabetes mellitus, renal insufficiency (19,47).

Although ubiquitous, biofilm formation is a well-known trigger in the pathogenesis of prosthesis vascular graft infection (PVGI) (46,48). In fact, it contains all elements needed for bacterial growth, acts as a barrier for antibiotics decreasing their efficacy. It favored delayed infection and their chronicity. The three principal ways of PVGI are bacterial exposure during surgery, contiguous infectious process and hematogenous spread (49). In our series, no case of SVC graft infection secondary to hematogenous spread is reported as in literature.

Microbiological findings are consistent with literature where *Staphylococcus* organisms (MSSA and CoNS), MRSA and gram-negative bacteria (such as *Pseudomonas aeruginosa*) are the main causative microorganism of aortic graft infection (36,49). No case of infection by enterobacteria was noticed contrary to study on abdominal aortic graft infection with aorto-

enteric fistula. MRSA is particularly virulent with the ability to destroy native vasculature (49). Furthermore, MRSA graft infection showed a significantly lower one-year survival contrary to no MRSA graft infection (47.1 vs 78.6%; $p=0.016$ respectively) (36). Gram-negative bacteria such as *Pseudomonas aeruginosa* are high virulence microorganism due to the production of toxins elastase and protease allowing erosion of intima and media layer of vessel (49). Recent guidelines on PVGI advice a graft excision whenever possible for major graft infection to MRSA, *Pseudomonas aeruginosa* or multidrug resistant microorganism (45).

Concerning thoracic vascular graft infection to candida species, few data are available. Medical treatment based on antifungal therapy, graft-sparing surgical management or graft excision have been used for thoracic aortic graft infection to *Candida* species. Results are controversy with failure and success with all three options (50–52). In any feasible case, authors advice surgical graft excision in association with closed long term follow up due to indolent candidemia. When excision is high risk surgery, graft-sparing strategy associated with suppressive antifungal therapy seems reasonable option (53). In previous study, no case of SVC graft infection to *Candida albicans* were reported. In our study, identified risk factor for candidemia in Patient 5 and 6 are neoadjuvant chemotherapy and broad-spectrum antibiotic therapy.

Limitations

This study presents some limitations. This is a retrospective study with a high number of patients lost to follow-up after discharge. Data concerning adjuvant therapy or microbiological results were not always available in medical records. Consequently, assessment of the graft infection on the adjuvant treatment were not feasible. Secondly, a small number of patients with graft infection is included although the population is extracted from a national database.

The rate of SVC graft infection might be underestimated but it reflects the scarcity of this complication.

Conclusion

In conclusion, SVC graft infection is rare and dreaded complication. Treatment should be at least a surgical graft-sparing strategy with an extensive debridement and the use of a pedicled flap to cover the infected graft in association with an antibiotic therapy. Early-onset graft infection secondary to empyema without BPF, high risk patient or low-virulent pathogen seems appropriate criteria for a graft-sparing approach. Graft removal might be reasonable in case of late graft infection, in presence of bronchopleural fistula, virulent or resistant microorganism (Gram negative bacteria, MRSA, PA, candida species). Reconstruction in a contaminated region might not be mandatory in case of graft thrombosis, the absence of superior vena cava syndrome and the presence of venous collateralization. We do not recommend medical conservative treatment due to poor results in eradicate the infection and a higher in-hospital mortality rate.

Conclusion

La prise en charge des infections de prothèses synthétiques de veine cave supérieure est rare, associée à une haute morbidité avec une contamination septique par continuité : médiastinite ou empyème pleural avec ou sans fistule broncho-pleurale. Les facteurs favorisants identifiés sont la bronchopneumopathie obstructive, la survenue d'une médiastinite, d'un empyème, d'une fistule broncho-pleurale, et la transfusion sanguine. La prise en charge pose la question de la conservation du pontage prothétique au cours d'une reprise chirurgicale pour médiastinite ou pyothorax chez des patients fragiles, avec des traitements oncologiques adjuvants en attente. La conservation de la prothèse synthétique en milieu septique va dépendre essentiellement de la virulence du germe causal, de la possibilité d'exclure la fistule broncho-pleurale et du retentissement clinique d'une thrombose du pontage cave. Il paraît ainsi raisonnable dans les infections précoces de prothèse de veine cave supérieure secondaire à une médiastinite à staphylocoque multi-sensible ou d'empyème sans fistule broncho-pleurale de réaliser une chirurgie conservatrice basée sur des lavages, débridements locaux et lambeaux de comblement notamment épiploïques. En cas de germes multi-résistants, d'espèces pyocyaniques, d'infection à candida albicans, d'infection de prothèse tardive ou de fistule broncho-pleurale, l'ablation de la prothèse semble préférable avec ou sans remplacement selon la tolérance et la chronicité du syndrome cave supérieur en cas d'obstruction du pontage.

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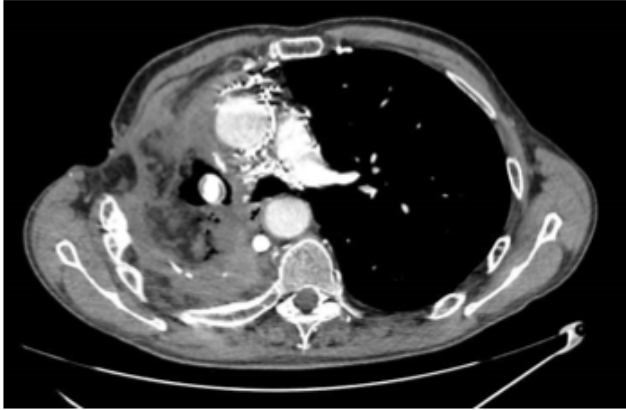
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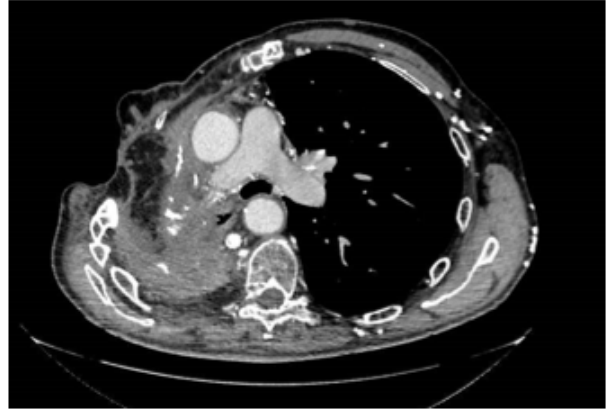
2013;28(5):557-60.

Annexe I

a.

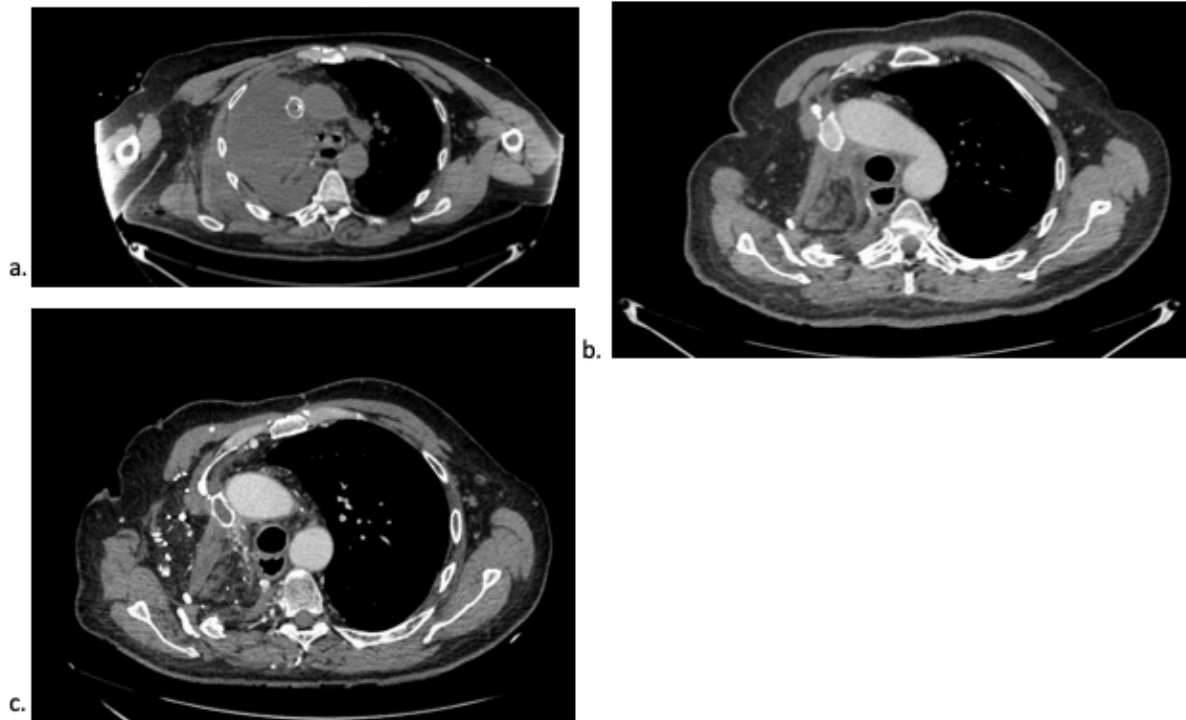


b.



Computed tomography scanner of patient 6. a. At diagnosis of graft infection recurrence, computed tomography scanner shows perigraft air bubble. b. After graft removal, pleural space filled of pectoralis muscle and anterior serratus muscle flap.

Annexe II



Computed Tomography scanner of patient 5. At initial diagnosis, right pleural space full off liquid and air bubbles around the right bronchial stump. b. After first graft-sparing surgery consisted in thoracoplasty, thoracostomy and omental flap. c. Graft thrombosis at 1-year.

(Conseil national de l'ordre des médecins)

SERMENT D'HIPPOCRATE

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

Nom, Prénom

Signature

SERMENT D'HIPPOCRATE

En présence des Maîtres de cette FACULTE et de mes chers CONDISCIPLES, je promets et je jure d'être fidèle aux lois de l'Honneur et de la Probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent et je n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes MAÎTRES, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les HOMMES m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'OPPROBRE et méprisé de mes confrères si j'y manque.

Nom, Prénom

Signature

FILAIRE Laura

Expérience française sur la prise en charge des infections de prothèses synthétiques de veine cave supérieure après exérèses de tumeurs intra-thoraciques

Thèse pour le Doctorat en Médecine, Clermont-Ferrand, 2019

RESUME

Contexte : Peu de données sont disponibles dans la littérature sur la prise en charge des infections de prothèses de veine cave supérieure (VCS) au décours de chirurgie thoracique oncologique.

Objectif : L'objectif est de rapporter l'expérience française sur la prise en charge des infections de prothèses synthétiques de VCS.

Méthodes : Entre 2005 et 2018, un total de 111 patients ayant eu un remplacement par prothèse synthétique de VCS après exérèse de tumeurs intra-thoraciques a été rétrospectivement sélectionné à partir d'EPITHOR. L'étude a reçu l'accord du comité d'éthique de la société française de chirurgie thoracique et cardiovasculaire (numéro 2018-10-20-7-52-3-FILa). L'infection de prothèse était définie selon les critères de Fitzgerald.

Résultats : Les prothèses en Polytetrafluoroéthylène (PTFE) et Dacron ont été utilisées chez 109 et 2 patients respectivement. Douze patients se sont compliqués d'une infection du pontage en PTFE (10.8%) par contamination locale : médiastinite, empyème et fistule bronchopleurale ($p < 0.001$). Les facteurs de risques d'infection de prothèse de VCS étaient par la présence d'une bronchopneumopathie chronique obstructive (OR 20,97 ; 95%IC 3,35-212,70 ; $p = 0,003$) et la survenue de complications iatrogènes (OR 9,09 ; 95%IC 1,12-88,66; $p = 0.0038$). La prise en charge a consisté soit en une antibiothérapie avec drainage thoracique ($n = 2$), soit en une reprise chirurgicale avec conservation de la prothèse ($n = 10$). Six ont été réopérées pour persistance de l'infection dont deux avec l'ablation de la prothèse.

Conclusion : La prise en charge des infections de prothèses synthétiques de VCS est un vrai challenge dont le succès est lié à la possibilité de stérilisation du médiastin, de la cavité pleurale et d'exclusion de la fistule broncho-pleurale.

MOTS CLEFS : infection de prothèse, reconstruction de Veine Cave Supérieure, cancer du poumon non à petites cellules, empyème, tumeurs médiastinales, médiastinites

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DATE DE LA SOUTENANCE : 18 octobre 2019