Circumstances of bronchiolitis obliterans development after lung transplantation: analysis of risk factors

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Abstract

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Bronchiolitis obliterans after lung transplantation is the major factor which limits the long term survival. It affects 35—68 % of those patients who survive longer than 3 months. Nowadays, the results of treatment and evaluation of bronchiolitis obliterans risk factors are not very encouraging. Although several risk factors of the development of bronchiolitits obliterans have already been identified, their role and importance have not been clearly defined yet.
The objective of this article is to give an overview of the current international knowledge in treatment strategies and analyse to international trends in the research of risk factors of the development of this complication together with available results. Special attention is given to donor and recipient risk factors. ***(Tab. 2, Fig. 1, Ref. 32.)***
Key words: bronchiolitis obliterans, lung transplantation, risk factors.

Abstrakt

Vývoj obliterujúcej bronchiolitídy po transplantácii pľúc a analýza rizikových faktorov
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Potransplantačná obliterujúca bronchiolitída je významným faktorom, ktorý limituje dlhodobé prežívanie. Postihuje 35—68 % pacientov prežívajúcich viac ako 3 mesiace po transplantácii pľúc. Súčasné výsledky liečby a hodnotenia rizikových faktorov obliterujúcej bronchiolitídy nie sú veľmi povzbudivé. Hoci niekoľko rizikových faktorov tejto komplikácie sa už podarilo identifikovať, ich úlohu a závažnosť sa doteraz nepodarilo určiť presne.
Práca podáva prehľad súčasných medzinárodných poznatkov a dostupných výsledkov v stratégii liečby a analýzu medzinárodných trendov vo výskume rizikových faktorov vedúcich k vzniku obliterujúcej bronchiolitídy. Donorským a recipientskym rizikovým faktorom sa v práci venuje zvláštna pozornosť. *(Tab. 2, obr. 1, lit. 32.)*
Kľúčové slová: obliterujúca bronchiolitída, transplantácia pľúc, rizikové faktory.

Abbreviations:
BO — bronchiolitis obliterans
BOS — bronchiolitis obliterans syndrome
TBB — transbronchial biopsy
FEV1 — forced expiratory volume in 1 second
BAL — bronchoalveolar lavage
BAR — bronchial artery revascularization
CMV — cytomegalovirus
HLA — human leucocyte antigen system
ATG — anti-thymocyte globulin, immunosuppressant
MMF — mycophenolate mofetil, immunosuppressant

Zoznam použitých skratiek:
BO — bronchiolitis obliterans
BOS — bronchiolitis obliterans syndróm
TBB — transbronchiálna biopsia
FEV1 — úsilný 1-sekundový výdych
BAL — bronchoalveolárna laváž
BAR — revaskularizácia bronchiálnej artérie
CMV — cytomegalovírus
HLA — hlavný humánnny histokompatibilný systém
ATG — antithymocytárny globulín, imunosupresívum
MMF — mykofenolát mofetil, imunosupresívum

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Národný ústav tuberkulózy a respiračných chorôb v Bratislave a Klinik für Herz-, Thorax Chirurgie vo Viedni

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Tab. 1. Working formulation for classification and grading of pulmonary rejection.

A) Acute rejection
   0. Grade 0 – No significant abnormality
   1. Grade 1 – Minimal acute rejection
      a) With evidence of bronchiolar inflammation
      b) Without evidence of bronchiolar inflammation
      c) With large airway inflammation
      d) No bronchioles are present
   2. Grade 2 – Mild acute rejection
      a) With evidence of bronchiolar inflammation
      b) Without evidence of bronchiolar inflammation
      c) With large airway inflammation
      d) No bronchioles to evaluate
   3. Grade 3 – Moderate acute rejection
      a) With evidence of bronchiolar inflammation
      b) Without evidence of bronchiolar inflammation
      c) With large airway inflammation
      d) No bronchioles to evaluate
   4. Grade 4 – Severe acute rejection
      a) With evidence of bronchiolar inflammation
      b) Without evidence of bronchiolar inflammation
      c) With large airway inflammation
      d) No bronchioles to evaluate
B) Active airway damage without scarring
   1. Lymphocytic bronchitis
   2. Lymphocytic bronchiolitis
C) Chronic airway rejection
   1. Bronchiolitis obliterans – subtotal
      a) Active
      b) Inactive
   2. Bronchiolitis obliterans – total
      a) Active
      b) Inactive
D) Chronic vascular rejection
E) Vasculitis

Tab. 1. Pracovná klasifikácia a stupeň pľúcnej rejekcie.

A) Akútna rejekcia
   0. Stupeň 0 – Bez patologického nálezu
   1. Stupeň 1 – Minimálna akútna rejekcia
      a) So známkami bronchiolárneho zápalu
      b) Bez známok bronchiolárneho zápalu
      c) So známkami zápalu väčších dýchacích ciest (bronchov)
      d) Bronchioly neprítomné
   2. Stupeň 2 – Mierna akútna rejekcia
      a) So známkami bronchiolárneho zápalu
      b) Bez známok bronchiolárneho zápalu
      c) So známkami zápalu väčších dýchacích ciest (bronchov)
      d) Bronchioly neprítomné (nehodnotiteľné)
   3. Stupeň 3 – Stredne ťažká akútna rejekcia
      a) So známkami bronchiolárneho zápalu
      b) Bez známok bronchiolárneho zápalu
      c) So známkami zápalu väčších dýchacích ciest (bronchov)
      d) Bronchioly neprítomné (nehodnotiteľné)
   4. Stupeň 4 – Ťažká akútna rejekcia
      a) So známkami bronchiolárneho zápalu
      b) Bez známok bronchiolárneho zápalu
      c) So známkami zápalu väčších dýchacích ciest (bronchov)
      d) Bronchioly neprítomné (nehodnotiteľné)
B) Aktívne poškodenie dýchacích ciest bez procesu jazvenia
   1. Lymfocytárna bronchitída
   2. Lymfocytárna bronchiolitída
C) Chronická rejekcia dýchacích ciest
   1. Bronchiolitis obliterans – subtotálna
      a) Aktívna
      b) Neaktívna
   2. Bronchiolitis obliterans – totálna (celková)
      a) Aktívna
      b) Neaktívna
D) Chronická vaskulárna rejekcia
E) Vasculitis

Bronchiolitis obliterans (BO) after lung transplantation is the major factor limiting long term survival (Heng et al., 1998; Husain et al., 1999; Boehler et al., 1998). It is found in a variety of settings, not only as a complication of lung and heart-lung transplantation (affecting 34 % to 39 % of patients, usually in the first 2 years after transplantation) (Husain et al., 1999; Schlesinger et al., 1998) and bone marrow transplantation, but also in rheumatoid arthritis, after inhalation of toxic agents such as nitrogen dioxide, after ingestion of certain drugs such as penicillamine and ingestion of the East Asian vegetable Sauropus androgynous, and as a rare complication of adenovirus, influenza type A, measles, and Mycoplasma pneumoniae infections in children (Boehler et al., 1998; Schlesinger et al., 1998). All the abovementioned factors result in an injury of a bronchiolar epithelium. During the repair process an excessive proliferation of granulation tissue may consequently lead to narrowing or obliteration of the airway lumen. Therefore, obliterative or constructive bronchiolitis is being defined as a inflamation and fibrosis occurring predominantly in the walls and contiguous tissues of membranous and respiratory bronchioles with resultant narrowing of their lumens (Schlesinger et al., 1998).

Diagnosis, classification

To confirm the diagnosis of BO it is necessary to obtain a sample of tissue by transbronchial (TBB) or open lung biopsy. In addition, this diagnosis must be classified by a histologic result (Table 1) as well as by an objective clinical marker. In 1993, an expert group from the International Society for Heart and Lung Transplantation defined that the forced expiratory volume in 1 second (FEV1) is the most reliable marker. As the symptoms and signs (i.e. shortness of breath and chronic productive cough) of early BO are nonspecific, a decrease of FEV1 may occur before any clinical symptoms appear. Therefore FEV1 is a consistent indicator of chronic pulmonary graft dysfunction.

The term bronchiolitis obliterans syndrome (BOS) was adopted to describe such a dysfunction, which is not explained by acute rejection, infection and problems of the bronchial anastomosis (Cooper et al., 1993). The BOS grading system is established on a posttransplant baseline value of FEV1 (the averages of the two best measurements taken in the period between the 3rd and 6th week), which classifies belonging to one among the four categories. The system is shown in Table 2. This grading system was widely adopted and now is commonly reported in clinical studies worldwide.

Tab. 2. BOS staging system.

0. No significant abnormality: FEV1 >80%
   a) Without pathologic evidence of obliterative bronchiolitis
   b) With pathologic evidence of obliterative bronchiolitis
1. Mild obliterative bronchiolitis syndrome: FEV1 66% to 80%
   a) Without pathologic evidence of obliterative bronchiolitis
   b) With pathologic evidence of obliterative bronchiolitis
2. Moderate obliterative bronchiolitis syndrome: FEV1 51% to 65%
   a) Without pathologic evidence of obliterative bronchiolitis
   b) With pathologic evidence of obliterative bronchiolitis
3. Severe obliterative bronchiolitis syndrome: FEV1 <50%
   a) Without pathologic evidence of obliterative bronchiolitis
   b) With pathologic evidence of obliterative bronchiolitis

Tab. 2. Štádia syndrómu obliterujúcej bronchiolitídy.

0. Bez patologického nálezu: FEV1 >80%
   a) Bez histopatologického nálezu obliterujúcej bronchiolitídy
   b) S histopatologickým nálezom obliterujúcej bronchiolitídy
1. Mierny stupeň syndrómu obliterujúcej bronchiolitídy: FEV1 66%-80%
   a) Bez histopatologického nálezu obliterujúcej bronchiolitídy
   b) S histopatologickým nálezom obliterujúcej bronchiolitídy
2. Stredne ťažký stupeň syndrómu obliterujúcej bronchiolitídy: FEV1 51%-65%
   a) Bez histopatologického nálezu obliterujúcej bronchiolitídy
   b) S histopatologickým nálezom obliterujúcej bronchiolitídy
3. Ťažký ťažký stupeň syndrómu obliterujúcej bronchiolitídy: FEV1 <50%
   a) Bez histopatologického nálezu obliterujúcej bronchiolitídy
   b) S histopatologickým nálezom obliterujúcej bronchiolitídy

Risk factors

Since the early descriptions of disorders circumstances, which inable the BO development after lung transplantation, have been searched for. One of the difficulties associated with the earlier reports resides in the inconsistent definition of BO itself and relatively late publication of a clinical definition for bronchiolitis obliterans syndrome (BOS) (Boehler et al., 1998). Therefore, as it was already mentioned above, in 1993 (1996 respectively), a clinically applicable system for the staging of chronic rejection after lung transplantation was created by an expert group from the International Society for Heart and Lung Transplantation (Berry et al., 1990; Cooper et al., 1993; Yousem et al., 1996).

Up to now the following risk factors are being identified: Acute rejection, Donor risk factors (i.e. airway ischemia, preservation damage, age of donor, ischemia time, cause of death, pulmonary history), Recipient risk factors, Type of transplantantation and other potential risk factors.

Acute rejection

An acute rejection appears to be the major risk factor for BO. Acute rejection is histopathologically characterized by perivascular mononuclear infiltrates and a lymphocytic bronchitis/bronchiolitis. Acute rejection is orchestrated by helper T-lymphocytes, which recognize donor major histocompatibility complex epitopes and secrete cytokines stimulating prolifearation of cytotoxic T-lymphocytes. During acute rejection, donor-specific alloreactive lymphocytes have been found in bronchoalveolar lavage (BAL) fluid and transbronchial biopsies. The number of authors in their articles confirmed that the frequency of acute rejection episodes was associated with an increased risk for BO, but also suggested that the degree of rejection played a role (Husain et al., 1999; Boehler et al., 1998). Finally it must to be assumed that organizing pneumonia, bacterial pneumonia or fungal pneumonia, and increasing severity and frequency of cytomegalovirus infections potentiate the effect of acute rejection (Girgis et al., 1996).

Donor risk factors

Airway ischemia, bronchial artery revascularization. The airway ischemia and consequently the direct revascularization of the transplant airways can also play a significant role in the process of BO development. According to several authors, initial ischemic injury starts with the interruption of bronchial artery circulation at transplantation. Therefore, reanastomosis of the bronchial arterial circulation with the recipient∞s mammary artery or to the recipient∞s ascending aorta was recomended.

The lungs have a dual blood supply. By the pulmonary artery that provides venous blood under low pressure and the bronchial arteries that provide oxygenated blood under arterial pressure. Therefore it is logical to assume that routine bronchial artery revascularisation (BAR) is reasonable. The main argument for not reestablishing the bronchial artery circulation during lung transplantation is that it is technically difficult, unreliable, prolongs donor organ ischemia time, and increases the risk of perioperative bleeding. In addition, early results after lung transplantation — single lung, as well as sequential bilateral lung — are so positive nowadays, that it may be argued whether BAR is really necessary (Patterson, 1993; Pettersson et al., 1997). Consequently some surgeons question whether it is acceptable to add another operative risk to the procedure. The knowledge about the role of the bronchial artery circulation in the transplanted lung and the impact of successful BAR on outcome after lung transplantation is still very limited. Bronchial ischemia could result in airway necrosis, anastomic dehicence, anastomic and bronchial stenosis, and bronchomalacia. One might speculate whether, in addition, ischemia could contribute to reperfusion injury, reduce the ability of lungs to resist and fight infections, change the pattern of rejections, or contribute to early development of BOS. The early Toronto experience (Patterson et al., 1990) demonstrated beyond any doubts that en bloc double lung transplantation with tracheal anastomosis without BAR should not to be performed. In single and sequential bilateral lung transplantation, which has an acceptable low incidence of bronchial problems, the donor bronchus is divided and anastomosed very close to the lung. In these cases, the bronchus survives on the pulmonary artery blood supply (desatured blood under low pressure). Ingrowth of new vessels from the surroundings could be facilitated by wrapping of the anastomosis with omentum. A successful BAR requires a special technique for organ harvesting, identification of the bronchial arteries, a good conduit, good exposure of the bronchial artery openings in the donor descending aorta, and an anastomotic technique that allows revascularization of several bronchial arteries (Pettersson et al., 1997).

The technique of BAR has been developed to prove its safety and justification. Only a long-term follow-up of a sufficient number of patients can show whether BAR is justified and can contribute to the improved results after lung transplantation.

Diffuse alveolar damage (preservation damage). According to several authors (Bando et al., 1995; Heng et al., 1998; Boehler et al., 1998), factors, which do not correlate with the incidance of BO are as follows: age of recipient and donor (in adults), sex, ABO blood group, the recipient∞s underlying disease, donor ischemic time, and the occurrence of diffuse alveolar damage. In literature the incidence of histologically verified diffuse alveolar damages is being reported very sporadically and rarely (In Saint Martin's study it was described only in one case (1 %) (Saint Martin et al., 1996)).

Donor age and graft ischemic time. Increased graft ischemic time and donor age belong among the risk factors for early death after heart transplantation, but the effect of these variables on survival after lung transplantation has not been determined in a large, multinational study. However, Novick et al. noted that very young or old donor age was associated with a decreased early survival, whereas the interaction between donor age and ischemic time was a significant predictor of 1 year mortality after transplantation (Novick et al., 1999). Due to the given critical shortage of donor lung grafts, cautious expansion of donor acceptance criteria (specially as regards ischemic time) is advisable. Lung transplantation are currently limited by donor shortage and the need for a short organ ischemic time. Several studies tried to evaluate prolonged donor organ ischemia and its effect on overal survival. Kshettry et al. concluded that the prolonged donor allograft ischemic time is not associated with an adverse effect on survival (Kshettry et al., 1996).

Mechanisms of death. Pulmonary dysfunction, often delayed in presentation, is among the sequelae of major trauma. Transplantation of lungs from donors involved in major trauma therefore carries a risk of early graft dysfunction. Sporadically reported cases highlight the potential risks of transplanting lungs from traumatic donors. However, according to the present experiences the use of donors involved in major trauma does not increase the risk of early complications after lung transplantation (Waller et al., 1995; Waller et al., 1995).

Pulmonary history of donor (e.g. smoking). As it was already mentioned above, lung transplantation is limited by shortage of suitable donors. To address this shortage a lot of transplant centers worldwide began to use marginal donor lungs, which do not meet all the previous rigorous criteria. On the basis of their data, it is assumed that successful outcome of lung transplantation can be achieved with the use of marginal donors. As for the donor∞s smoking history for the development of BO, the available documentation is rather poor and the reported experience is sporadic and rare (Shumway et al., 1994; Sundaresan et al., 1995; Marques et al., 1997; Gabbay et al., 1999).

Type of transplant

Type of transplantation (Single/ bilateral, re-transplantation). While lung retransplantation remains the only therapeutic option in early or late graft failure, its value is viewed controversially. According to Hanover experience, the acturial freedom from obliterative bronchiolitis (stage 3) at 1 and 2 years was calculated at 88 and 27 % (primary grafts: 88% vs 72%) (Shafers et al., 1995). Other studies assume that BO does not recur in an accelerated manner after retransplantation, although pulmonary function does worsen again by 2 years (Novick et al., 1995). To conclude retransplantation is a realistic option in early and late graft failure after lung transplantation, however, this modality is appropriate only in selected ambulatory patients who are operated on at the experienced centers. In view of scarcity of lung donors, patient selection for retransplantation should remain strict and should be giuded by the outcome data reviewed elsewhere (Shafers et al., 1995; Novick et al., 1998).

Due to the inferior graft survival compared with the first transplant and the shortage of lung allografts, questions have been raised as to whether retransplantation should continue to be performed (Boehler et al., 1998). It seems that retransplantation remains the ultimate therapeutic option in BO. In fact, early mortality after retransplantation is clearly higher than after primary transplantation, due to increase incidence in infections (Schafers et al., 1995).

Other potential risk factors

Other potential risk factors have been also identified. Many centers have reported that cytomegalovirus (CMV) pneumonitis, other respiratory viral, bacterial and fungal infections are also significant risk factors for BO. HLA matching and its potential relationship to BO was investigated by several groups, but the issue remains controversial (Itescu et al., 1997; Weinberg et al., 1997).

Treatment

Obliterative bronchiolitis is the main complication which limits long-term success of lung transplantation. It affects 35-68% of patients who survive longer than 3 months after lung transplantation (Bando et al., 1995). In the Stanford experience (Reichenspurner et al., 1995), the acturial freedom from BO after lung transplantation was 29 % at 5 years. Acturial survival for patients with BO was 44 % at 5 years versus 63 % for those without.

In the last decade, several therapies for treating this complication after lung transplantation have emerged, but it has to be assumed that the range of available treatment options is narrow and disappointing (Boehler et al., 1998). For the treatment of BO the following regimens and strategies are being used: Augmentation of corticosteroids and cytolytic therapy, inhaled cyclosporine, methotrexate, administration of new immunosuppressives (tacrolimus, sirolimus, mycophenolate mofetil) and other immune-modulating therapies (total lymphoid irradiation, photopheresis, allogenic bone marrow transplantation).

Although no protocol is universally accepted for the treatment of BO, augmentation of corticosteroids and cytolytic therapy have been used as initial therapies in the past (Boehler et al., 1998). Methylprednisolone, 0.5 to 1g daily for 3 consecutive days, is followed by a 3- to 4-week tapering course of prednisone. The cytolytic therapy, which contains the administration of antilymphocyte antibodies (Anti-Thymocyte Globulin ATG) between 7 and 14 days, is also applied together with the previous one.

Methotrexate has been used successfuly for many years to treat recurrent or resistant rejection after heart transplantation (Briffa and Morris, 1997). The successful use of this drug in lung transplantation was reported by Toronto group in 1996 (Dusmet et al., 1996).

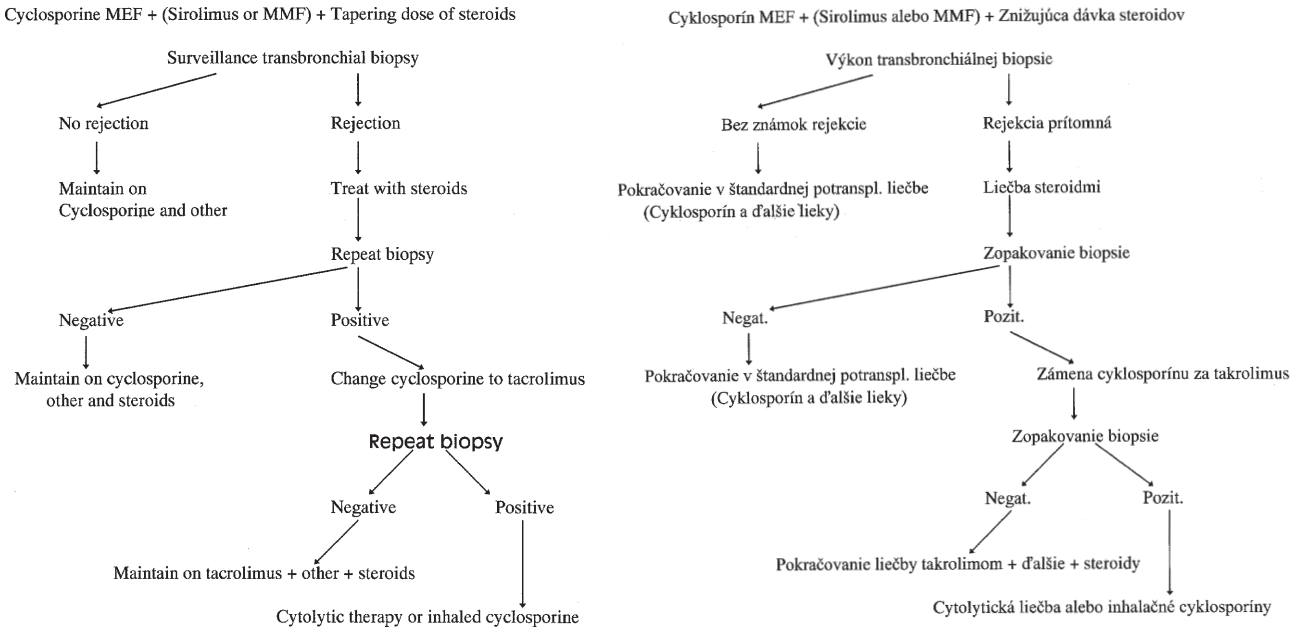

Fig. 1. Flow diagram showing suggested new treatment strategies. MEF: microemulsion formulation; MMF: mycophenolate mofetil.
Obr. 1. Algoritmus odporúčanej stratégie liečby. MEF: mikroemulzná forma liečiva; MMF: mykfenolát mofetil.

Tacrolimus, sirolimus and mycophenolate mofetil (MMF) belong among the new immunosuppressives. The mechanisms of their action is reported elsewhere (Briffa and Morris, 1997; Pereszlenyi et al., 2000). These drugs replaced the former immunosuppressives in standard postransplant immunosuppressive protocols.

Inhaled corticosteroids play an important role in treatment of asthma and chronic inflamatory diseases of airways. As inflammation of the airways is also an important feature of early BO, administration of aerosolized steroids and other medicaments is necessary. Aerosolized cyclosporine was also tried in treatment of BO. Its impact and success in treatment of BO was published elsewhere (Iacono et al., 1996).

Other immune-modulating treatment strategies used against BO include: extracorporeal photochemotherapy, plasmapheresis, total lymhoid irradiation and allogenic bone marrow transplantation (to achieve chimerism). To date, the numbers of patients treated with these strategies are too small to be conclusive (Briffa and Morris, 1997; Boehler et al., 1998).

For some new suggested treatment strategies see Figure 1 (Briffa and Morris, 1997).

Conclusion

At the present time, the results of treatment of established BO are not very encouraging. After more than 15 years of experience with lung transplantation, the 5 years survival after lung transplantation is still less than 60 % (Briffa and Morris, 1997; Pereszlenyi et al., 2000). As it was already mentioned above, BO is the major factor, which limits long term survival after lung transplantation. So, what are those potential possibilities against this threatening complication? Emphasis should be made on prevention of events known to be associated with the high risk of BO development. On the other hand, early diagnosis and treatment by new immunosuppressive regimens, application of new treatment strategies, which were already desribe above, are also very important. Further investigation of the of BO pathogenesis and progress in immunobiology will surely bring a solution for this threatening, devastating process after (heart-) lung transplantation (Boehler et al., 1998).

A number of randomized prospective studies, retrospective investigations, international exchange of experiences, cooperation in new treatment strategies development are the most important steps to be performed in the future. May be all of these or a certain combination of treatment strategies will help to improve the results in long-term survival.

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