International Journal of Cardiology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Chronic thromboembolic pulmonary hypertension (CTEPH): Updated Recommendations from the Cologne Consensus Conference 2018

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ARTICLE INFO

Article history:
Received 9 August 2018
Accepted 24 August 2018
Available online xxxx

Keywords:
Chronic thromboembolic pulmonary hypertension
Chronic thromboembolic disease
Pulmonary endarterectomy
Balloon pulmonary angioplasty
Medical therapy

ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is a subgroup of pulmonary hypertension that differs from all other forms of PH in terms of its pathophysiology, patient characteristics and treatment. For implementation of the European Guidelines on Diagnosis and Treatment of Pulmonary Hypertension in Germany, the Cologne Consensus Conference 2016 was held and last updated in spring of 2018. One of the working groups was dedicated to CTEPH, practical and controversial issues were commented and updated. In every patient with suspected PH, CTEPH or chronic thromboembolic disease (CTED, i.e. symptomatic residual vasculopathy without pulmonary hypertension) should be excluded. Primary treatment is surgical pulmonary endarterectomy (PEA) in a multidisciplinary CTEPH centre. Inoperable patients or patients with persistent or recurrent CTEPH after PEA are candidates for targeted drug therapy. There is increasing experience with balloon pulmonary angioplasty (BPA) for inoperable patients; this option, like PEA, is reserved for specialised centres with expertise in this treatment method.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a specific type of pulmonary hypertension (PH) [1,2] that is characterised by obstruction or occlusion of subsegmental, segmental or larger pulmonary arteries by postembolic fibrotic material. Typical pathoanatomical findings are intimal irregularity, stenoses with ring-, web- or slit-like forms and pouch defects, tapered vascular stenosis or complete occlusion caused by fibrotic intraluminal material, occasionally with an overlying thrombus. Anastomoses between bronchial arteries and precapillary pulmonary arterioles and between bronchial arteries and pulmonary veins with hypertrophic remodelling of the pulmonary veins are also found [3].

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https://doi.org/10.1016/j.ijcard.2018.08.079
0167-5273/

Table 1
Group 4 in the clinical classification of PH.

Chronic thromboembolic pulmonary hypertension (CTEPH) and other pulmonary artery obstructions
4.1 CTEPH
4.2 Other pulmonary artery obstructions
4.2.1 Angiosarcoma
4.2.2 Other intravascular tumours
4.2.3 Arteritis
4.2.4 Congenital pulmonary artery stenosis
4.2.5. Parasites (echinococcus-related hydatidosis)

2. Definitions

CTEPH is categorised as Group 4 in the classification of PH [1] (Table 1), and the diagnosis is based on the following criteria:

- PH confirmed by right heart catheterisation (mean pulmonary arterial pressure ≥25 mm Hg and pulmonary arterial wedge pressure (PAWP) ≤15 mm Hg at rest) and
- Mismatch on ventilation/perfusion (V/Q) scintigraphy (usually V/Q single-photon emission computed tomography [SPECT]) with at least one large perfusion defect in one segment or in two subsegments, or evidence of pulmonary vascular lesions on computed tomography (CT) and/or magnetic resonance imaging (MRI) or pulmonary angiography.
- These findings should be obtained after at least 3 months of effective anticoagulation

Chronic thromboembolic pulmonary vascular disease without PH (CTED) has the same criteria as listed above except for the evidence of PH at rest. With similar symptoms and reduction in quality of life, these patients are offered the same surgical or interventional treatment as patients with CTEPH (Table 2) [4].

Table 2
Recommendations for CTEPH.

Recommendation	Level of recommendation	Level of evidence
In PE survivors with exercise dyspnoea, CTEPH should be considered.	IIa	C
Life-long anticoagulation is recommended for all patients with CTEPH.	I	C
It is recommended that for all patients with CTEPH the assessment of operability and decisions regarding other treatment strategies should be made by a multidisciplinary team of experts.	I	C
Surgical PEA in deep hypothermia and circulatory arrest is recommended for CTEPH patients at an experienced PEA centre (>30–50 operations per year).	I	C
Riociguat is recommended for symptomatic patients who have been classified as having persistent/recurrent CTEPH after PEA or inoperable CTEPH by a multidisciplinary CTEPH team including at least one surgeon.	I	B
Off-label use of targeted PAH drugs may be considered in symptomatic patients with persistent/recurrent CTEPH after surgical treatment or with inoperable CTEPH.	IIb	B
Interventional BPA may be considered in patients who are technically inoperable or have an unfavourable risk/benefit ratio for PEA as assessed by a CTEPH team.	IIb	C
Screening for CTEPH in asymptomatic survivors of PE is currently not recommended.	III	C

BPA = balloon pulmonary angioplasty; CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension; PE = pulmonary embolism; PEA = pulmonary endarterectomy.

Comments: Despite the clear criteria, CTEPH can be difficult to diagnose and appropriate evaluation is often delayed. Especially in patients with comorbidities, diagnosis may be challenging, therefore all patients should be referred to a PH expert centre promptly [1,2].

The main differential diagnoses besides PAH are heart failure with preserved ejection fraction (HFpEF) or rare diseases such as mediastinal fibrosis, tumours of the pulmonary arteries, pulmonary vasculitis, and congenital or acquired pulmonary artery stenoses.

3. Epidemiology and risk factors

The incidence of CTEPH is thought to be 4 per 1 million adults [5]. It is difficult to obtain exact numbers for the incidence of CTEPH due to the lack of specific symptoms, misdiagnoses due to the diagnostic complexity of CTEPH and a large number of suspected cases where CTEPH remains undiagnosed. Information on the incidence of CTEPH after acute pulmonary embolism is also variable and ranges between 0.4 and 9.1% [6–9]. The reasons for the range of values are the difficulty in distinguishing between an acute pulmonary embolism and a recurrent embolism in pre-existing CTEPH and heterogeneous inclusion criteria, observation periods, and methods of confirming the diagnosis (echocardiography versus invasive measurements).

In most cases, CTEPH is associated with a prior venous thromboembolism. For example, in an international prospective CTEPH database, 74.8% of CTEPH patients had a history of acute pulmonary embolism and 56.1% had a history of deep vein thrombosis [10].

Although CTEPH is a thromboembolic disease, patients generally do not have a defined disturbance in coagulation and/or fibrinolysis. However, elevated levels of Factor VIII [8] and phospholipid antibodies/lupus anticoagulans are significantly more common in CTEPH than in PAH [8,11]. CTEPH patients have higher percentages of blood types A, B and AB compared with the general population [12–14], which is linked to elevated plasma Factor VIII levels [11].

4. Pathological mechanisms

The consequence of elevated pulmonary artery pressures is right ventricular strain resulting in right ventricular hypertrophy and dilatation, which can lead to death due to right-sided heart failure, if left untreated. The underlying cause of the vascular disease in CTEPH is vascular wall remodelling due to thromboembolism, with subsequent remodelling of the peripheral resistance vasculature of the lungs. This cannot be distinguished from the remodelling observed in PAH. It is thought that a pulmonary embolism is transformed into a fibrotic vascular occlusion via the interplay of several factors including inflammation [12], infection [15], inhibition of vascular regeneration [16,17], circulating microparticles [18], abnormal fibrinogen [19], splenectomy [14,18], and abnormal circulating phospholipids with reduced thrombus resolution [18].

5. Diagnostics

5.1. Screening

Based on current evidence routine screening for CTEPH is not recommended for survivors of an acute pulmonary embolism [1]. A significant number of patients with CTEPH develop the disease without a history of a clinically apparent pulmonary embolism.

Comments: While there is no scientific justification for screening asymptomatic patients, it has been shown that examination of persistently symptomatic patients after acute PE results in a diagnosis of CTEPH/CTED in 8.5% of cases [20]. Furthermore, it has been reported that there is not always a “honeymoon period” between the occurrence of an acute pulmonary embolism and the development of CTEPH, but rather that a number of patients never become symptom-free again after an acute pulmonary embolism [20,21]. Therefore, steps should be

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taken to rule out CTEPH in persistently symptomatic patients after acute pulmonary embolism and at least 3 months of effective anticoagulation.

5.2. Clinical presentation

The median age of patients at diagnosis is 63 years with both sexes being affected equally [10], whereas paediatric patients are rare [22]. The predominant symptom of CTEPH is exercise-induced dyspnoea; other symptoms are non-specific or absent in early CTEPH. Signs of chronic right-sided heart failure only become evident in advanced disease. Early diagnosis remains a challenge and should be pursued for reasons of prognosis [23]. There is a median latency period of 14 months between the onset of symptoms and diagnosis at expert centres. The diagnostic algorithm is shown in Fig. 1.

Comments: The ESC/ERS guidelines do not distinguish between functional and imaging-based diagnostic tests and, if there is evidence of CTEPH, recommend echocardiography. If this suggests an intermediate or high probability of PH, V/Q lung scan is recommended. Because echocardiography can miss both CTEPH and CTED [24], it seems, at least in cases of patients with pronounced symptoms, inappropriate to stop the diagnostic process if echocardiography results in a determination of low probability of PH, or to simply carry out a follow-up echocardiogram after 3–6 months. Because both CTEPH and CTED may have signs of pulmonary perfusion anomalies that are detectable by cardiopulmonary exercise testing (CPET) (Fig. 2) [24,25], this test should be performed if there is a clinical suspicion of CTED/CTEPH and a low echocardiographic probability of PH. As the degree of vascular obstruction and the haemodynamics of CTEPH correlate poorly, and because there are patients who have symptoms but only minor functional limitations, and patients with pathological scintigraphy findings but no objective limitations, functional diagnostic testing can prove helpful in determining the significance of the pathological findings observed in the imaging tests.

If there is a strong clinical suspicion of PH after echocardiography and, where appropriate, CPET, imaging techniques should be used, and an invasive haemodynamic assessment conducted via right heart catheterisation (see Fig. 1).

5.3. Radiological/nuclear medicine diagnostics

While multi-detector CT pulmonary angiography (CTPA) is the investigation of choice to diagnose acute pulmonary embolism, V/Q scintigraphy (preferably with single photon emission computed tomography; SPECT) remains the initial imaging modality of choice for CTEPH [1], as it has a 96–97% sensitivity and a 90–95% specificity for the diagnosis [26]. In idiopathic PAH and pulmonary veno-occlusive disease (PVOD), V/Q SPECT scans are typically normal or show non-segmental defects [27]. Recent work suggests that both V/Q SPECT and modern CTPA may be accurate methods for detecting CTEPH, with excellent diagnostic accuracy at expert centres [28,29].

Comments: A V/Q SPECT without perfusion defects largely rules out CTEPH. In patients with PH, a V/Q mismatch in at least one segment, or in two subsegments, indicates the possible presence of CTEPH. V/Q SPECT involves low radiation exposure and can also be used in patients with advanced renal failure. In the current era it should be performed as a SPECT investigation [30,31], as in comparative studies V/Q SPECT is

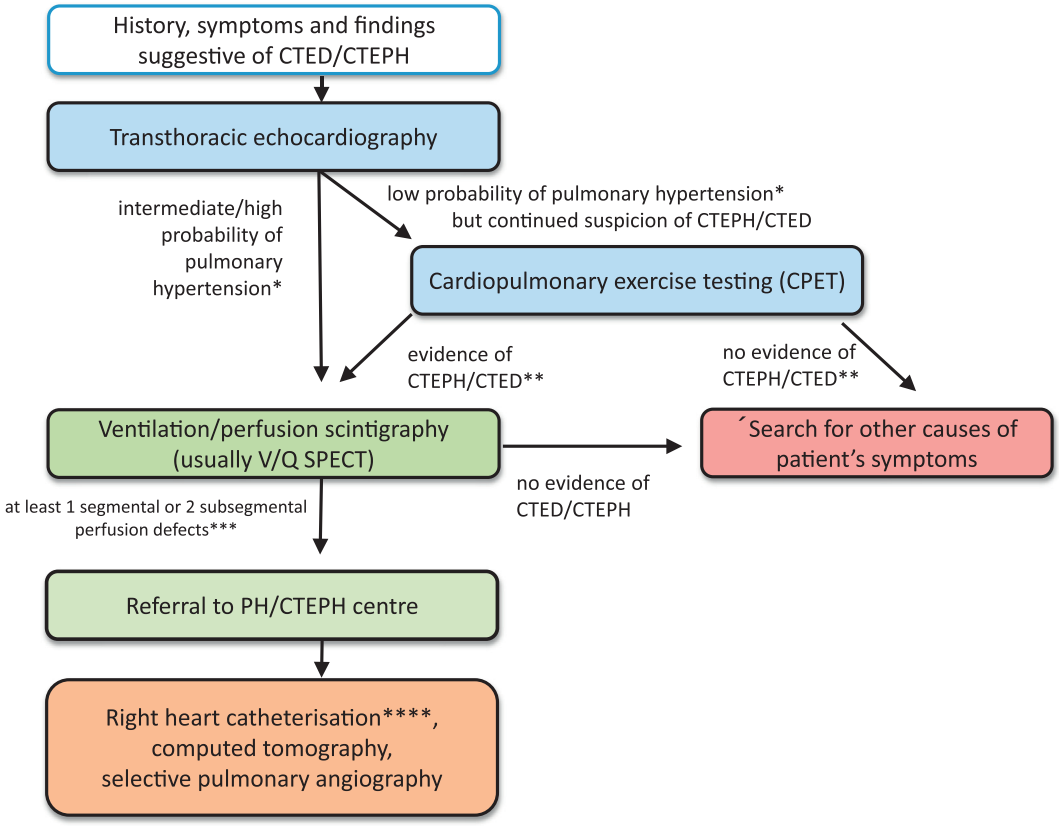

Fig. 1. Diagnostic algorithm for CTEPH * see Table 7A and Table 7B in pocket guide "Diagnostik und Therapie der pulmonalen Hypertonie" by the German Society for Cardiology and Cardiovascular Research (Deutsche Gesellschaft für Kardiologie – Herz-und Kreislaufforschung). ** Signs of CTEPH/CTED on cardiopulmonary exercise testing include limited exercise capacity and evidence of a pulmonary perfusion disorder (reduced $PETCO_2$, elevated $P(a\text{-}ET)CO_2$, EQ O_2, EQ CO_2, VE/VCO_2 slope or $P(A\text{-}a)\ O_2$). *** or evidence of pulmonary artery clots/obstructions using other imaging techniques such as computed tomography, magnetic resonance imaging or conventional pulmonary angiography **** if necessary, coronary angiography CO_2 = carbon dioxide; CTED = chronic thromboembolic pulmonary vascular disease without pulmonary hypertension; CTEPH = chronic thromboembolic pulmonary hypertension; EQ = respiratory equivalent; O_2 = oxygen; $P(a\text{-}A)CO_2$ = partial pressure of arterial/alveolar carbon dioxide; $P(a\text{-}ET)CO_2$ = partial pressure of arterial end-tidal carbon dioxide; $PETCO_2$ = partial pressure of end-tidal carbon dioxide; PH = pulmonary hypertension; VE/VCO_2 = minute ventilation/carbon dioxide output.

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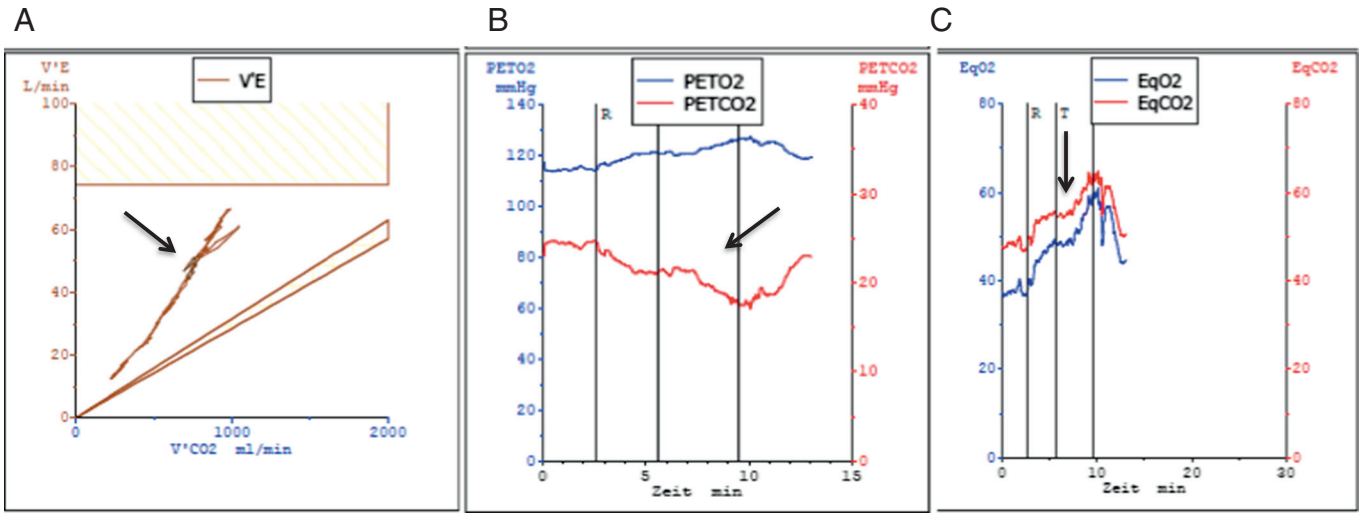

Fig. 2. Cardiopulmonary exercise test of a patient with severe CTEPH with A) increased slope of minute ventilation/CO2 exhalation(VE/VCO2, low and decreasing end-tidal carbon dioxide tension (PETCO2) and C) elevated and increasing ventilatory equivalents for oxygen (EQO_2) and carbon dioxide ($EQCO_2$) as signs of pulmonary perfusion defects with ineffective ventilation.

superior to planar V/Q scintigraphy [32] (see Fig. 3). Despite the recommendations in the guidelines in favour of V/Q, this technique is still not performed consistently as part of a PH diagnostic work-up; for example, being only performed in approximately one in two patients in a North American PH cohort of nearly 800 patients [33].

5.4. CT of the chest

Multidetector CTPA is an established imaging modality for confirming CTEPH [28]. However, it cannot definitively rule out CTEPH [1,26]. CTPA can detect typical findings, comorbidities and complications of the disease, such pulmonary artery dilatation with subsequent compression of the left main coronary artery or bleeding from bronchial artery collaterals. A high resolution CT scan of the chest produces images of the lung parenchyma and identifies structural lung changes and bronchial disease, as well as lung infarcts, vascular and pericardial malformations and thoracic wall deformities. Perfusion inequalities manifest as a mosaic perfusion pattern, with hypertransparent areas corresponding to decreased perfusion. Although a mosaic perfusion pattern is common in CTEPH, it can also be observed in up to 12% of patients with PAH [34].

Comments: Current work on CTPA using collimators with spatial resolution in the sub-millimetre range is promising in terms of characterising segmental manifestations of CTEPH, with a resolution similar to selective digital subtraction angiography (DSA) [28,35]. Direct changes such as vessel wall thickening and irregularities, occlusions, filling defects and mosaic patterns are important in evaluating and planning surgical therapy [36–38], post-stenotic vascular dilatations, and intravascular rings and webs can be displayed. A new development in CT imaging is the dual energy CT (DECT), which can measure the contrast agent uptake in the parenchyma as an expression of perfusion (Fig. 4). Initial results suggest that this modality has a high sensitivity for perfusion deficits [39].

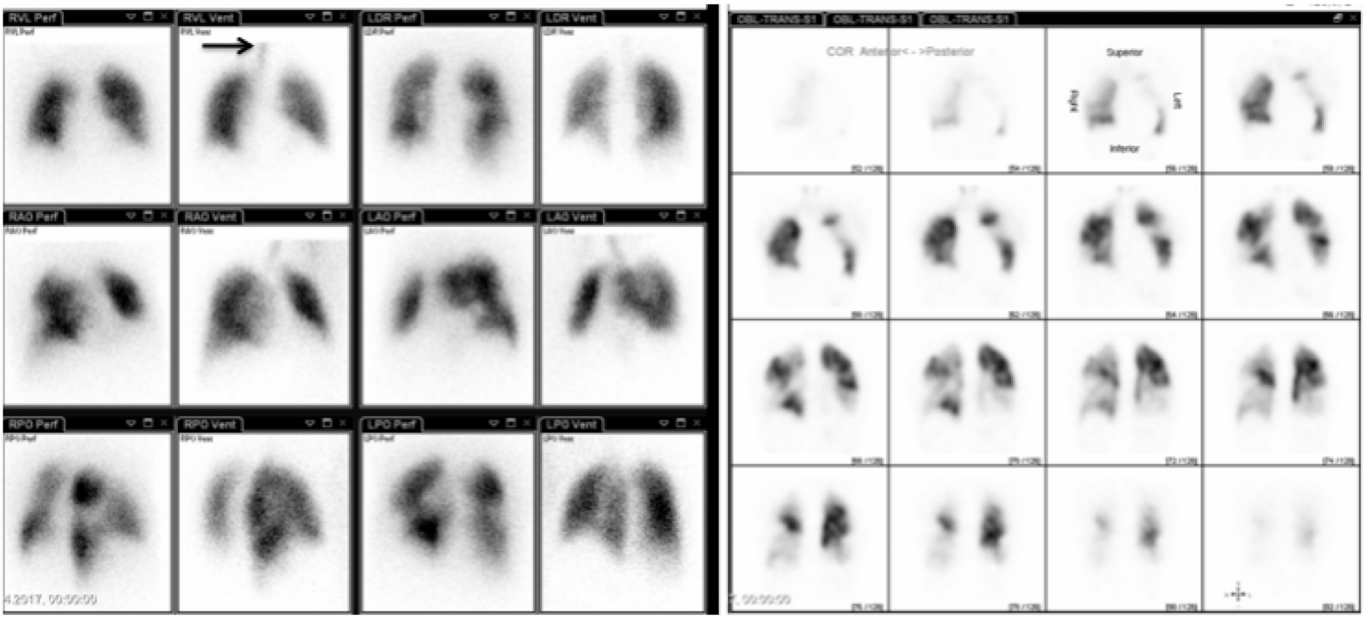

Fig. 3. Ventilation-perfusion scintigraphy in a patient with CTED. A) planar views in 6 projections showing perfusion defects with mismatch to ventilation. Ventilation scans can be recognized by the tracer signal of the trachea (arrow), which is absent in the perfusion scans. B) Single photon emission computed tomography (SPECT) showing multiple segmental perfusion defects.

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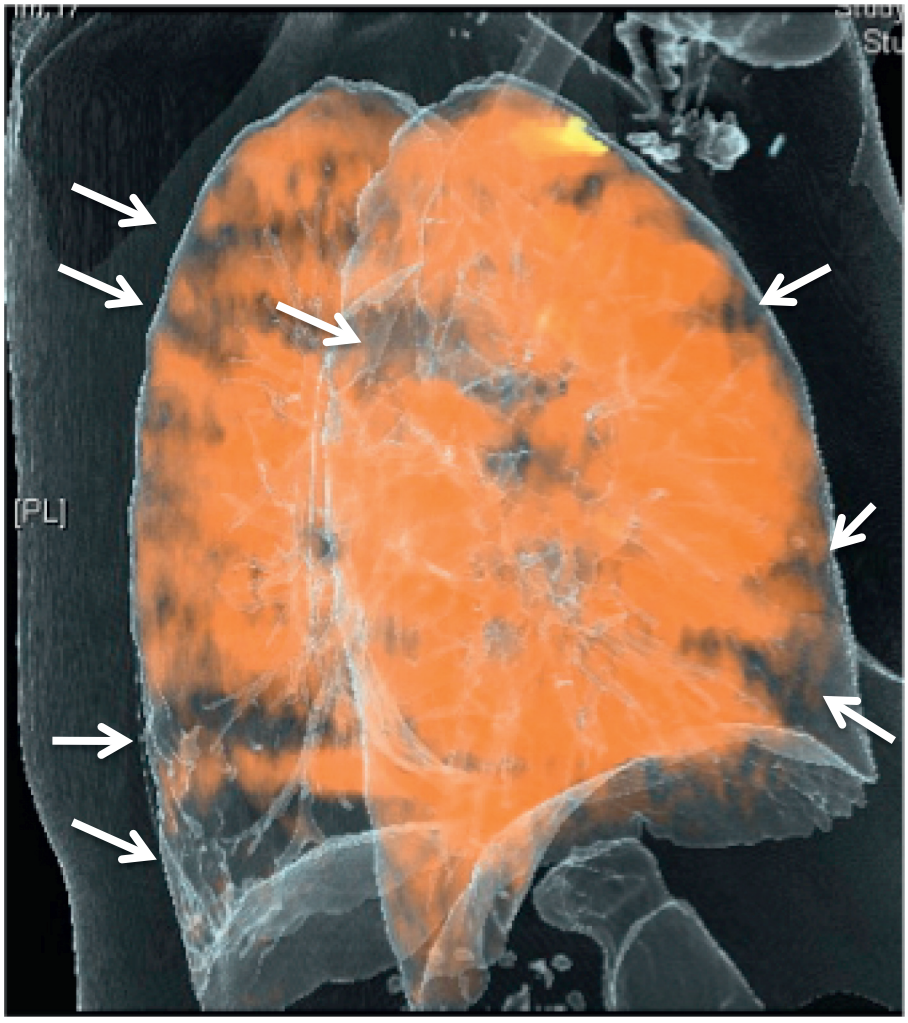

Fig. 4. Dual-energy computed tomography derived iodine map depicting multiple perfusion defects.

5.5. Magnetic resonance pulmonary angiography (MRA) and other imaging techniques

MRA is currently considered inferior to CT [36], but this modality, as well as cone beam CT [40,41], dual-energy CT (see Fig. 4), angioscopy [42], intravascular ultrasound and optical coherence tomography (OCT), are increasingly used as complementary investigations providing additional information, depending on local experience.

Comments: The spatial resolution of MRA for contrast-enhanced imaging of the pulmonary vasculature is limited for technological reasons and to date remains insufficient for depicting subtle intravascular findings. The results of investigations conducted at specialised centres on perfusion imaging and changes in segmental post-operative perfusion are available [43].

5.6. Pulmonary angiography

The final step in confirming the diagnosis of CTEPH and assessing technical suitability for surgery is selective pulmonary angiography in at least two planes (anterior–posterior and lateral projections). Typical signs of CTEPH are webs, ring-like stenoses, pouches, tortuous lesions and complete vascular obstructions [44] (see Fig. 5).

Comments: Pulmonary angiography should be performed side-selective in an anterior-posterior and lateral projection at a CTEPH centre that has the relevant experience and works closely with an experienced surgical team. Angiography plays a key role in determining whether surgical or interventional therapies are feasible. In addition to visualising the exact vascular morphology, angiography also can help to assess central and subpleural-capillary filling (see Fig. 5). Poor subpleural perfusion in the context of PH is thought to be associated with distal vessel angiopathy or other primary lung diseases. This is also associated with a higher surgical risk [45]. Angiographic imaging of subsegmental stenoses and obstructions is becoming increasingly significant, especially with the advances in balloon angioplasty of the pulmonary arteries (BPA). Cone-beam CT is recently used in combination with pulmonary angiography for an improved depiction especially of peripheral lesions in the pulmonary arteries [41].

5.7. Right heart catheterisation

A right heart catheterisation which records pressure measurements in the right atrium, right ventricle, and the pulmonary artery (systolic, diastolic and mean pulmonary arterial pressures [PAP] and PAWP) as well as determining cardiac output volume and oxygen saturation (pulmonary arterial, vena cava) and the calculation of pulmonary vascular resistance is obligatory. Determining the correct PAWP in patients with CTEPH can be difficult, therefore measurement of the LVEDP may be necessary. Pre-operative and post-operative PVR are long-term predictors of prognosis [46].

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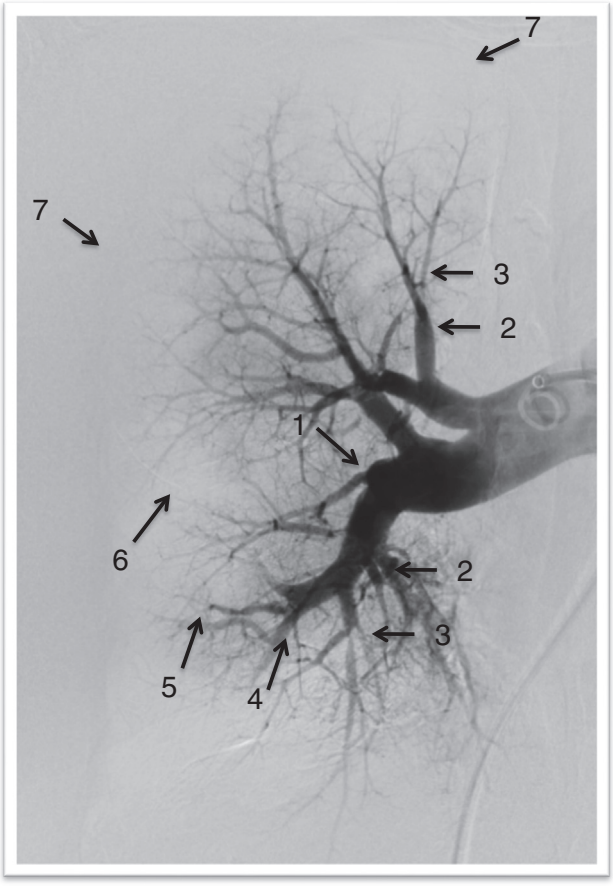

Fig. 5. Pulmonary angiography of the right lung in a patient with CTEPH with ring-like stenosis [1], wall irregularities [2], abrupt narrowing [3], webs [4], perfusion defects [5], complete vascular obstructions [6] and decreased subpleural-capillary filling [7].

6. Treatment of CTEPH

6.1. Pulmonary endarterectomy (PEA)

PEA is the treatment of choice for CTEPH provided there are no serious contraindications (such as comorbidities) [1] (see Fig. 6). The intra-hospital fatality rate depends on the surgical experience, which corresponds with the annual number of PEAs. In Europe, specialised centres (>50 PEAs/year) have a case fatality of ≤3.5% [47], in centres that perform 11–50 PEAs per year the case fatality is 4.7% [6] and in centres who perform fewer than 11 PEAs/year it is 7.4% [6]. In centres with a smaller number of cases, the proportion of patients who are deemed inoperable is higher than in centres with higher numbers of PEA cases. The surgery should therefore take place in a CTEPH centre with an adequate number of operations and a low case fatality [48]. In addition to having ample experience in diagnosing and treating CTEPH, a CTEPH centre should have an multidisciplinary team composed of specialists in respiratory medicine, cardiology, radiology, nuclear medicine, intensive care and anaesthesiology as well as an experienced PEA surgeon [48].

The majority of patients experience substantial post-operative relief of symptoms and a significant improvement of haemodynamics [47,48]. In contrast to surgical embolectomy for acute pulmonary embolism, the treatment of CTEPH necessitates a true bilateral endarterectomy through the medial layer of the pulmonary arteries. To do this, phases of circulatory arrest in deep hypothermia are necessary [47] in order to keep the surgical field free of blood via the bronchopulmonary collaterals and at the same time reliably protect neurocognitive function [49].

Comments: Whether a patient with CTEPH can be successfully treated by PEA is determined by multiple factors that cannot easily be standardised; principally, these include the technical operability and the risk benefit ratio for PEA (accessibility of the obstructions, pre-operative haemodynamics, comorbidities), the expertise of the surgical team and the available resources. Advanced age in itself does not constitute a contraindication to surgery, nor is there a PVR threshold or a limit to the extent of RV dysfunction that would rule out PEA.

The expertise of both the surgeon and the CTEPH team is essential in determining which changes are deemed too "distal" or too "peripheral", and thus which patients are classified as inoperable. The same applies to the correlation between accessible obstructions and the extent of pathologically altered haemodynamics. The combination of primarily "distal" obstructions and a high PVR constitutes a risk factor, but is not a contraindication for PEA.

In cases of CTEPH with a very high PVR but only a moderate proximal obstruction pattern, ~~is~~ relevant microvasculopathy is suspected. Nonetheless, PEA may be useful in such cases to significantly reduce the PVR and thus the RV stress. The presence of microvasculopathy may be the reason for residual post-surgical PH in approximately 50% of patients who have had PEA surgery, however this does not mean that the operation was not successful [50].

The option of intra- and post-operative ECMO therapy is part of the recommended standard of care at CTEPH centres [1], especially for severe cases (e.g. PVR > 15 Wood units) [51–53]. Acute respiratory distress due to early post-operative reperfusion oedema may be bridged with veno-venous ECMO. In contrast, veno-arterial ECMO support is indicated for right ventricular pump failure in persistent severe PH or as bridging to lung transplantation.

Patients who do not undergo PEA or suffer from persistent or recurrent PH after PEA face a poor prognosis without additional therapy [10].

Comments on the treatment algorithm:

1. A CTEPH centre should have experience in diagnosing and treating patients with CTEPH and PAH. At CTEPH centres, patient care is managed by a multidisciplinary team: specialists in respiratory medicine, cardiology, radiology, and nuclear medicine working in close collaboration with a PEA surgeon whose team performs >20 PEAs annually. The recommendation to get a second opinion has been removed from the current ESC/ERS treatment algorithm for CTEPH. However, in cases of doubt it is necessary to request a second opinion at another experienced CTEPH centre [54].
2. The algorithm now differentiates between technically operable and technically inoperable patients. In addition, for technically operable patients there is mention of a "non-acceptable" risk/benefit ratio in the presence of comorbidities, although there is no definition for this ratio. Because the assessment of both technically operable and inoperable patients and those with an "unacceptable risk/benefit ratio" hinges crucially on the experience and expertise of the surgeon and the corresponding team, obtaining a second opinion at another experienced CTEPH centre is recommended in cases where there is doubt. The cases of patients who refuse surgery should be discussed with a PEA surgeon and, where applicable, these patients should meet with a PEA surgeon for an informative discussion, before long-term medical therapy is initiated.

6.2. Medical therapy

Supportive medical treatment for CTEPH consists of anticoagulants and diuretics, and long-term oxygen therapy in cases of hypoxaemia [1]. Lifelong anticoagulation is recommended even after PEA, and no data exist on the efficacy and safety of new oral anticoagulants for CTEPH [1,2]. Further supportive measures are recommended, in keeping with the recommendations for treating patients with PAH [55].

Comments: The recommendations for anticoagulation in CTEPH are derived primarily from the recommendations for anticoagulation after

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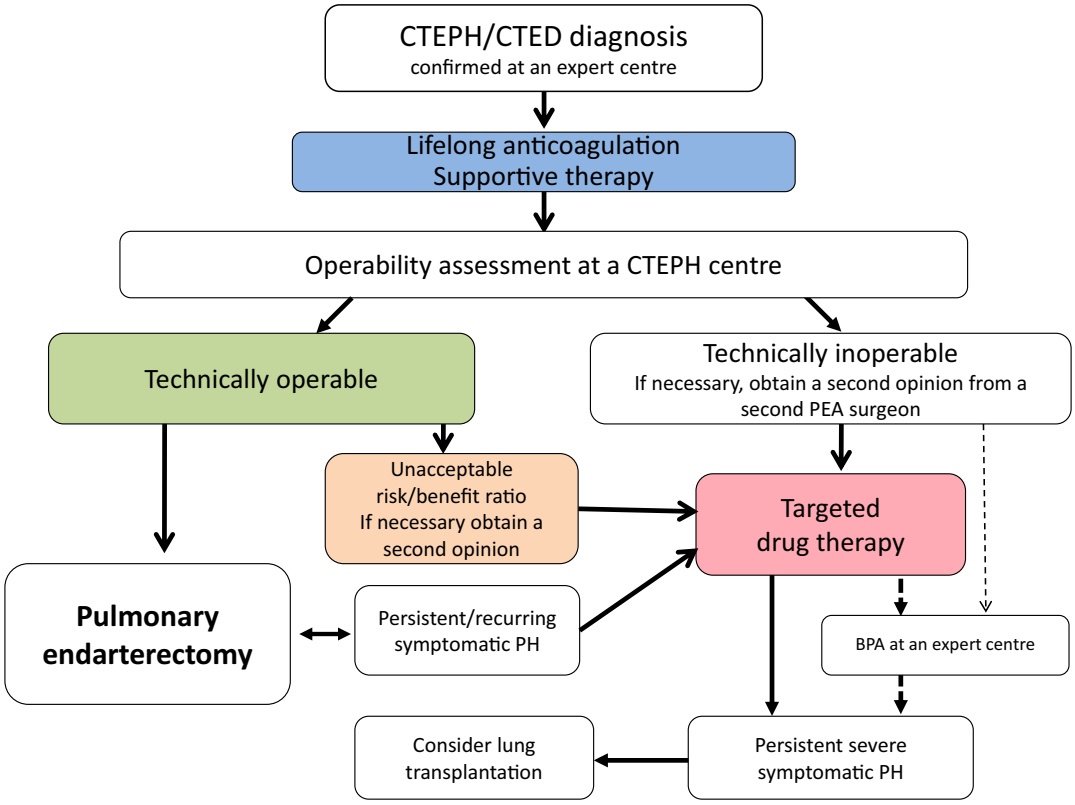

Fig. 6. Therapeutic algorithm for CTEPH [1] BPA = balloon pulmonary angioplasty; CTED = chronic thromboembolic pulmonary vascular disease without pulmonary hypertension; CTEPH = chronic thromboembolic pulmonary hypertension; PH = pulmonary hypertension

recurrent pulmonary embolisms, as there is a lack of reliable evidence from randomised controlled clinical trials (RCT) on the effect of anticoagulation in CTEPH patients [2]. Both "classical" oral anticoagulants (coumarin derivatives) and non-vitamin-K-dependent oral anticoagulants (NOACs), which inhibit Factor Xa or prothrombin, are currently available as therapy in the post-acute phase of a pulmonary embolism. Owing to decades of clinical experience with vitamin K antagonists, they are still considered the standard treatment for CTEPH according to the current guidelines [1]. On the basis of the individual risk/benefit assessment or in patients whose CTEPH cannot be well controlled with vitamin K-antagonists, a switch can be made to a NOAC, although there is less evidence on the treatment of CTEPH with NOACs [2]. Routine vena cava filter placement is not justified based on the available evidence [1].

The positive effects of controlled, "low-dose" exercise training have also been demonstrated for CTEPH [56].

6.3. Therapy with PH medications

Pulmonary microvascular disease in CTEPH has provided the rationale for the use of drugs approved for PH [10]. Currently only the oral soluble guanylate cyclase (sGC) stimulator, riociguat, has been approved for the treatment of inoperable or persistent/recurrent CTEPH after PEA, however it can be expected that combination therapies will also be available for administration in future, first results have been published.

Targeted medical treatment of CTEPH may be considered in patients with an unacceptable risk/benefit ratio for PEA [1]. Patients with persistent or recurrent PH after PEA are also candidates for targeted medical treatment [1].

The pre-operative use of PH therapy in patients with an indication for PEA and severe haemodynamic compromise has not yet been supported by scientific evidence. The effects were relatively small [57] in one RCT and one retrospective study indicated no difference in post-operative outcomes, but there was a significant delay in performing surgery in patients treated with medical therapies [58]. Prospective RCTs are needed in patients who may benefit from medical treatment [1], for example, patients with a high PVR and technically challenging anatomy. After PEA, patients should continue to be managed at a CTEPH centre, with at least one haemodynamic re-assessment by means of right heart catheterisation at 6–12 months post-intervention [1]. Repeat imaging is only necessary if there is evidence of persistent PH.

Comments: Additional data on medical therapy in CTEPH are now available from the open-label, single-arm extension of the CHEST study, which demonstrated a sustained effect of riociguat on physical endurance and clinical disease course [59]. However, these are not controlled data. For example, improvements in the 6-minute walk distance and NT-proBNP after 3 months persisted over the next 2 years, and, in contrast to studies in PAH patients, there was a significant correlation between improvement in 6-minute walk distance and survival. The following conditions apply to the use of riociguat in patients with CTEPH:

- Technical inoperability according to an interdisciplinary CTEPH team including an experienced PEA surgeon;
- A poor risk benefit ratio for PEA according to the CTEPH team
- Relevant post-operative PH after PEA;
- Initiation of treatment at a PH centre
- Close blood pressure monitoring during the adjustment phase.

First results of a randomised placebo-controlled study with the dual endothelin receptor antagonist macitentan (MERIT study) have been published showing significant improvement in 6-minute walk distance, haemodynamics and NTproBNP in the treatment group [60,61].

Incompatibility or an insufficient therapeutic response that requires combination therapy may be the reasons for the off-label use of PAH

Please cite this article as: H. Wilkens, et al., Chronic thromboembolic pulmonary hypertension (CTEPH): Updated Recommendations from the Cologne Consensus Conference 2018, Int J Cardiol (2018), https://doi.org/10.1016/j.ijcard.2018.08.079

medications in patients with CTEPH. Such treatments should only be undertaken at PH centres.

In the CTEPH registry, treatment with PAH drugs was a predictor of poor outcome, presumably because of a bias towards more severe patients in this group. Dedicated studies are under way testing the role of medical treatment prior to and following PEA, and BPA. Currently, no recommendations can be based on study data.

There is a risk that the initiation of PAH-specific medication will delay surgery in operable patients resulting in surgery with more advanced disease and a correspondingly poorer prognosis [55].

Therapy outcomes must be monitored closely; where appropriate, the option of PEA or BPA should be re-evaluated.

6.4. Balloon pulmonary angioplasty (BPA)

BPA is a percutaneous interventional treatment option for patients with inoperable CTEPH. This procedure involves treatment of vascular CTEPH lesions with semi-compliant balloons at relatively low pressures (about 6–10 atm), in several sessions. Since its first reported use in a small patient series ($n = 18$) in 2001 [62], BPA has been refined considerably, in particular in Japan, a country in which PEA is not widely performed [63–65]. BPA is now also being used increasingly in inoperable patients in Europe [66,67].

Comments: BPA therapy is performed over multiple sessions, each of which is usually limited to working on one lobe and at most one additional segment of the lung. Injuries are largely avoided by the consistent use of dilatation balloons that have a smaller diameter than the lumen of the target vessel. Even so, serious and fatal complications have been reported, primarily bleeding caused by balloon or wire-induced pulmonary artery perforation and reperfusion oedema resulting in variations of lung injury, with desaturation, hemoptysis, infiltrations and ARDS, depending on the severity. The initially high rate of complications, with a periprocedural mortality of up to 10% [62], has been lowered substantially and was recently reported to be between 0 and 1% [63–65,68]. At the same time, the short- and medium-term haemodynamics and clinical effects are promising. Re-stenosis and re-obstruction appear to be rare and stenting of the pulmonary vasculature is not necessary. However, there are only rare data on long-term outcomes [69], and no controlled trials.

In Europe BPA is performed in patients who are inoperable, and have accessible lesions [63,65]. The principal diagnostic imaging technique used is pulmonary angiography, which is occasionally supplemented by CT angiography. Biplane digital subtraction angiography (DSA) is considered the standard, however C-arm CT is superior to conventional DSA for visualising intravascular lesions in the subsegmental pulmonary arteries [41].

Before BPA is considered, PEA must definitively be definitively ruled out as an appropriate treatment option. Meanwhile, even hybrid approaches combining PEA surgery with intraoperative BPA have been described [70]. To develop the therapeutic strategy in each individual CTEPH patients, a multidisciplinary conference with experienced PEA surgeons, interventionalists and PH specialists is mandatory. As long as no systematic long-term data for BPA are available from countries in which PEA surgery is well established, this technique should be performed at those centres that also offer PEA. This will ensure that the question of operability will be definitively determined and that the procedure is established to begin with at centres that manage a sufficient number of patients. The German CTEPH centres currently collect their BPA data in a shared prospective database in order to evaluate a number of factors including which patients do or do not particularly benefit from this procedure [67].

In the algorithm of the ESC/ERS guidelines, the next step recommended to immediately follow “technically inoperable” for PEA is “BPA”, but to date there are no data to support this. In German-speaking countries there is a consensus that BPA should not be used until other established techniques have been exhausted. These include drug therapies recommended for inoperable patients. In patients with CTED there is currently insufficient experience to support treatment with BPA.

After all other treatment options have been exhausted, lung transplantation may be considered for eligible patients (no significant comorbidity, biological age <60 years). In this situation, the patient should be referred to a transplantation centre in a timely manner.

6.5. Pulmonary artery sarcoma

The primary tumours of the pulmonary artery are the highly malignant and extremely rare sarcomas [71], which are also listed in Group 4 of the clinical classification of PH (see Table 1). Originating from the pulmonary valve, the intima of the main trunk of the pulmonary artery or the bulbus cordis, the predominantly intraluminal growth results in stenoses of the pulmonary vasculature. Thrombus apposition and embolisation of thrombi or tumour portions in peripheral sections of the pulmonary circulation result in progressive right-sided heart strain. A suspected diagnosis is based on a mosaic of clinical, laboratory and imaging findings. The following observations are indicative of this diagnosis:

- Central space-occupying mass in the pulmonary artery involving the main trunk of the pulmonary artery, the pulmonary valve or the right ventricular outflow tract.
- Bulging of a central “thrombus” in the direction of the main stem or the pulmonary valve (positive eclipse sign) [72]
- “Thrombus” increases in size despite adequate anticoagulation [73]
- Pressure gradient observed during right heart catheterisation, with drop in pressure beyond the central “thrombus”
- No history of pulmonary embolism
- Uptake of contrast medium by the “thrombus” on MRI or CT diagnostic scans
- Increased radionuclide uptake on a positron emission tomography-CT scan [74]
- B symptoms

The prognosis for a pulmonary artery sarcoma is poor. The mean survival after diagnosis is 17 months. The treatment of choice is resection of the tumour. Even from a palliative perspective, this operation is justified to reduce the tumour mass or remove a high-grade obstruction of the right ventricular outflow tract. During the operation, tissue samples for histology are secured first before the peripheral anomalies are resected using a type of tumour endarterectomy, similar to the PEA technique used in CTEPH. Depending on the location and infiltration of the central tumour portion, resection and prosthetic replacement of the pulmonary artery, the pulmonary main stem or the pulmonary valve up into the right ventricular outflow tract may be necessary from an oncological perspective. Lung metastases are removed by means of atypical resection to the point of pneumonectomy.

The post-operative management corresponds to that for PEA, although anticoagulation is not necessary. Most patients are advised to undergo prolonged thromboembolism prophylaxis with low-molecular-weight heparin at therapeutic doses for 6 weeks.

Depending on the histological subtyping and the patient's clinical condition, adjuvant doxorubicin/ifosfamide-based chemotherapy is currently recommended in the context of, or analogous to, the IAWS 1-2006 registry analysis. The soft-tissue sarcoma working group offers a number of other open-for-enrolment or planned studies in which patients can be included.

Patients who receive surgery and adjuvant treatment have the best prognosis. Long-term survival data of >7 years after the primary procedure have been reported. Systemic metastases are rare. Accordingly, repeat surgery or metastasectomy is indicated [75].

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Conflicts of interest/author disclosures

HW has received fees for consultations and/or lectures from Actelion, Bayer, Boehringer Ingelheim, GSK, Novartis, Pfizer und Roche.

SK has received speaker's and/or consultant fees from Actelion, Bayer, Boehringer Ingelheim, Bristol-Myers, Daiichi-Sankyo, GSK, Pfizer.

IML has received speaker's and/or consultant fees from Actelion, AOP Orphan, Astra-Zeneca, Bayer-Schering, Cordis, Daiichi-Sankyo, Edwards, GSK, Medtronic, Novartis, Pfizer, Servier, United Therapeutics.

ACB has received speaker's and/or consultant fees from Philips, Guerbet, General Electric GE.

MG has received speaker's and/or consultant fees from Actelion, AOP Orphan, GlaxoSmithKline.

FG has received speaker's fees from Actelion; research grants to institution from Actelion.

AG has received fees for consultations and/or lectures from Actelion, Bayer, Bracco Imaging, Hermes Medical Solutions, Pfizer and Siemens Medical Solutions.

CG has received speaker's and/or consultant fees from BMS, Novartis, Boehringer, Bayer, MSD and Roche.

SG has received speaker's and/or consultant fees from Actelion, Bayer, GSK and Pfizer.

MH has received speaker's and/or consultant fees from Actelion, Bayer, Berlin Chemie, Boehringer, GSK, MSD, Novartis, Pfizer, United Therapeutics.

JB has nothing to disclose.

MMH has received fees for consultations and/or lectures from Actelion, Bayer, Gilead, GSK, MSD and Pfizer.

WK has nothing to disclose.

TK has received speaker's and/or consultant fees from Actelion, Bayer, GSK, Pfizer.

UK has received fees for consultations and/or lectures from Actelion, Bayer Healthcare.

ML has received fees for consultations and/or lectures from Actelion, Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, MSD and Pfizer.

BCM has received fees for consultations and/or lectures from Bayer, MSD and Siemens Healthcare.

KMO has received fees for consultations and/or lectures from Actelion, Bayer, GSK, and United Therapeutics.

HJS has nothing to disclose.

MS has nothing to disclose.

HJS has received speaker's and/or consultant fees from Actelion, Bayer, GSK.

SU receives grants from the Swiss National Science Foundation and the Zurich Lung. She has received speaker fees and unrestricted grant money from Actelion, Bayer, Orpha-Swiss.

CBW has received speaker's fees or consultant honoraria from Bayer AG, BTG, MSD and Pfizer.

EM has received speaker's and/or consultant fees from Actelion, Bayer, MSD and Pfizer.

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Please cite this article as: H. Wilkens, et al., Chronic thromboembolic pulmonary hypertension (CTEPH): Updated Recommendations from the Cologne Consensus Conference 2018, Int J Cardiol (2018), https://doi.org/10.1016/j.ijcard.2018.08.079

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Please cite this article as: H. Wilkens, et al., Chronic thromboembolic pulmonary hypertension (CTEPH): Updated Recommendations from the Cologne Consensus Conference 2018, Int J Cardiol (2018), https://doi.org/10.1016/j.ijcard.2018.08.079