International consensus on severe lung cancer—the first edition

重症肺癌国际共识——第一版

Introduction

引言

Lung cancer is one of the most prevalent and lethal cancers worldwide. The traditional treatments include surgery, chemotherapy, radiotherapy and interventional therapy. The survival of lung cancer patients has dramatically been prolonged in recent years with the availability of targeted therapies, antiangiogenic agents and immune checkpoint inhibitors (ICIs). Meanwhile, technologies for the molecular detection of lung cancer have also advanced rapidly: the detection of single driver genes has evolved to cover combined multi-gene analysis, and whole exome sequencing (WES) has increasingly been applied in the clinical setting. In addition, life support technologies, including ventilators, artificial liver, and artificial kidney as well as extracorporeal membrane oxygenation (ECMO), have further matured, providing powerful forms of life support for patients with various acute and critical diseases. However, most clinical studies have only enrolled patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores from 0 to 1, with few patients having PS scores of 2; patients with a PS score of 3 or 4 have been typically excluded. Therefore, due to the lack of high-quality evidence, supportive care is recommended for patients with a PS score of 3 to 4 in the current guidelines. In the real-world, however, approximately 25% of lung cancer patients present with PS score of 3 or 4 or attain scores between 3 and 4 during the course of treatment. Certain patients with high PS scores can benefit from individualized anti-tumor treatment plus appropriate life-support techniques. In 2017, the Lung Cancer Research Team at the First Affiliated Hospital of Guangzhou Medical College & Institute of Respiratory Diseases for the first time pioneered the concept of "advanced severe lung cancer" and argued that standardized therapy for chronic obstructive pulmonary disease (COPD) plus anti-tumor therapy can improve both quality of life and prognosis in patients with lung cancer combined with COPD. The authors also found that the early detection of lung cancer driver genes and timely targeted therapy can be successful in treating patients with advanced severe lung adenocarcinoma with a PS score of 4. In 2019, the concept of advanced severe lung cancer was further developed in a featured article that indicated "Advanced severe lung cancer: does not refer to end-stage lung cancer but rather to stage IIIB, IIIC and IV lung cancers with a PS score of 2–4, which can result from a variety of factors related to the disease itself or anti-tumor

drugs and which are highly likely to benefit from the currently available systemic anti-tumor therapies".

肺癌是全世界最普遍和最致命的癌症之一。传统的治疗方法包括手术、化疗、放疗和介入治疗。近年来，随着靶向治疗、抗血管生成药物和免疫检查点抑制剂(ICI)的出现，肺癌患者的生存期显著延长。与此同时，肺癌的分子检测技术也在飞速发展：单一驱动基因的检测已经发展到多基因联合分析，全外显子组测序（WES）越来越多地应用于临床。此外，呼吸机、人工肝、人工肾以及体外膜肺氧合（ECMO）等生命支持技术进一步成熟，为各种急危重症患者提供有力的生命支持。然而，大多数临床研究只纳入了东部肿瘤协作组(ECOG)体能状态(PS)评分从 0 到 1 的患者，很少有 PS 评分为 2 的患者；PS 评分为 3 或 4 的患者通常被排除在外。因此，由于缺乏高质量证据，目前指南推荐对 PS 评分为 3～4 分的患者进行支持治疗。然而，在真实世界中，大约 25%的肺癌患者在治疗过程中的 PS 评分为 3 或 4 分或达到 3 至 4 分之间。某些高 PS 评分的患者可以从个体化的抗肿瘤治疗和适当的生命支持技术中受益。2017 年，广州医学院第一附属医院&呼吸疾病研究所肺癌研究团队首次提出“晚期重症肺癌”概念，提出规范化治疗慢性阻塞性肺疾病(COPD)加抗肿瘤治疗可以改善合并 COPD 的肺癌患者的生活质量和预后。作者还发现，早期发现肺癌驱动基因，及时进行靶向治疗，可以成功治疗 PS 评分 4 分的晚期重症肺腺癌患者。2019 年，晚期重症肺癌的概念进一步发展，专题文章指出“晚期重症肺癌不是指终末期肺癌，而是指 PS 评分为 2-4 的ⅢB、ⅢC 和Ⅳ期肺癌，这可能是由多种与疾病本身相关的因素或抗肿瘤药物引起的，并且极有可能从目前可用的全身抗肿瘤疗法中受益”。

In recent years, with the advances in lung cancer diagnosis and treatment techniques and life support technologies, more clinical studies have enrolled patients with a PS score of 2, and some real-world studies have enrolled patients with PS scores of 3–4. Even for patients with early-stage lung cancer, studies have shown that patients with poor PS scores and co-morbidities have a reduced chance of undergoing surgery and an increased mortality rate; nevertheless, survival benefit may still be obtained through surgical modifications combined with individualized and multidisciplinary treatment. Therefore, the concept of severe lung cancer should not be limited to advanced lung cancer, but applied to all lung cancer patients. In particular, due to the increase in treatment options as well as substantially prolonged survival, the majority of patients may have a PS score between 2 and 4 for a certain period of time due to a variety of reasons. How to provide timely and reasonable treatment for these lung cancer patients has become a critically important real-world research topic. Therefore, we invited lung cancer experts at home and abroad to consider this issue, and this group has reached the following consensus.

近年来，随着肺癌诊疗技术和生命支持技术的进步，越来越多的临床研究纳入了 PS 评分为 2 分的患者，有些真实世界研究纳入了 PS 评分为 3-4 分的患者。研究表明，即使对于早期肺癌患者，PS 评分较差和合并症的患者接受手术的机会减少，死亡率增加；尽管如此，通过手术改进结合个体化和多学科治疗，仍有可能获得生存获益。因此，重症肺癌的概念不应仅限于晚期肺癌，而应应用于所有肺癌患者。特别是，由于治疗选择的增加以及生存期的显著延长，大多数患者由于各种原因在一定时间段内的 PS 评分可能在 2 到 4 之间。如何为这些肺癌患者提供及时合理的治疗已成为真实世界中至关重要的研究课题。因此，我们邀请了国内外肺癌专家来考虑这个问题，本组达成了以下共识。

Methods

方法

This consensus was conceived and developed by 87 experts with significant experience in the field. The expert group was divided into 5 subgroups that formulated questions for each topic. The Population, Intervention, Comparison, and Outcome (PICO) framework was used to facilitate systematic literature review. Various databases including PubMed, EMBASE and the Cochrane Library were systematically searched using key words such as lung cancer, poor PS, comorbidities, complications, adverse events (AEs), chemotherapy, radiotherapy, surgery, interventional therapy, epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), targeted therapy, antiangiogenic therapy, ICIs and supportive treatment for relevant articles published between January 2000 and March 2021. Each subgroup responded to related topics and developed key guidelines, which were consolidated into 10 key issues (definition, common causes, benefit of diagnosis and treatments, basic diagnosis and treatment techniques, specific diagnosis and treatment strategies, surgical treatment, radiotherapy, interventional techniques, anti-tumor drugs, and life support techniques). The findings were graded based on the Oxford Centre of Evidence-Based Medicine’s Levels of Evidence. Five of us drafted (C Zhou, S Li, J Liu, Q Chu and L Miao) the manuscript and submitted it to all 5 subgroups for discussion and revision. The drafts were distributed to the entire panel of experts and edited multiple times until each participant finally approved it.

这一共识是由 87 位在该领域具有丰富经验的专家构思并制定的。专家组分为 5 个小组，为每个主题制定问题。人群、干预、比较和结果(PICO)框架用于促进系统性的文献复习。使用肺癌、PS 差、合并症、并发症、不良事件（AE）、化疗、放疗、手术、介入治疗、表皮生长因子受体（EGFR）、间变性淋巴瘤激酶(ALK)、靶向治疗、抗血管生成治疗、ICIs 和支持治疗等关键词系统地检索了包括 PubMed、EMBASE 和 Cochrane 图书馆在内的各种数据库在 2000 年 1 月至 2021 年 3 月之间发表的相关文章。每个亚组回答相关主题并制

定关键指南，将其合并为 10 个关键议题（定义、常见病因、诊疗获益、基础诊疗技术、具体诊疗策略、手术治疗、放疗、介入技术、抗肿瘤药物、生命支持技术）。这些发现根据牛津循证医学中心的证据水平进行分级。我们五个人（C Zhou、S Li、J Liu、Q Chu 和 L Miao）起草了手稿，并提交给所有 5 个小组讨论和修订。将草稿分发给全体专家组并反复编辑，直到每位参与者最终批准为止。

Consensus 1: the concept of severe lung cancer

共识 1：重症肺癌的概念

Severe lung cancer is a disease in which the patient has a PS score between 2 and 4 in certain stages due to various acute or chronic co-morbidities, the tumor itself, and/or treatment-related AEs but which has a high probability of achieving survival benefit and/or improvement in the PS score after supportive care and anti-tumor treatment on the basis of dynamic and precise testing. This concept addresses three domains:

重症肺癌是指由于各种急性或慢性合并症、肿瘤本身和/或治疗相关的 AE，患者在某些阶段的 PS 评分在 2 到 4 之间的疾病，但很有可能在动态精确检测的基础上的支持治疗和抗肿瘤治疗后的实现生存获益和/或 PS 评分的改善。这个概念涉及三个领域：

Etiology *病因*

Three main factors may cause severe lung cancer: (I) various acute and chronic co-morbidities such as heart failure (HF) and COPD; (II) the tumor itself, which may cause massive cardiac and pleural effusions and obstruction of large airways; and (III) various treatment-related AEs such as severe infection due to chemotherapy-induced myelosuppression, interstitial pneumonia due to tyrosine kinase inhibitor (TKI) use, and severe immune-related adverse reactions.

三个重要因素可能导致重症肺癌：(Ⅰ)各种急性和慢性合并症，如心力衰竭(HF)和 COPD；(Ⅱ)肿瘤本身，可引起大量心包和胸腔积液、阻塞大气道；和(Ⅲ)化疗引起的骨髓抑制所致的严重感染、酪氨酸激酶抑制剂（TKI）引起的间质性肺炎、免疫相关的严重不良反应等各种治疗相关的 AEs(不良事件)。

Targeted populations *目标人群*

Severe lung cancer is a category distinct from end-stage lung cancer. End-stage lung cancer is referred to patients who do not benefit of any specific treatments except palliative care to alleviate symptoms. However, severe lung cancer not only refers to lung cancer patients with PS scores between 2 and 4 in certain stages but also includes those who would enjoy a survival benefit and/or improvement in the PS score with various techniques and individualized multidisciplinary treatment.

重症肺癌是不同于终末期肺癌的一个类别。终末期肺癌是指除了缓解症状的姑息治疗外，无法从任何特定治疗中受益的患者。然而，重症肺癌不仅指 PS 评分在 2～4 分之间的某些分期的肺癌患者，还包括通过各种技术和个体化多学科治疗获得生存获益和/或 PS 评分改善的患者。

The value of diagnosis and treatment ***诊疗价值***

Treatments must be of viable benefit when performed in patients with severe lung cancer. The value of treatment depends on the state-of-the-art of modern medical technologies. The combination of three such technologies is particularly important: (I) dynamic and precise detection, which enables the timely identification of patients who may benefit from the treatment; (II) powerful life support technologies, which create suitable conditions for various anti-tumor treatments; and (III) anti-tumor treatments, which should be applied individually and thus are highly effective and safe.

对重症肺癌患者进行治疗时，必须具有切实可行的益处。治疗的价值取决于最先进的现代医疗技术。三项技术的结合尤为重要：(Ⅰ)动态精准检测，及时识别可能从治疗中受益的患者；(Ⅱ)强大的生命支持技术，为各种抗肿瘤治疗创造适宜的条件；和(Ⅲ)抗肿瘤治疗，应单独应用，高效安全。

Consensus 2: common causes of severe lung cancer

共识 2：重症肺癌的常见病因

Three main factors may cause severe lung cancer: (I) various acute and chronic co-morbidities such as HF and COPD; (II) the tumor itself, which may cause massive cardiac and pleural effusions and obstruction of large airways; and (III) various treatment-related AEs such as surgical complications, radiation injury, severe infections due to chemotherapy-induced myelosuppression, interstitial pneumonia due to TKI use, and severe immune-related adverse reactions.

三个重要因素可能导致重症肺癌：(Ⅰ)各种急慢性合并症，如 HF 和 COPD；(Ⅱ)肿瘤本身，可引起大量心包和胸腔积液、阻塞大气道；和(Ⅲ)手术并发症、放射损伤、化疗引起的骨髓抑制所致的严重感染、TKI 引起的间质性肺炎和免疫相关的严重不良反应等各种治疗相关的 AEs(不良事件)。

Acute and chronic co-morbidities ***急性和慢性合并症***

It was found that 87.3% of lung cancer patients had at least one comorbidity and 15.3% had severe comorbidity scores. Nieder et al. reported that lung cancer patients without comorbidities had lower PS scores. Another study also showed a positive correlation between a simplified comorbidity score and the PS score. A study investigated

the survival rate of lung cancer patients with comorbidities was significantly lower than that of patients without comorbidities.

结果发现，87.3%的肺癌患者至少有一种合并症，15.3%有严重的合并症。Nieder 等报道，没有合并症的肺癌患者的 PS 评分较低。另一项研究也显示简单的合并症与 PS 评分之间呈正相关。一项研究调查了有合并症的肺癌患者的生存率明显低于没有合并症的患者。

Heart failure **心衰**

The incidence of HF combined with lung cancer is increasing annually, and patients with HF are in fact more likely to develop cancer. HF increases the risk of death in all lung cancer patients [hazard ratio (HR) =1.85]; for patients with early-stage lung cancer, HF decreases the likelihood of undergoing surgery and increases postoperative complications.

心衰合并肺癌的发生率逐年增加，事实上心衰患者更容易患上癌症。心衰增加所有肺癌患者的死亡风险[风险比(HR)=1.85]；对于早期肺癌患者，HF(心衰)降低了接受手术的可能性并增加了术后并发症。

COPD(慢阻肺)

COPD is a risk factor for lung cancer and it is present in 40–70% of lung cancer patients. It is reported that 50.2% of non-small cell lung cancer (NSCLC) patients have COPD. One-third of lung cancer patients with coexisting COPD are not indicated for surgical treatment due to poor lung function. A meta-analysis also showed that coexisting COPD was associated with a lower survival rate and a higher rate of postoperative pulmonary complications in lung cancer patients.

COPD(慢阻肺)是肺癌的一个危险因素，存在于 40-70%的肺癌患者中。据报道，50.2%的非小细胞肺癌(NSCLC)患者有 COPD(慢阻肺)。由于肺功能差，三分之一合并 COPD(慢阻肺)的肺癌患者不适合手术治疗。一项 meta 分析也表明，合并 COPD(慢阻肺)与肺癌患者较低的生存率和较高的术后肺部并发症发生率相关。

Interstitial lung disease (ILD)**间质性肺病(ILD)**

A large amount of epidemiological has confirmed a close relationship between ILD and lung cancer. The risk of lung cancer in ILD is 3.5–7.3 times that in the general population, approximately 10–20%. Fifteen percent of ILD patients may die from lung cancer, and the incidence of ILD at the time of lung cancer diagnosis is between 2.4–10.9%. The incidence of lung cancer in the whole course of idiopathic pulmonary fibrosis (IPF) is greater than 50%. Moreover, lung cancer is associated with increased mortality in patients with IPF. Among IPF patients who undergo surgery for lung cancer, postoperative acute exacerbation of IPF is reported to occur in approximately

20%, with an associated mortality of about 50%. The 5-year survival rate of stage IA lung cancer patients with ILD was significantly lower than that of those without ILD (54.2% vs. 88.3%, P<0.0001). In patients with lung cancer and ILD, various anti-cancer treatments may also induce acute exacerbation of ILD.

大量流行病学已经证实 ILD(间质性肺病)与肺癌之间密切相关。ILD(间质性肺病)患者患肺癌的风险是普通人群的 3.5-7.3 倍，约为 10-20%。15%的 ILD(间质性肺病)患者可能死于肺癌，肺癌诊断时 ILD 的发生率在 2.4-10.9%之间。在特发性肺纤维化(IPF)的整个病程中肺癌的发生率大于 50%。此外，肺癌与 IPF(特发性肺纤维化)患者死亡率增加有关。在接受肺癌手术的 IPF(特发性肺纤维化)患者中，据报道约 20%的 IPF 术后急剧恶化，相关死亡率约为 50%。合并 ILD(间质性肺病)的ⅠA 期肺癌患者的 5 年生存率显著低于无 ILD 的患者（54.2%：88.3%，P<0.0001）。在肺癌合并 ILD(间质性肺病)患者中，各种抗癌治疗也可能诱发 ILD 急剧恶化。

Obesity **肥胖**

Abdominal obesity is a risk factor for lung cancer. In the obese population, the presence of adipose tissue around the thorax, abdomen and viscera reduces lung volume and impairs airway stability. Obese patients have difficulties in coughing up phlegm and turning over in bed, leading to increased perioperative and postoperative complications, and morbid obesity is a risk factor for mortality.

腹部肥胖是肺癌的危险因素。在肥胖人群中，胸部、腹部和内脏周围脂肪组织的存在会减少肺容量并损害气道稳定性。肥胖患者咳痰困难、在床上翻身困难，导致围手术期和术后并发症增加，病态肥胖是导致死亡的一个危险因素。

Lung cancer itself ***肺癌本身***

Lung cancer itself can lead to a variety of acute and critical complications that require urgent management, and timely management of these complications improve patients' quality of life and PS scores.

肺癌本身可导致多种急危重症，需要紧急处理，及时处理这些并发症可提高患者的生活质量和 PS 评分。

Pleural effusion **胸腔积液**

Pleural effusion occurs in 40% of lung cancer patients, and malignant pleural effusion is a poor prognostic factor. The PS score markedly increases as the severity of pleural effusion increases. A poor PS score is also a risk factor for poor prognosis in patients with pleural effusion.

40%的肺癌患者会出现胸腔积液，恶性胸腔积液是预后不良因素。随着胸腔积液严重程度的增加，PS 评分显著增加。较差的 PS 评分也是胸腔积液患者预后不良的危险因素。

Pericardial effusion **心包积液**

Pericardial effusion occurs in approximately 3% of lung cancer patients, and more than one-third of the cases of malignant pericardial effusions are caused by lung cancer. Pericardial effusion is a risk factor for decreased survival in lung cancer. Neoplastic pericardial effusion (NPE) patients with PS ≥2 have a worse prognosis.

大约 3%的肺癌患者会出现心包积液，超过三分之一的恶性心包积液是由肺癌引起的。心包积液是肺癌生存率下降的危险因素。PS≥2 的肿瘤性心包积液(NPE)患者预后较差。

Airway stenosis **气道狭窄**

Tracheal or bronchial proximal stenoses occurs as a complication in 20–30% of lung cancers, resulting in dyspnea, a poor PS score and poor prognosis. Resolving airway obstruction can rapidly improve the clinical condition and quality of life and decrease PS scores.

气管或支气管近端狭窄是 20%-30%肺癌的并发症，导致呼吸困难、PS 评分不佳和预后不良。解决气道阻塞可以迅速改善临床状况和生活质量，降低 PS 评分。

Venous thromboembolism (VTE)**静脉血栓栓塞症(VTE)**

VTE, including lower extremity deep vein thrombosis and pulmonary embolism, occurs in 13.9% of lung cancer patients. Cancer is a risk factor for VTE, with an HR of 4.7. VTE is 20 times more common in lung cancer patients than in people without cancer. VTE is also a significant cause of death in patients with lung cancer.

VTE(静脉血栓栓塞症)，包括下肢深静脉血栓形成和肺栓塞，发生在 13.9%的肺癌患者中。癌症是 VTE(静脉血栓栓塞症)的危险因素，HR 为 4.7。VTE(静脉血栓栓塞症)在肺癌患者中的发生率是非癌症患者的 20 倍。VTE(静脉血栓栓塞症)也是肺癌患者死亡的一个重要原因。

Treatment-related AEs ***治疗相关的不良事件(AEs)***

Surgery, radiotherapy, chemotherapy, targeted therapy, antivascular therapy, and immunotherapy are often associated with serious AEs will worsen PS scores; however, timely management of these AEs may improve the PS score.

手术、放疗、化疗、靶向治疗、抗血管治疗和免疫治疗往往与严重的 AE(不良事件)相关，会使 PS 评分恶化；然而，及时处理这些 AEs(不良事件)可能会改善 PS 评分。

Postoperative lung injury **术后肺损伤**

A meta-analysis revealed that the total incidence of postoperative lung injury was 4.3% for thoracic surgery, and the overall attributable mortality for postoperative lung injury was up to 26.5%; the 1-year survival rate was found to be significantly lower in patients with lung injury.

一项 meta 分析显示，胸外科术后肺损伤的总发生率为 4.3%，术后肺损伤的总体归因死亡率高达 26.5%；肺损伤患者的 1 年生存率显著降低。

Cerebral radiation necrosis **放射性脑坏死**

Retrospective studies have reported that in patients with metastatic brain tumors, cerebral radiation necrosis occurred in 4.7% to 9.2% of patients undergoing stereotactic radiotherapy, at radiotherapy doses ranging from 18 to 30 Gy. The incidence of cerebral radiation necrosis was 25–50% in patients treated with brachytherapy.

回顾性研究报道，在转移性脑肿瘤患者中，4.7%-9.2%的接受立体定向放疗的患者发生放射性脑坏死，放疗剂量范围为 18Gy-30Gy。在接受近距离放射治疗的患者中，放射性脑坏死的发生率为 25-50%。

Chemotherapy-induced neutropenia accompanied by infection **化疗引起的中性粒细胞减少症伴感染**

Neutropenia is a common hematologic toxicity induced by chemotherapeutic agents. Prolonged neutropenia is associated with increased risk of infection. The reported rate of mortality is 11.2% in lung cancer patients with febrile neutropenia.

中性粒细胞减少症是一种常见的由化疗药物引起的血液学毒性。长期中性粒细胞减少与感染风险增加有关。据报道，发热性中性粒细胞减少症的肺癌患者的死亡率为 11.2%。

Bleeding caused by angiogenesis inhibitors **血管生成抑制剂引起的出血**

In a meta-analysis including 12,617 patients with a variety of solid tumors, the incidence of hemorrhage was 30.4% after bevacizumab use, with 3.5% being high grade; the risk for fatal bleeding was only 0.8%, but was significantly elevated in lung cancer [relative risk (RR) =5.02].

在一项包括 12,617 例各种实体瘤患者的 meta 分析中，使用贝伐珠单抗后出血发生率为 30.4%，其中 3.5%为高级别；致命性出血的风险仅为 0.8%，但在肺癌中显著升高[相对风险(RR)=5.02]。

TKI-associated ILD

TKI(酪氨酸激酶抑制剂)相关 ILD(间质性肺病)

A meta-analysis showed that the incidence of all-grade and high-grade (≥ grade 3) ILD associated with EGFRTKIs was 1.6% and 0.9%, with a mortality of 13.0%.

一项 meta 分析显示，与 EGFR-TKI 相关的所有级别和高级别（≥3 级）ILD(间质性肺病)的发生率分别为 1.6%和 0.9%，死亡率为 13.0%。

In another meta-analysis, the incidence of all-grade and high-grade ILD associated with ALK-TKIs was 2.14% and 1.33%, respectively.

在另一项 meta 分析中，与 ALK-TKI 相关的全级别和高级别 ILD(间质性肺病)的发生率分别为 2.14%和 1.33%。

Checkpoint inhibitor-related pneumonitis (CIP)**检查点抑制剂相关性肺炎(CIP)**

The incidence of CIP was found to be 3–5% in clinical studies and 7–13% in real-world studies, with a case-fatality rate of 12.8–22.7%. The severity of CIP is positively correlated with the PS score.

在临床研究中发现 CIP(检查点抑制剂相关性肺炎)的发生率为 3-5%，在真实世界研究中为 7-13%，病死率为 12.8-22.7%。CIP(检查点抑制剂相关性肺炎)的严重程度与 PS 评分呈正相关。

Consensus 3: benefits of the diagnosis of and treatment for severe lung cancer

共识 3：重症肺癌诊治获益

Severe lung cancer is different from end-stage lung cancer, and the benefits of clinical treatment is worthy of emphasis. When a PS score is placed between 2 and 4, it should be aware that the PS score is stage-specific, “reversible”, or “fluctuating”. It should also be evident whether the survival benefit can be obtained in severe lung cancer patients through individualized treatment with the currently available techniques (recommendation category: B; level of evidence: 2a).

重症肺癌与终末期肺癌不同，临床治疗的益处值得强调。当 PS 评分介于 2 和 4 之间时，应注意 PS 分数是阶段特定的、“可逆的”或“波动的”。通过现有技术的个体化治疗能否在重症肺癌患者中获得生存获益也应该是显而易见的（推荐类别：B；证据级别：2a）。

Reversibility of the PS score

PS 分数的可逆性

One study investigated the efficacy and feasibility of gefitinib for patients with advanced NSCLC and found the PS improvement rate to be 79%; in particular, 68% of the 22 patients improved from PS 3–4 at baseline to PS 0 or 1. A retrospective study analyzing chemotherapy for advanced NSCLC with a PS score ≥2 showed that 45.26% of the patients had improved PS scores. In patients with massive pleural and pericardial effusion, drainage rapidly relieved the symptoms. In patients with major airway obstruction, timely and effective local treatment immediately alleviated the symptoms related to the airway obstruction. Thus, the PS score is reversible, and the key lies in resolving the immediate causes [e.g., oncologic emergencies] of the poor PS score.

一项研究调查了吉非替尼对晚期 NSCLC 患者的疗效和可行性，发现 PS 改善率为 79%；特别是，22 例患者中有 68%的患者从基线时的 PS 3-4 改善到 PS0 或 1。一项分析 PS 评分

≥2 的晚期 NSCLC 化疗的回顾性研究表明，45.26%的患者改善了 PS 评分。对于大量胸腔积液和心包积液的患者，引流可迅速缓解症状。对于较大气道阻塞的患者，及时有效的局部治疗可立即缓解与气道阻塞相关的症状。因此，PS 评分是可逆的，关键在于解决 PS 评分不佳的直接原因[例如肿瘤急症]。

PS scores fluctuation

PS 分数波动

In patients with lung cancer accompanied by chronic disease(s), the recurrence or exacerbation of the underlying disease may lead to fluctuations in the PS score. A study of 882 lung cancer patients showed a negative correlation between PS score and increasing severity of the comorbidities. A previous study analyzing NSCLC with a PS ≥2 showed that the score was improved in 91.7% of the patients after aggressive ventilatory support and management of the vital organ-centered comorbidities. In another study, 40% of 70 lung cancer patients with a PS score of 2–3 had underlying disease of the lungs; after treatment with anlotinib plus S-1, the PS score decreased and displayed stage-specific fluctuations.

在合并一种或多种慢性病的肺癌患者中，基础疾病的复发或恶化可能导致 PS 评分的波动。一项针对 882 例肺癌患者的研究表明，PS 评分与合并症严重程度的增加呈负相关。早先的一项分析 PS≥2 的 NSCLC 的研究表明，在积极的通气支持和以重要器官为中心的合并症管理后，91.7%的患者的 PS 评分得到改善。在另一项研究中，70 名 PS 评分为 2-3 的肺癌患者中有 40%有肺部基础疾病；用安罗替尼加 S-1(替吉奥)治疗后，PS 评分降低并显示出特定阶段的波动。

Consensus 4: basic diagnosis and treatment techniques for severe lung cancer

共识 4：重症肺癌基础诊疗技术

The relative value of severe lung cancer treatment depends on the advances made in modern medical technology. The combination of three clinical technologies is particularly important: (I) dynamic and precise detection, which enables the timely identification of patients who may benefit from the treatment; (II) powerful life support technologies, which create the conditions needed for various anti-tumor treatments; and (III) individualized anti-tumor treatments that are highly effective and safe.

重症肺癌治疗的相对价值取决于现代医疗技术的进步。三项临床技术的结合尤为重要：(Ⅰ)动态精准检测，能够及时识别可能从治疗中受益的患者；(Ⅱ)强大的生命支持技术，为各种抗肿瘤治疗创造条件；和(Ⅲ)高效安全的个体化抗肿瘤治疗。

Dynamic and precise detection (recommendation category: A; level of evidence: 1b)

动态精准检测（推荐类别：A；证据级别：1b）

The past decades have witnessed the transition of lung cancer treatment from traditional chemotherapy to precision therapy. Targeted therapies are preferred for patients with driver gene-positive tumors; for patients without driver genes, non-targeted therapy biomarkers should be detected in order to identify those patients in which there is potential benefit. Clinicians should test tissue specimens whenever possible. However, tissue specimens may not be obtainable for genotyping in some patients, in which case liquid biopsy should be performed. Tumors are highly heterogeneous, and puncture specimens can only reflect the localized lesions. Moreover, the genetic status and tumor status may change after antitumor therapy, and subsequent treatments based only on the results of the initial specimen may be inaccurate. Therefore, the pathological type and genetic status should be dynamically examined throughout the course of treatment. Liquid biopsy has the advantages of easy access, low invasiveness, and good repeatability, all of which enable dynamic detection.

过去几十年，肺癌治疗已从传统化疗向精准治疗的转变。驱动基因阳性的肿瘤患者首选靶向治疗；对于没有驱动基因的患者，应检测非靶向治疗生物标志物，以确定那些有潜在获益的患者。临床医生应尽可能检测组织标本。然而，在某些患者中可能无法获得用于基因分型的组织标本，在这种情况下应进行液体活检。肿瘤具有高度异质性，而穿刺标本只能反映局部病变。此外，抗肿瘤治疗后基因状态和肿瘤情况可能会发生变化，因此，仅根据初始标本的结果进行后续治疗可能不准确。因此，应在整个治疗过程中动态检查病理类型和基因状态。液体活检具有取材容易、侵袭性小、重复性好等优点，可实现动态检测。

Life support techniques (recommendation: B; level of evidence: 2a)

生命支持技术（推荐：B；证据级别：2a）

Patients with severe lung cancer should be given appropriate life support so as to enable subsequent anti-tumor treatment. Many novel life support technologies including non-invasive/invasive ventilation, liver replacement, kidney replacement, and ECMO have saved the lives for many of critically ill patients.

重症肺癌患者应给予适当的生命支持，以便能够进行后续的抗肿瘤治疗。无创/有创通气、肝脏替代、肾脏替代、ECMO(体外膜肺氧合)等多项生命支持新技术挽救了许多危重患者的生命。

Anti-tumor treatments (recommendation: B; level of evidence: 2a)

抗肿瘤治疗（推荐：B；证据级别：2a）

Anti-tumor treatment and life support do not conflict with each other. Clinicians should treat both symptoms and their causes: when actively managing complications and comorbidities, the most appropriate anti-tumor treatment

needs to be identified. At present, anti-tumor treatments include surgery, chemotherapy, radiotherapy, interventional therapy, angiogenesis inhibitors, targeted therapy and immunotherapy or any combinations of them. The antitumor treatments should be used flexibly, and those drugs having the highest efficacy and lowest toxicity are obviously preferred.

抗肿瘤治疗与生命支持并不冲突。临床医生应对症状及病因进行治疗：在积极处理并发症和合并症时，需要确定最合适的抗肿瘤治疗。目前，抗肿瘤治疗包括手术、化疗、放疗、介入治疗、血管生成抑制剂、靶向治疗和免疫治疗或其任意组合。抗肿瘤治疗应灵活使用，显然应首选疗效最高、毒性最低的药物。

Consensus 5: specific diagnostic and treatment strategies for severe lung cancer

共识 5：重症肺癌的具体诊治策略

There is currently no well-controlled, prospective clinical evidence available for determining the optimal treatments for severe lung cancer; however, indirect data from research on patients with PS 0–1 may be useful for making decisions. Flexible and individualized treatment strategies can be adopted, which include but are not limited to: “treatment of both the lung cancer and other lung diseases”, “selection of treatment approaches according to the PS score”, “escalation and de-escalation of anti-tumor drugs”, “dynamic and precise detection”, “smart combinations for increasing efficacy and reducing toxicity” and “multidisciplinary participation, and individualized and comprehensive treatment”.

目前没有较好对照的前瞻性临床证据用于确定重症肺癌的最佳治疗方案；然而，来自 PS 0-1 患者研究的间接数据可能有助于做出决策。可采取灵活的个体化治疗策略，包括但不限于：“同时治疗肺癌和其他肺部疾病”，“根据 PS 评分选择治疗方法”，“逐步增减抗肿瘤药物”，“动态精确检测”，“智能组合增效减毒”和“多学科参与，个体化综合治疗”。

Treatment of both lung cancer and other lung diseases (recommendation category: B; level of evidence: 2a)

同时治疗肺癌和其他肺部疾病（推荐类别：B；证据级别：2a）

During the treatment of lung cancer, the management of other acute and chronic respiratory diseases such as COPD, ILD, pulmonary embolism, and lung infections must not be neglected. Zhang et al. found the overall diagnostic rate of COPD was only 7.1% (50 of 705 lung cancer patients meeting the diagnosis criteria of COPD), and the treatment for stable and acute exacerbation of COPD was 27.1% and 46.8%, respectively. Poor management of COPD can lead to a decrease in patients’ quality of life, decrease in therapeutic efficiency, and worsening of the prognosis. In a previous study, patients receiving anti-tumor therapy plus proper COPD

management had significantly longer progression-free survival (PFS) and overall survival (OS) compared to those treated with anti-tumor therapy alone. In a real-world study in the Republic of Korea that retrieved clinical information from a medical information system, 113 of 8,014 NSCLC patients were found to have unsuspected pulmonary emboli (PE), and the results showed that the mortality rate was 4.1 times higher in those patients who did not receive anticoagulation therapy than in those who did. The treatment protocols for lung cancer are selected based on the PS score, which can be directly affected by pulmonary comorbidities and complications. Therefore, controlling for comorbidities or complications as well as treating lung cancer is important, and such findings represent the primary and secondary aspects of the "contradiction" involved in the treatment of severe lung cancer. While the primary aspect is undoubtedly important, the primary and secondary aspects can be impact each other. Therefore, the management of severe lung cancer requires that attention be paid to both the primary and secondary aspects (i.e., both the lung cancer and that other lung diseases require treatment).

在肺癌治疗期间，不能忽视 COPD(慢阻肺)、ILD(间质性肺病)、肺栓塞、肺部感染等其他急慢性呼吸系统疾病的管理。张等人发现 COPD(慢阻肺)的总体诊断率仅为 7.1%（705 例符合 COPD 诊断标准的肺癌患者中有 50 例），COPD 稳定期和急性发作期的治疗率分别为 27.1%和 46.8%。COPD(慢阻肺)管理不善可导致患者生活质量下降、治疗效果下降和预后恶化。在之前的一项研究中，与仅接受抗肿瘤治疗的患者相比，接受抗肿瘤治疗加适当 COPD(慢阻肺)管理的患者的无进展生存期(PFS)和总生存期(OS)显著更长。韩国进行的一项从医疗信息系统中检索临床信息的真实世界研究中，在 8,014 例 NSCLC 患者中发现了 113 例有意外的肺栓塞(PE)，结果显示未接受抗凝治疗患者的死亡率高出接受过抗凝治疗者的 4.1 倍。肺癌的治疗方案是根据 PS 评分选择的，PS 评分可以直接受到肺部合并症和并发症的影响。因此，不但治疗肺癌很重要，控制合并症或并发症也很重要，上述发现代表了重症肺癌治疗“矛盾”的主要和次要方面。虽然主要方面无疑很重要，但主要和次要方面会相互影响。因此，重症肺癌的治疗需要兼顾主、次两方面（即肺癌和其他肺部疾病都需要治疗）。

Dynamic and precise detection (recommendation category: A; level of evidence: 1b)

动态精准检测（推荐类别：A；证据级别：1b）

At present, targeted therapy is mainly used in driver gene-positive patients; the use of anti-vascular therapy is typically avoided in high-risk patients; immunotherapy is not a precise treatment as it is preferred only in certain select populations and should be avoided in the high-risk groups; and chemotherapy has only a limited tissue-specific effect. Dynamic and precise detection for a timely identification of targets is particularly important

for patients with severe lung cancer over their lifetimes.

目前靶向治疗主要用于驱动基因阳性患者；高危患者通常避免使用抗血管治疗；免疫疗法不是一种精确的治疗方法，因为它仅适用于某些特定人群，应避免用于高危人群；而化疗只有有限的组织特异性作用。动态精准检测以及时识别靶点对重症肺癌患者的终生尤为重要。

Chemotherapy targets (recommendation category: C; level of evidence: 2a)

化疗的靶点（推荐类别：C；证据级别：2a）

Many studies have been devoted to identifying predictors of chemotherapy efficacy. It is reported that high excision repair cross complementing-group 1 (ERCC1) expression is associated with decreased efficacy of platinum agents, high ribonucleotide reductase subunit 1 (RRM1) expression is associated with poor efficacy of gemcitabine, increased thymidylate synthase (TS) expression is associated with poor efficacy of pemetrexed, and class III beta-tubulin (TUBB3) is associated with resistance to toxoids. However, currently these biomarkers are not considered clinically useful and thus require further investigation.

许多研究致力于确定化疗疗效的预测因子。据报道，切除修复交叉互补基因 1(ERCC1)高表达与铂类药物疗效降低有关，核糖核苷酸还原酶亚基 1(RRM1)高表达与吉西他滨疗效差有关，胸苷酸合酶(TS)表达增加与培美曲塞的疗效差有关，而III类 β -微管蛋白(TUBB3)与对类毒素的耐药性有关。然而，目前不认可这些生物标志物在临床上有用，因此需要进一步探索。

Targets used in targeted therapies (recommendation category: A; level of evidence: 1a)

靶向治疗中使用的靶点（推荐类别：A；证据级别：1a）

Currently, the driver genes routinely tested in clinical laboratories include EGFR, ALK, ROS1, KRAS, HER-2, BRAF V600, RET fusion, MET amplification, and MET14 exon skipping. Targeted therapy requires the detection of specific targets, and only precisely targeted therapy can work quickly and effectively. However, drug resistance can occur during targeted therapy, and a repeated detection of the relevant targets is needed to determine the mechanisms of resistance. For example, approximately 50% of patients with EGFR-sensitive mutations treated with first- and second-generation EGFR-TKIs develop T790M mutations, which can be effectively treated with third-generation TKIs.

目前，临床实验室常规检测的驱动基因包括 EGFR、ALK、ROS1、KRAS、HER-2、BRAF V600、RET 融合、MET 扩增和 MET14 外显子跳跃。靶向治疗需要检测特定的靶点，只有精准的靶向治疗才能快速有效地发挥作用。然而，靶向治疗过程中会出现耐药性，因此，需要

对相关靶点进行反复检测，以确定耐药机制。例如，使用第一代和第二代 EGFR-TKI 治疗的 EGFR 敏感突变患者中，大约 50%会发生 T790M 突变，可以使用第三代 TKI 进行有效治疗。

Targets of anti-angiogenesis therapies (recommendation category: C; level of evidence: 1a)

抗血管生成治疗的靶点（推荐类别：C；证据级别：1a）

Currently, single-target drugs include bevacizumab (VEGF-A) and ramucirumab (VEGFR-2), multi-target (targeting VEGFR, PDGFR, FGFR, RAF, etc.) small-molecule TKIs include anlotinib, apatinib, sunitinib, sorafenib, nintedanib, and fruquintinib, and pan-target drugs include vascular endothelial inhibitors. A phase II/III clinical study involving 878 NSCLC patients randomly assigned carboplatin + paclitaxel (PC) or PC + bevacizumab (BPC). The results showed that patients with high baseline VEGF-A had higher response to BPC than those with PC; and bevacizumab was beneficial to PFS in patients with low baseline intercellular adhesion molecule (ICAM). Another study to investigate the biomarkers of bevacizumab combined with chemotherapy for NSCLC patients showed that VEGF-A was not associated with response to bevacizumab, but low VEGF-A was associated with favorable PFS and OS. However, there are still no reliable predictive biomarker for the efficacy of antivascular therapy. The use of these drugs has no clear requirement for the PS score, and the current suggested treatment strategy is to avoid contraindications such as patients at high risk of bleeding, in an active thrombotic phase, having high risk pulmonary cavity, and/or uncontrollable hypertension.

目前，单靶点药物包括贝伐珠单抗（VEGF-A）和雷莫芦单抗（VEGFR-2），多靶点（靶向 VEGFR、PDGFR、FGFR、RAF 等）小分子 TKI 包括安罗替尼、阿帕替尼、舒尼替尼、索拉非尼、尼达尼布和呋喹替尼，泛靶点药物包括血管内皮抑制剂。一项Ⅱ/Ⅲ期临床研究，包括 878 例 NSCLC 患者，随机分配卡铂+紫杉醇(PC)或 PC+贝伐珠单抗(BPC)。结果显示基线 VEGF-A 高的患者对 BPC(紫杉醇+卡铂+贝伐珠单抗)的应答高于 PC(紫杉醇+卡铂)患者；而贝伐珠单抗对基线细胞间粘附分子（ICAM）低的患者具有 PFS 获益。另一项探讨贝伐珠单抗联合化疗治疗 NSCLC 患者的生物标志物的研究表明，VEGF-A 与对贝伐珠单抗的应答无关，但 VEGF-A 低与良好的 PFS 和 OS 相关。然而，对于抗血管治疗的疗效，仍然没有可靠的预测性生物标志物。这些药物的使用对 PS 评分没有明确要求，目前建议的治疗策略是避免用于有出血风险高、血栓活动期、肺空洞风险高和/或无法控制的高血压等禁忌症的患者。

Immunotherapy targets (recommendation category: B; level of evidence: 1a)

免疫治疗靶点（推荐类别：B；证据级别：1a）

Patients with high levels of PD-L1 expression are reportedly more likely to respond to immunotherapy. Le et al. demonstrated a positive correlation between efficacy and mismatch repair-deficient (dMMR)/ microsatellite-instability-high (MSI-H). In 2017, the US FDA approved pembrolizumab for any solid tumor with a specific genetic biomarker for MSI-H or dMMR. The CheckMate 227 study showed tumor mutational burden (TMB) was a positive marker, but the KEYNOTE-189 and KEYNOTE-021 studies presented in 2019 World Conference on Lung Cancer (WCLC) reported that TMB did not predict the efficacy of immunotherapy combined with chemotherapy. POLE/POLD1 mutations are reportedly associated with a good efficacy of ICI. In addition, tumor neoantigens, tumor infiltrating lymphocytes, transcriptional features of the immune response and the microbiome are all reportedly related to the efficacy of immunotherapy. Recently, multiple studies have focused on factors related to hyperprogression, such as MDM2/MDM4 amplification, EGFR amplification and genes at 11q13, such as cyclin D1 (CCND1), and fibroblast growth factor (FGF) 3, 4, 19.

据报道，PD-L1 表达水平高的患者更有可能对免疫疗法产生应答。Le 等人证明疗效与错配修复缺陷（dMMR）/微卫星不稳定性高（MSI-H）之间呈正相关。2017 年，美国 FDA 批准帕博利珠单抗用于任何具有MSI-H(微卫星不稳定性高)或dMMR(错配修复缺陷)特定遗传生物标志物的实体瘤。CheckMate 227 研究显示肿瘤突变负荷(TMB)是阳性标志物，但 2019 年世界肺癌大会(WCLC)上发表的 KEYNOTE-189 和 KEYNOTE-021 研究报告称 TMB 不能预测免疫疗法联合化疗的疗效。据报道，POLE/POLD1 突变与 ICI(免疫检查点抑制剂)的疗效好有关。此外，据报道，肿瘤新抗原、肿瘤浸润淋巴细胞、免疫应答的转录特征和微生物组都与免疫治疗的疗效有关。最近，多项研究聚焦于与超进展相关的因素上，如 MDM2/MDM4 扩增、EGFR 扩增和 11q13 基因，如细胞周期蛋白 D1(CCND1)和成纤维细胞生长因子(FGF)3、4、19。

PS score and escalation/de-escalation strategies (recommendation category: B; level of evidence: 3a)

PS 评分和升/降级策略（推荐类别：B；证据级别：3a）

The efficacy and toxicity of different anti-tumor drugs vary. For patients with severe lung cancer, a low-toxicity, high-efficacy regimen (or even a combination regimen)—but not a first-line standard regimen—can be used at first, with the aim of breaking the vicious cycle between the tumor and the severe disease status, which is known as an “escalation strategy”; in contrast, once the disease status has improved, a more tolerable standard anti-tumor regimen can be applied according to the patient’s specific situation and needs, known as a “de-escalation strategy”. The PS score is used as a stratifying factor for guiding treatment in all of the currently available guidelines on lung cancer. Patients with severe lung cancer typically have a poor PS score. However, PS scores fluctuate and are

reversible. Therefore, patients with severe lung cancer should have their treatment options chosen according to their PS scores. For patients with a poor PS score, it is important to identify the etiology and actively manage any comorbidities and complications. A low-toxicity and high-efficacy anti-tumor regimen can be applied at first, and then the anti-tumor regimen may be adjusted once the PS score has improved. Thus, the PS score-based escalation and de-escalation strategy refers to the strategy of escalating or deescalating the use of antitumor regimen according to the efficacies and toxicities of anti-tumor drugs in patients with different PS scores on the basis of the treatment protocols recommended by the currently available guidelines. A recent study has also suggested that for patients with small cell lung cancer (SCLC) with poor PS scores, the reasons for the poor scores should be actively sought out and chemotherapy utilized at first, followed by immunotherapy once the PS score has improved.

不同抗肿瘤药物的疗效和毒性各不相同。对于重症肺癌患者，可以首先采用低毒、高效的方案（甚至联合方案）——但不是一线标准方案——旨在打破肿瘤与重病状态之间的恶性循环，称之为“升级策略”；与此相反，一旦病情好转，可以根据患者的具体情况和需求，可以采用更能耐受标准的抗肿瘤方案，称为“降级策略”。PS 评分在所有当前可用的肺癌指南中作为指导治疗的分层因素。重症肺癌患者 PS 评分通常较差。但是，PS 分数会波动并且是可逆的。因此，重症肺癌患者应根据其 PS 评分选择治疗方案。对于 PS 评分较差的患者，重要的是确定病因并积极处理任何合并症和并发症。可先采用低毒高效的抗肿瘤方案，待 PS 评分改善后再调整抗肿瘤方案。因此，基于 PS 评分的逐步升级和降级策略是指在当前可用的指南推荐的治疗方案的基础上，根据抗肿瘤药物对不同 PS 评分患者的疗效和毒性，逐步升级或降级使用抗肿瘤方案的策略。最近一项研究同样认为，对于 PS 评分较差的小细胞肺癌（SCLC）患者，应积极寻找评分较差的原因，首先采用化疗，待 PS 评分改善后再进行免疫治疗。

Optimizing combination treatments for increasing efficacy and reducing toxicity (recommendation category: B; level of evidence: 1a)

优化联合治疗以增效减毒（推荐类别：B；证据级别：1a）

Chemotherapy, radiotherapy, anti-vascular therapy, targeted therapy, and immunotherapy have different anti-tumor mechanisms, and all of them have their own advantages and adverse effects. Appropriate combination therapy can achieve better efficacy while reducing adverse effects. In the global phase III IMpower150 study, immunotherapy combined with anti-vascular therapy + chemotherapy was more effective than anti-vascular therapy + chemotherapy in treating NSCLC patients with a high tumor burden, liver metastases, and positive driver genes (EGFR/ ALK), along with fewer fatal AE (i.e., immune-associated pneumonia). In another phase III trial (NEJ026)

comparing the effectiveness and safety of erlotinib plus bevacizumab vs. erlotinib alone, the combination group displayed better efficacy, and no interstitial pneumonia was noted in the combination group. The combinations of antiangiogenic agents with EGFR-TKI increase the antitumor efficacy and overcome the resistance of EGFRTKI. A recent study compared the efficacy and safety of a regimen of combining anlotinib and S-1 vs. anlotinib monotherapy in treating patients with advanced squamous cell lung cancer having a poor PS scores [2–3]. The combination group had significantly longer OS, and there was no grade 3 or higher toxicity.

化疗、放疗、抗血管治疗、靶向治疗和免疫治疗具有不同的抗肿瘤机制，各有优势和不良反应。恰当的联合治疗可以在减少不良反应的同时取得更好的疗效。在全球Ⅲ期IMpower150 研究中，免疫治疗联合抗血管疗法+化疗比抗血管疗法+化疗治疗肿瘤负荷高、肝转移、驱动基因（EGFR/ALK）阳性的 NSCLC 患者更有效， 而且致命 AE（即免疫相关性肺炎）更少。在另一项比较厄洛替尼+贝伐珠单抗与单独厄洛替尼的有效性和安全性的Ⅲ期试验(NEJ026)中，联合组显示出更好的疗效，并且联合组未观察到间质性肺炎。抗血管生成药物与 EGFR-TKI 的组合增加了抗肿瘤效果并克服了 EGFR-TKI 的耐药性。最近一项研究比较了联合安罗替尼和 S-1 的方案与安罗替尼单药治疗 PS 评分较差[2-3]的晚期肺鳞癌患者的疗效与安全性。联合组的 OS 显著更长，并且没有 3 级或更严重的毒性。

Multidisciplinary participation, and individualized and comprehensive treatment (recommendation category: A; level of evidence: 1b)

多学科参与，个体化综合治疗（推荐类别：A；证据级别：1b）

Patients with severe lung cancer need the participation of different disciplines, mutual communication and collaboration, and the development of individualized and comprehensive treatment. In addition, patients' active cooperation is also very important. Bossert et al. interviewed 15 patients with stage IV lung cancer with comorbidities and found that they believed that patients played an active role in multidisciplinary treatment. A prospective study showed that compared with conventional preoperative pulmonary rehabilitation, preoperative multidisciplinary pulmonary rehabilitation therapy can reduce postoperative complication rate (48.3% vs. 28.6%, P=0.2428). The determination of the cause of severe lung cancer, the choice of anti-tumor treatment, the treatment of comorbidities and complications, and the implementation of life support technology all require multidisciplinary participation. Multiple studies have shown multidisciplinary team (MDT) approach in the treatment of lung cancer can improve quality of life and OS rate of patients.

重症肺癌患者需要不同学科的参与、相互沟通与协作，开展个体化的综合治疗。此外，

患者的积极配合也很重要。Bossert 等访视了 15 名有合并症的Ⅳ期肺癌患者，他们认为患者在多学科治疗中发挥了积极作用。一项前瞻性研究表明，与常规术前肺康复相比，术前多学科肺康复治疗可降低术后并发症发生率（48.3%：28.6%，P=0.2428）。重症肺癌病因的确定、抗肿瘤治疗的选择、合并症和并发症的治疗、生命支持技术的实施，都需要多学科的参与。多项研究表明，多学科团队（MDT）方法治疗肺癌可以提高患者的生活质量和 OS 率。

Consensus 6: application of surgery in patients with severe lung cancer

共识 6：手术在重症肺癌患者中的应用

Patients with early-stage lung cancer can also have various other underlying diseases such as cardiopulmonary comorbidities, which limit the feasibility of conventional surgery. For patients with early-stage severe lung cancer and various comorbidities, a variety of sophisticated modern testing, examination, treatment, and life support technologies can be used to ensure successful preoperative assessment, intraoperative protection, and postoperative support; meanwhile, a MDT can be engaged to enable optimal coordination and cooperation among the related departments including thoracic surgery, anesthesiology, respiratory and critical care, and nutrition (recommendation category: B; level of evidence: 2a). The most common reason for surgery in patients with early-stage severe lung cancer is lung cancer accompanied by COPD. Here we describe the application of surgery to such patients.

早期肺癌患者还可能有各种其他基础疾病，如心肺合并症，这制约了常规手术的可行性。对于早期重症肺癌及各种合并症患者，可采用多种先进的现代检测、检查、治疗和生命支持技术，确保术前评估、术中保护和术后支持的成功；同时，可以参加 MDT(多学科团队)以实现相关科室之间的最佳协调与合作，包括胸外科、麻醉科、呼吸和重症监护以及营养科（推荐类别：B；证据级别：2a）。早期重症肺癌患者最常见的手术原因是肺癌合并 COPD(慢阻肺)。在此，我们描述手术对此类患者的应用。

Pre-operative assessment *术前评估*

Pulmonary function tests **肺功能检查**

Pulmonary function tests are of critical importance prior to lung surgery. The widely recognized contraindications to surgery include: a predicted baseline forced expiratory volume in one second (FEV1) of less than 40%; a predicted postoperative FEV1 value of less than 30%; and a predicted diffusion capacity of the lung for carbon monoxide (DLCO) of less than 40%. Ventilation test: pulmonary ventilation is a dynamic temporal process involving the entry of air into and carbon dioxide exit from the alveoli. The commonly used indicators include

ventilation at rest, alveolar ventilation, maximal voluntary ventilation (MVV), timed vital capacity, and certain flow rate indicators. Clinically, COPD patients mostly present with obstructive ventilation dysfunction [i.e., decreased flow rate (the FEV1/FVC ratio)], which can be classified as follows: mild COPD (predicted FEV1/ FVC <70%, FEV1 ≥80%); predicted moderate COPD (predicted FEV1/FVC <70%, 50%≤ FEV1 <80%); severe COPD (predicted FEV1/FVC <70%, 30%≤ FEV1 <50%); and very severe COPD (predicted FEV1/FVC <70%, FEV1 <30%). Lung diffusion testing measures how well the lungs exchange gases. As a measure of alveolar-capillary membrane functional efficiency, it is important for detecting early lung and airway lesions, assessing the severity of the disease and forming its prognosis, evaluating the efficacy of drugs or other treatments, and identifying the cause of the dyspnea. Locating the lesions and assessing the functional operability are highly valuable. The normal values for DLCO are 28.84±4.84 mL/mmHg/min for men and 22.13±3.09 mL/mmHg/min for women. Diffusion impairment can be divided into three levels based on severity: mild (predicted ≥60% but <80%), moderate (predicted ≥40% but <60%), and severe (predicted <40%). In general, patients with mild ventilatory dysfunction can tolerate single-lobe resection; for patients with moderate to severe ventilatory dysfunction, the feasibility of lobectomy should be assessed in a comprehensive manner; for patients with very severe ventilatory dysfunction or those with accompanying moderate or severe diffusion dysfunction, surgery requires extreme caution.

在肺部手术之前，肺功能检查至关重要。公认的手术禁忌症包括：预测的基线第一秒用力呼气量(FEV1)小于 40%；预测的术后 FEV1(第一秒用力呼气量)值小于 30%；预测的肺一氧化碳弥散量(DLCO)低于 40%。通气试验：肺通气是一个动态多变的过程，涉及空气进入肺泡和二氧化碳从肺泡排出。常用的指标包括静息通气、肺泡通气、最大自主通气量（MVV)、定时肺活量和某些流速指标。临床上，COPD(慢阻肺)患者多表现为阻塞性通气功能障碍[即流速降低(FEV1/FVC 比值)]，可分为：轻度 COPD(慢阻肺）（预测 FEV1/FVC<70%， FEV1≥80%）；预测的中度 COPD(慢阻肺）（预测 FEV1/FVC<70%，50%≤FEV1<80%)；重度 COPD(慢阻肺）（预测 FEV1/FVC<70%，30%≤FEV1<50%)；和非常严重的 COPD(慢阻肺)（预测 FEV1/FVC<70%，FEV1<30%)。肺扩散试验衡量肺交换气体的情况。作为肺泡-毛细血管膜功能效率的衡量指标，它对于发现早期肺和气道病变、评估疾病严重程度和形成其预后、评估药物或其他治疗的疗效以及确定呼吸困难的原因具有重要意义。对病灶的定位和功能的评估非常有价值。DLCO(一氧化碳弥散量)的正常值男性为 28.84±4.84mL/mmHg/min，女性为 22.13±3.09mL/mmHg/min。根据严重程度弥散障碍可分为三个级别：轻度（预计≥60%但<80%)、中度（预计≥40%但<60%）和重度（预计<40%)。一般情况下，轻度通气功能障碍患者可以耐受单叶切除；对于中重度通

气功能障碍患者，应综合评估肺叶切除术的可行性；对于非常严重的通气功能障碍或伴有中度或重度弥散功能障碍的患者，手术需要格外谨慎。

Breathing and nutritional support **呼吸和营养支持**

Breathing functionality and nutritional support are also important and necessary. Perioperative physical therapy can enhance postoperative respiratory function recovery. Also, a low body mass index (BMI) is associated with postoperative negative nitrogen balance. There is evidence that postoperative complications are markedly increased in patients with a BMI of below 14 kg/m2. A randomized controlled study showed enteral nutrition plus accelerated rehabilitation reduced postoperative complications and improved postoperative recovery, compared with conventional nutrition therapy.

呼吸功能和营养支持同样重要和必要。围手术期物理疗法可以促进术后呼吸功能的恢复。此外，低体重指数(BMI)与术后负氮平衡有关。

Pharmacotherapy **药物治疗**

All lung cancer patients with accompanying COPD can receive standardized COPD treatment for at least 1 week in order to improve their lung function. Nebulizers and oral medications are preferred for pharmacotherapy. The most commonly used nebulized medications include hormones, acetylcholine receptor antagonists and β2-agonists; leukotriene receptor antagonists or theophylline may also be used; and if necessary, antibiotics should be used to control chronic inflammation.

所有伴 COPD(慢阻肺)的肺癌患者都可以接受至少 1 周的标准化 COPD 治疗，以改善其肺功能。雾化和口服药物是首选的药物治疗。最常用的雾化药物包括激素、乙酰胆碱受体拮抗剂和 β 2 受体激动剂；也可以使用白三烯受体拮抗剂或茶碱；如有必要，应使用抗生素控制慢性炎症。

Blood gas analysis **血气分析**

The arterial partial pressures of oxygen and carbon dioxide are also important measures of postoperative complications, especially in patients who are unable to cooperate with ventilation and diffusion capacity tests. Carbon dioxide retention is a more important indicator than hypoxemia.

动脉氧分压和二氧化碳分压也是衡量术后并发症的重要指标，尤其是不能配合通气和弥散能力检测的患者。二氧化碳潴留是比低氧血症更重要的指标。

Cardiac color ultrasound **心脏彩超**

In addition to the assessment of cardiac structure and valve function, cardiac color ultrasound also affords the ejection fraction (EF) value (50% or higher allows a safe surgery). The presence of pulmonary hypertension is also

a contraindication to pulmonary surgery.

除了评估心脏结构和瓣膜功能外，心脏彩超还提供射血分数(EF)值（≥50%可安全手术）。存在肺动脉高压也是肺部手术的禁忌症。

Pulmonary ventilation/perfusion scan **肺通气/灌注扫描**

Pulmonary perfusion imaging reveals any blood perfusion in lung tissues, and the commonly used radiopharmaceutical for this purpose is Tc-labeled macroalbumin (Tc-MAA). Pulmonary ventilation imaging reflects the gas filling the airways and alveoli. Pulmonary ventilation/perfusion scan can assist the assessment of split/lobar lung function, thus determining the local function of the resected lung tissue and predicting the residual lung function after the surgery.

肺灌注成像显示肺组织的所有血液灌注，常用的放射性药物是锝标记的大颗粒聚合人血清白蛋白(Tc-MAA)。肺通气成像反映气道和肺泡的气体。肺通气/灌注扫描可协助评估分侧/肺叶肺功能，从而确定切除肺组织的局部功能并预测术后的残余肺功能。

Pre-operative assessment of functional exercise capacity **功能运动能力的术前评估**

In clinical practice, the stair-climbing test is obviously not an objective way to measure the cardiopulmonary function and surgical tolerance in surgical patients. In contrast, the six-minute walk test (6MWT) has been used to evaluate the efficacy of therapeutic interventions in patients with moderate to severe cardiopulmonary disease and to measure the functional status of patients. It is widely recognized as a simple, and reliable tool for evaluating cardiopulmonary function. 6MWT was officially released by the American Thoracic Society (ATS) in 2002, along with a comprehensive guideline. The incidences of pulmonary complications (36.9%), atrial fibrillation (11.5%), and blood transfusion (9.0%) significantly increased after lobectomy in patients, with a 6MWT <500 m, and the average hospital stay was also up to 7 days (6 days in patients with a 6MWT >500 m). Similarly, the risk of pulmonary complications increased in patients with a 6MWT <300 m.

在临床实践中，登楼梯试验显然不是衡量手术患者心肺功能和手术耐受性的客观方法。相比之下，六分钟步行试验(6MWT)已被用于评估治疗干预对中重度心肺疾病患者的疗效并衡量患者的功能状态。普遍认为这是评估心肺功能的一种简单而可靠的工具。6MWT(6分钟步行试验)由美国胸科学会(ATS)于2002年正式发布，并附有综合指南。6MWT(6分钟步行试验)<500米的患者，肺叶切除术后肺部并发症（36.9%）、房颤（11.5%）和输血（9.0%）发生率显著增加，平均住院时间也长达7天（6MWT>500米的患者为6天）。同样，6MWT(6分钟步行试验)<300米的患者肺部并发症的风险增加。

Three-dimensional (3D) reconstruction **三维(3D)重建**

3D reconstruction of the lungs has been increasingly used for pulmonary surgery planning, especially during sublobar resections. Based on preoperative thin-section computed tomography (CT), 3D reconstruction of lung segments, pulmonary vessels, and bronchi can display the microscopic structures in a more intuitive manner. In addition, it allows more detailed measurement of the local lung volume, which assists in determining the functional loss after lung surgery.

肺的 3D 重建越来越多地用于肺部手术设计，尤其是在亚肺叶切除术中。基于术前薄层计算机断层扫描（CT），肺段、肺血管和支气管的 3D 重建可以更直观地显示微小结构。此外，允许更详细地测定局部肺容积，有助于确定肺部术后的功能丧失。

Intraoperative assurance *术中保证*

Surgical planning **手术计划**

Lobectomy vs. sublobectomy: anatomic lobectomy is superior to sublobectomy (segmentectomy or wedge resection) for patients with stage I NSCLC. However, many COPD patients have impaired lung function, which may affect their ability to tolerate the procedure. Compared with lobectomy, sublobectomy may result in a significantly higher rate of local recurrence. However, patients who cannot tolerate lobectomy should only undergo sublobar resection. The selection of potential patients eligible for lobectomy should be based on a series of cardiopulmonary function tests prior to the surgery: (I) no carbon dioxide retention is found upon blood gas tests; (II) echocardiography reveals good cardiac function (with an EF >50%); (III) pulmonary diffusion capacity must be at least moderate; (IV) preoperative 6MWT should be more than grade 2; and (V) pulmonary ventilation/perfusion scan with 3D reconstruction of lung tissue is recommended. Preoperative assessment of lung function in the target area is essential for surgical planning and outcome prediction and enables accurate quantitative characterization of ventilation and perfusion capacity at the lobe or even segment level. If the tumor is located in a lobe afflicted with severe emphysema, patients must undergo resection of the lung cancer while simultaneously removing the poorly functioning lung tissue, which in turn improves lung function. This phenomenon is called “the lung volume reduction effect”. For example, some patients with poor lung function resulting in shortness of breath can safely undergo pneumonectomy for both lung cancer and lung volume reduction at an acceptable level of risk, and the procedure may even improve their lung capacity. In another study, upper lobectomy showed a volume reduction effect, suggesting patients with a lower preoperative FEV1.0% of predicted had a greater “volume reduction effect” with an increase in FEV1.0 after upper lobectomy.

肺叶切除术与亚肺叶切除术：对于 I 期 NSCLC 患者，解剖性肺叶切除术优于亚肺叶切除术（肺段切除术或楔形切除术）。然而，许多 COPD(慢阻肺)患者的肺功能受损，这可能

会影响其对操作的耐受能力。与肺叶切除术相比，亚肺叶切除术的局部复发率可能显著更高。然而，不能耐受肺叶切除术的患者只能进行亚肺叶切除术。潜在适合肺叶切除术患者的选择应根据术前一系列的心肺功能检查：(Ⅰ)血气分析未发现二氧化碳潴留；(Ⅱ)超声心动图显示心功能良好（EF>50%）；(Ⅲ)肺弥散容量至少中等；(Ⅳ)术前 6MWT(6 分钟步行试验)应≥2 级；和(Ⅴ)推荐使用肺组织 3D 重建进行肺通气/灌注扫描。目标区域的术前肺功能评估对于手术计划和预后预测至关重要，并且能够准确定量肺叶甚至肺段水平的通气特征和灌注能力。如果肿瘤位于有严重肺气肿的肺叶，患者必须接受肺癌切除术，同时去除功能不良的肺组织，进而改善肺功能。这种现象被称为“肺减容效应”。例如，一些肺功能差而呼吸急促的患者在可接受的风险水平下可以安全地接受肺癌和肺减容的肺切除术，该手术甚至可能提高他们的肺活量。在另一项研究中，上叶切除术显示出减容效果，表明术前 FEV1.0%预测值较低的患者在上叶切除术后 FEV1.0 增加，具有更显著的“减容效果”。

Intraoperative assessment **术中评估**

Intraoperative hypoxic preconditioning (HPC) or ischemic preconditioning (IPC) is an important component of the intraoperative assessment that is performed to determine the surgical approach. Studies have shown that HPC or IPC can improve the tolerance of cells, tissues, organs, and even the organism itself to subsequent severe hypoxia or ischemia. HPC also improves postoperative oxygenation, enhances lung function recovery, and reduces the length of hospital stay. During the surgery, it may be feasible to lower the inhaled oxygen concentration to below 50% while the operator clamps the pulmonary artery to the target lobe to block the blood supply. Meanwhile, the oxygenation index [the arterial partial oxygen pressure (PaO2)/fraction of inspired oxygen (FiO2)] must be ≥200 (with no significant change in vital signs) for 10 minutes. Lobectomy is considered safe and feasible if these conditions are met.

术中缺氧预处理(HPC)或缺血预处理(IPC)是术中评估的重要组成部分，目的是确定手术方法。研究表明，HPC(缺氧预处理)或 IPC(缺血预处理)可以提高细胞、组织、器官甚至机体本身对以后严重缺氧或缺血的耐受性。HPC(缺氧预处理)还可以提高术后氧合，促进肺功能恢复，缩短住院时间。在手术过程中，操作者夹住目标肺叶的肺动脉阻断血液供应，将吸入的氧浓度降到 50%以下可能是可行的。其间，氧合指数[动脉氧分压(Pa02)/吸入氧分数(Fi02)]必须≥200(生命体征无明显变化)10 分钟。如果满足这些条件，就认为可安全进行肺叶切除术。

Postoperative support ***术后支持***

Lung infection **肺部感染**

Pulmonary infection and pneumonia are major causes of postoperative morbidity and mortality. A Cochrane systematic review of seven randomized controlled trials highlighted the fact that combined corticosteroid/long-acting beta2 agonist (LABA) (fluticasone and salmeterol) increased the risk of pneumonia in COPD patients. Treatment of postoperative pulmonary infections begins with pathogenic exam of respiratory samples, followed by assessment for the presence of sepsis and risk factors for multidrug-resistant pathogens. Then, according to the results from a drug sensitivity test and the risk factors, adequate selection of antibiotics and the escalation or de-escalation principle is required.

肺部感染和肺炎是术后并发症和死亡的主要原因。对七项随机对照试验进行的 Cochrane 系统评价强调了这样一个事实，即联合使用糖皮质激素/长效 β 2 受体激动剂(LABA)(氟替卡松和沙美特罗)会增加 COPD(慢阻肺)患者的肺炎风险。术后肺部感染的治疗首先是对呼吸道样本进行病原学检查，然后评估是否存在败血症和多重耐药病原体的危险因素。然后，根据药物敏感性试验的结果和危险因素，需要选择足够好的抗生素和逐步升级或降级原则。

Persistent air leaks in the lungs **肺部持续漏气**

Pulmonary air leak is common in COPD patients, which may be explained by the fact that the impaired lung parenchyma and the diminished elastic recoil of the lungs after emphysema delay the healing of lung tissue. Lobectomy is associated with a higher rate of air leak than sublobectomy, which may be due to the fact that radical anatomical resection results in larger soft-tissue damage and a significantly longer healing time. Thus, in addition to intensive nutritional support, continuous negative-pressure suction and intrathoracic injection of adhesives are also critically important treatments after the surgery.

肺漏气在 COPD(慢阻肺)患者中很常见,这可能是由于肺气肿后肺实质受损和肺弹性回缩力减弱延迟了肺组织的愈合。与亚肺叶切除术相比，肺叶切除术的漏气率更高，这可能是由于根治性解剖切除造成更大范围的软组织损伤，因此愈合时间大大延长。因此，术后除了强化营养支持外，持续负压吸引和胸腔内注射粘合剂也是至关重要的治疗方法。

Atelectasis **肺不张**

Postoperative atelectasis can be treated with airway clearance techniques, including postural drainage and coughing, and bronchial suctioning using bronchoscopy or tracheal catheter as needed.

术后肺不张可以通过气道清除方法治疗，包括体位引流和咳嗽，根据需要使用支气管镜或气管导管进行支气管抽吸。

Consensus 7: application of radiotherapy techniques in patients with severe lung cancer

共识 7：放疗技术在重症肺癌患者中的应用

Radiotherapy is indicated in all stages of lung cancer. For patients with severe lung cancer, radiotherapy may play the following three roles: (I) radical radiotherapy for patients with severe disease who cannot tolerate surgery even in the early stage; (II) combination of precise radiotherapy with drugs in patients with locally advanced severe lung cancer to achieve the same purpose as radical treatment; and (III) palliative radiotherapy for patients with advanced severe lung cancer; its application in special areas can rapidly improve the severe symptoms, and its combinations with medical treatments can also benefit patients (recommendation category: B; level of evidence: 2a).

在肺癌的所有分期中放疗都适用。对于重症肺癌患者，放疗可能起到以下三个作用：（Ⅰ）对于早期不能耐受手术的重症患者进行根治性放疗；（Ⅱ）局部晚期重症肺癌患者精准放疗与药物联合，达到与根治性治疗相同的目的；和（Ⅲ）晚期重症肺癌患者的姑息放疗；其在特殊领域的应用可迅速改善重症症状，而其与内科治疗联合也可使患者受益（推荐类别：B；证据级别：2a）。

Radical radiotherapy for patients with severe disease who cannot tolerate surgery even in the early stages

早期不能耐受手术的重症患者的根治性放疗

Surgery remains the standard treatment modality for early-stage NSCLC. However, radiotherapy is also an effective treatment for those who cannot tolerate surgery for various reasons (e.g., advanced age, poor lung function, poor PS score, or the co-existence of other serious systemic diseases). One study found that stereotactic body radiation therapy (SBRT) and sublobar resection had similar 5-year survival rates in patients with stage I NSCLC who could not tolerate lobectomy (40.4% vs. 55.6%, P=0.124). SBRT or stereotactic ablative radiotherapy (SABR) is significantly more effective than conventional fractionated radiotherapy, with a 3-year local control rate of 73–91% and a 3-year OS rate of 43–60%. SBRT/SABR is the current standard radiotherapy modality for early-stage NSCLC. Previous clinical studies have shown that SBRT with a biologically equivalent dose (BED) of ≥100–105 Gy achieves better local control and OS, and a higher dose is associated with better outcomes. Therefore, the recommended dose of SBRT is to achieve BED of ≥100 Gy; however, the organ-threatening dose and the tolerability of patients should be strictly evaluated. Radical resection is also a standard treatment for early-stage SCLC (T1-2N0M0). As the case for NSCLC, SBRT/ SABR is also recommended for SCLC patients who cannot tolerate surgical treatment for some reason (e.g., advanced age, poor lung function, poor PS score, or the co-existence of other serious systemic diseases), with a recommended irradiation dose of BED ≥100 Gy, which can

achieve a 3-year local control rate of 96.1% and a 3-year OS rate of 34.0%.

手术仍然是早期 NSCLC 的标准治疗方式。然而，对于因各种原因（如高龄、肺功能差、PS 评分差或并存其他严重全身性疾病）不能耐受手术的患者，放疗也是一种有效的治疗方法。一项研究发现，立体定向放疗(SBRT)和亚肺叶切除术在不能耐受肺叶切除术的Ⅰ期 NSCLC 患者中具有相似的 5 年生存率（40.4%：55.6%，P=0.124）。SBRT(立体定向放疗)或立体定向消融放疗(SABR)的疗效显著优于常规分割放疗,3年局部控制率为73-91%，3 年 OS 率为 43-60%。SBRT/SABR(立体定向放疗/立体定向消融放疗)是目前早期 NSCLC 的标准放疗方式。既往临床研究表明，生物等效剂量（BED）≥100-105Gy 的 SBRT(立体定向放射治疗)可获得更好的局部控制和 OS,更高的剂量具有更好的效果。因此,SBRT(立体定向放射治疗)的推荐剂量是达到≥100Gy 的 BED(生物等效剂量)；然而，应严格评估危及器官的剂量和患者的耐受性。根治性切除术也是早期 SCLC(T1-2N0M0)的标准治疗方法。与 NSCLC 一样，对于因某种原因（如高龄、肺功能差、PS 评分差或并存其他严重全身性疾病）不能耐受手术治疗的 SCLC 患者，也推荐使用 SBRT/SABR(立体定向放疗/立体定向消融放疗)，推荐照射剂量 BED(生物等效剂量)≥100Gy，可达到 96.1%的 3 年局部控制率和 34.0%的 3 年 OS 率。

Radiotherapy for patients with locally advanced severe lung cancer

局部晚期重症肺癌患者的放射治疗

Durvalumab as consolidative immunotherapy following concurrent chemoradiotherapy (cCRT) is the standard treatment for patients with unresectable advanced NSCLC. However, cCRT may result in aggravated the toxicities and is thus mainly applicable to patients with a PS score of 0–1, while patients with poorer PS scores [2–4] often cannot tolerate cCRT. It was found that the incidence of grade 3–4 toxicities was significantly lower in the sequential chemoradiotherapy group than the cCRT group (4% vs. 18%); although the sequential chemoradiotherapy group had slightly inferior efficacy compared with the cCRT group, and the 3-year local control rate still reached 28.1% and the 3-year OS rate reached 18.1%. Therefore, sequential chemoradiotherapy or radiotherapy alone can be considered for patients with poor PS scores. EGFR-TKIs have demonstrated superior efficacy and safety over chemotherapy in advanced NSCLC patients with EGFR-sensitive mutations. The combinations of targeted therapy with radiotherapy are being explored in patients with EGFR-positive locally advanced NSCLC. A retrospective study presented at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting showed that, for EGFR-positive locally advanced NSCLC, the median PFS was 21.6 months and the median OS was 67.4 months in the EGFR-TKIs + concurrent radiotherapy group, the median PFS was 16.2

months in the radiotherapy + sequential EGFR-TKIs group, and the median PFS was 12.7 months in the radiotherapy alone group. Compared with conventional cCRT, radiotherapy combined with EGFR-TKIs is expected to improve the outcomes of EGFR-positive unresectable, locally advanced NSCLC. In terms of prospective studies, a phase III trial on osimertinib (LAURA) and a phase II study on icotinib (NCT03396185) are underway and the results are reportedly promising. Given the superior safety profile of targeted therapy, this treatment modality is particularly suitable for patients with severe lung cancer with poor PS scores.

度伐利尤单抗作为同步放化疗(cCRT)后的巩固免疫治疗是不可切除的晚期NSCLC患者的标准治疗方法。然而，cCRT(同步放化疗)可能会加重毒性，因此主要适用于 PS 评分为 0-1 的患者，而 PS 评分较差[2-4]的患者往往不能耐受 cCRT。结果发现，序贯放化疗组的 3-4 级毒性发生率显著低于 cCRT(同步放化疗)组（4%：18%)；虽然序贯放化疗组疗效略逊于 cCRT(同步放化疗)组，但 3 年局部控制率仍达 28.1%，3 年 OS 率达 18.1%。因此，对于 PS 评分较差的患者，可考虑序贯放化疗或单独放疗。EGFR-TKI 在 EGFR 敏感突变的晚期 NSCLC 患者中已证明疗效和安全性优于化疗。正在探索靶向治疗与放疗的联合疗法治疗 EGFR 阳性的局部晚期 NSCLC 患者。在 2020 年美国临床肿瘤学会(ASCO)年会上发表的一项回顾性研究表明，对于 EGFR 阳性局部晚期 NSCLC，EGFR-TKI+同步放疗组的中位 PFS 为 21.6 个月，中位 OS 为 67.4 个月，放疗+序贯 EGFR-TKI 组的中位 PFS 为 16.2 个月，单独放疗组的中位 PFS 为 12.7 个月。与传统 cCRT(同步放化疗)相比，放疗联合 EGFR-TKI 有望改善 EGFR 阳性不可切除局部晚期 NSCLC 的预后。在前瞻性研究方面，奥希替尼的III期试验(LAURA)和埃克替尼的 II 期研究(NCT03396185)正在进行中，据报道结果很有希望。鉴于靶向治疗优越的安全性，这种治疗方式特别适合于 PS 评分较差的重症肺癌患者。

Palliative radiotherapy in patients with advanced severe lung cancer ***晚期重症肺癌患者的姑息放疗***

Systemic therapy-based multidisciplinary treatment is the standard treatment for advanced lung cancer. For patients with severe lung cancer with poor PS scores, the values of radiotherapy mainly lie in: (I) palliative radiotherapy for local lesions to improve patients' PS scores; and (II) increasing the control rate of local lesions and improving survival when systemic treatment is effective. The central nervous system (CNS) is a common metastasis site of lung cancer, especially for patients with positive driver gene mutations. Brain metastases are a serious threat to patients' lives. Radiotherapy for brain metastases helps to control lesions, improve symptoms, and prolong survival. The most appropriate radiotherapy technique should be selected according to the pathological type of the malignancy, the number and extent of the brain metastases, and the distance to the threaten organs.

Compared with whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS) has the characteristics of a more precise localization, higher local dose, less damage to surrounding tissues, and less serious side effects, and thus in the preferred brain radiotherapy technique for patients with severe NSCLC. In particular, for patients with small brain metastases (maximal diameter of up to 3 cm) and of limited number (≤4), SRS is preferred. The JLGK0901 study found that SRS alone in the treatment of patients with 5–10 metastases is equivalent to 2–4 metastases. Compared with SRS alone, the combination of SRS and WBRT can reduce the probability of intracranial recurrence, but it has no benefit in improving long-term survival and increases the risk of cognitive impairment. Therefore, for patients with a limited number of metastases (≤10), SRS alone is the preferred local treatment. If the lesions are adjacent to vital centers, hypofractionated SRS may be considered to further reduce the side effects. SCLC has a high propensity to metastasize into the brain due to certain biological features, and therefore WBRT is recommended for SCLC patients. For those with oligometastases, SRS used as boost irradiation on the basis of WBRT can be considered to improve local control rate. In addition, brain necrosis and edema after radiotherapy for brain metastases, especially SRS, are also clinical issues. Li et al. reported that the biologically effective doses and gross tumor volume (BED × GTV) can effectively indicate the time interval and edema range of brain necrosis after radiotherapy, which can be used to guide the use of bevacizumab. Meningeal metastatic carcinoma is the spread of tumor cells in the circulating cerebrospinal fluid, and deposits form on the surface of the meninges and nerve roots, resulting in the absorption of cerebrospinal fluid. This causes a series of serious clinical symptoms, such as high intracranial pressure, mental change, abnormal gait, cranial nerve paralysis and secondary epilepsy. Meningeal metastases are often more threatening to patients' lives than brain parenchymal metastases. The diagnosis of meningeal metastasis depends on magnetic resonance imaging (MRI) and cerebrospinal fluid cytology. WBRT can improve the symptoms of patients with meningeal metastatic carcinoma and even afford survival benefits to some patients.

以全身治疗为基础的多学科治疗是晚期肺癌的标准治疗方法。对于 PS 评分较差的重症肺癌患者，放疗的价值主要在于：(Ⅰ)局部病灶姑息放疗，改善患者的 PS 评分；和(Ⅱ)全身治疗有效时，增加局部病灶控制率，改善生存。中枢神经系统(CNS)是肺癌的常见转移部位，特别是对于驱动基因突变阳性的患者。脑转移严重威胁患者的生命。脑转移瘤的放疗有助于控制病变、改善症状、延长生存。应根据恶性肿瘤的病理类型、脑转移灶的数量和范围以及与危险器官的距离选择最合适的放疗技术。与全脑放疗(WBRT)相比，立体定向放射外科(SRS)具有定位更精确、局部剂量更高、对周围组织损伤更小、严重副作用更少等特点，因此，是重症 NSCLC 患者首选的脑放疗技术。特别是对于小的脑转移

瘤(最大直径可达3cm)和数量有限(≤4)的患者，首选SRS(立体定向放射外科)。JLGK0901研究发现，单独使用SRS(立体定向放射外科)治疗5-10个转移灶的患者与2-4个转移灶的患者相当。与单独SRS(立体定向放射外科)相比，SRS联合WBRT(全脑放疗)可降低颅内复发概率，但对提高长期生存无益，增加认知障碍风险。因此，对于转移灶数量有限（≤10）的患者，单用SRS(立体定向放射外科)是首选的局部治疗。如果病变邻近重要中枢，可以考虑大分割SRS(立体定向放射外科)以进一步减少副作用。由于某些生物学特征，SCLC(小细胞肺癌)有很高的转移到大脑的倾向，因此推荐对 SCLC 患者进行WBRT(全脑放疗)。对于寡转移患者，可考虑在 WBRT(全脑放疗)的基础上采用 SRS(立体定向放射外科)作为推量照射，以提高局部控制率。此外，脑转移瘤放疗后尤其是SRS(立体定向放射外科)后的脑坏死和脑水肿也是临床问题。Li 等报道生物有效剂量和大体肿瘤体积（BED×GTV）可以有效指示放疗后脑坏死的时间间隔和水肿范围，可用于指导贝伐珠单抗的使用。脑膜转移癌是肿瘤细胞在循环脑脊液中播散，在脑膜和神经根表面形成沉积物，影响脑脊液吸收。这会导致一系列严重的临床症状，如颅内压升高、精神改变、步态异常、颅神经麻痹和继发性癫痫。脑膜转移通常比脑实质转移对患者的生命威胁更大。脑膜转移的诊断依赖于磁共振成像(MRI)和脑脊液细胞学检查。WBRT(全脑放疗)可以改善脑膜转移癌患者的症状，甚至为一些患者提供生存获益。

Local high-dose radiotherapy can also be considered for mass meningeal metastases. A ventricle-abdominal shunt can effectively alleviate the symptoms of the high intracranial pressure caused by meningeal metastatic carcinoma and promotes the smooth completion of WBRT. Intrathecal chemotherapy (e.g., pemetrexed) can solve the problem of the low intracranial blood drug concentration caused by peripheral intravenous administration due to the obstruction of the blood-brain barrier. In addition, Ommaya capsule implantation can effectively increase the blood concentration of cerebrospinal fluid and also provides a convenient, minimally invasive and continuous administration route for regular intrathecal chemotherapy. Palliative radiotherapy for other sites includes but is not limited to: (I) treatment of bone metastases, where it helps to relieve local pain and lower the incidence of bone related events such as pathological fractures and paraplegia; (II) treatment of hemoptysis in patients with central lung cancer accompanied by poorly controlled hemoptysis, palliative radiotherapy can help to stop hemorrhaging after the site of bleeding is clearly identified by endoscopic or radiological techniques; and (III) treatment of superior vena cava (SVC) syndrome: SCLC often presents as a centrally located mass that is often combined with SVC syndrome, which decreases patient quality of life. Hyperfractionated radiotherapy can be used to rapidly relieve the obstruction and alleviate the relevant symptoms. When the tumor is controlled after systemic therapy,

local radiotherapy for residual primary and/or metastatic lesions may achieve prolonged disease control and survival. Results of a phase II study in a Chinese NSCLC population published in 2015 showed that patients who received palliative radiotherapy for primary lesions in the chest had a 1-year local control rate of 78.8%, a median PFS of 9.0 months, and a median OS of 13.0 months. Palliative radiotherapy for metastases is also expected to prolong survival in patients with NSCLC. The results of a phase II study published in J Clin Oncol in 2019 showed that palliative radiotherapy for metastases significantly prolonged PFS (14.2 vs. 4.4 months, P=0.022) and OS (41.2 vs. 17.0 months, P=0.017) in NSCLC patients when systemic therapy was effective.

对于大肿块脑膜转移也可考虑局部大剂量放疗。脑室-腹腔分流术可有效缓解由脑膜转移癌引起的高颅压症状，促进 WBRT(全脑放疗)的顺利完成。鞘内化疗(如培美曲塞)可解决外周静脉给药因血脑屏障障碍所引起的颅内血药浓度低的问题。此外，Ommaya 囊植入可有效提高脑脊液血浓度，也为定期鞘内化疗提供了便捷、微创、连续给药途径。其他部位的姑息放疗包括但不限于：(Ⅰ)骨转移瘤的治疗，有助于缓解局部疼痛，降低病理性骨折、截瘫等骨相关事件的发生率；(Ⅱ)中央型肺癌患者合并咯血控制不佳的咯血的治疗，经内镜或影像学技术明确出血部位后，姑息放疗有助于止血；和(Ⅲ)上腔静脉(SVC)综合征的治疗：SCLC 常表现为位于中央的肿块，常合并 SVC(上腔静脉)综合征，降低患者的生活质量。超分割放疗可迅速解除梗阻，缓解相关症状。当全身治疗后肿瘤得到控制时，对残留的原发灶和/或转移灶进行局部放疗可延长疾病控制时间和生存期。2015 年发表的一项针对中国 NSCLC 人群的Ⅱ期研究结果显示，胸部原发灶接受姑息放疗的患者 1 年局部控制率为 78.8%，mPFS(中位无进展生存期)为 9.0 个月，mOS(中位总生存期)为 13.0 个月。转移灶姑息放疗也有望延长 NSCLC 患者的生存期。2019 年发表在《临床肿瘤学杂志》(J Clin Oncol)上的一项Ⅱ期研究结果表明，当全身治疗有效时，针对转移灶的姑息性放疗显著延长了 NSCLC 患者的 PFS（14.2：4.4 个月，P=0.022）和 OS（41.2：17.0 个月，P=0.017）。

Consensus 8: application of interventional techniques in patients with severe lung cancer

共识 8：介入技术在重症肺癌患者中的应用

Interventional techniques for lung tumors can be applied via the airway, chest wall, or blood vessels. Lung cancer patients can undergo a variety of acute and critical conditions such as large airway obstruction, acute pulmonary embolism, and hemoptysis. Proper interventional techniques can rapidly alleviate or control these clinical symptoms and improve PS scores, thus making other anti-tumor therapies possible and even achieving a cure for some specific types of lung cancers. (Recommendation category: B; level of evidence: 2a).

肺部肿瘤的介入技术可以通过气道、胸壁或血管进行。肺癌患者可出现大气道阻塞、急性肺栓塞、咯血等各种急危重症。适当的介入技术可以快速缓解或控制这些临床症状并改善 PS 评分，从而可能使用其他抗肿瘤疗法，甚至可以治愈某些特定类型的肺癌。（推荐类别：B；证据级别：2a）。

Interventional treatment of central airway obstruction (CAO)

中央气道阻塞(CAO)的介入治疗

Clinically, lung cancer-related CAO (which can be divided into endogenous, exogenous, and mixed types, depending on the tumor cell infiltration of the airway) can range from asymptomatic to life-threatening, and interventional therapy can rapidly alleviate symptoms and create opportunities for subsequent treatment in critically ill patients. The endogenous type can be treated by mechanical resection or ablation (including electrocoagulation/electrocision/loop electroexcision procedure, laser, argon plasma coagulation, photodynamic therapy, and cryotherapy). For the exogenous type, intervention techniques include dilatation and stent implantation. In certain patients, combinations of several different types of intervention are often used. In particular, the interventional techniques may be applied in combination with brachytherapy to achieve long-term benefit. With the participation of anesthesiologists, tracheal intubation and mechanical ventilation ensure a smooth and safe interventional treatment; during the operation, both a rigid bronchoscope and flexible endoscope are used to take advantage of their own particular advantages.

临床上肺癌相关的 CAO（中央气道阻塞，根据肿瘤细胞浸润气道的情况可分为内生性、外生性和混合型）可以从无症状到危及生命，介入治疗可以迅速缓解症状，为危重患者的后续治疗创造机会。内生型可通过机械切除或消融治疗（包括电凝/电切/环形电切术、激光、氩等离子体凝固术、光动力疗法和冷冻疗法）。对于外生型，介入技术包括扩张和支架植入。在某些患者中，经常联合使用几种不同类型的干预措施。特别是，介入技术可以与近距离放疗联合使用以实现长期获益。在麻醉师的参与下，气管插管和机械通气确保介入治疗的顺利和安全；在手术过程中，可使用硬质支气管镜和柔性内窥镜，以发挥各自的特殊优势。

Interventional treatment of peripheral lung cancer *周围型肺癌的介入治疗*

Most peripheral types of severe lung cancer are associated with old age, frailty, and poor lung function. Transbronchial biopsy and treatment techniques are being developed for early-stage peripheral lung cancer. Percutaneous interventional techniques are relatively more mature and have more clinical evidence of effectiveness and safety.

大多数周围类型的重症肺癌与年老、虚弱和肺功能差有关。正在开发早期周围型肺癌的经支气管活检和治疗技术。经皮介入技术相对更成熟，有更多的有效性和安全性临床证据。

Interventional treatment of hemoptysis in patients with lung cancer ***肺癌患者咯血的介入治疗***

Hemoptysis, a common symptom of lung cancer, can occur before diagnosis and during treatment. Life-threatening hemoptysis may occur in a small proportion of lung cancer patients. Bronchial artery embolization is usually the preferred option for hemoptysis, with a success rate of 60–90%. Transbronchial intervention techniques (including stenting) are also options.

咯血是肺癌的常见症状，可发生在诊断前和治疗期间。一小部分肺癌患者可能会出现致命性咯血。支气管动脉栓塞术通常是咯血的首选方法，成功率为 60-90%。也可选择经支气管介入技术（包括支架置入术）。

Interventional treatment of SVC syndrome ***上腔静脉综合征的介入治疗***

The incidence of SVC syndrome is 2–4% in lung cancer patients and up to 10% in SCLC patients. When SVC syndrome causes laryngeal and cerebral edema and hemodynamic instability, urgent endovascular stenting is required.

肺癌患者 SVC 综合征的发生率为 2-4%，在 SCLC 患者中高达 10%。当 SVC 综合征引起喉和脑水肿以及血流动力学不稳定时，需要紧急血管内支架置入术。

Consensus 9: application of anti-tumor drugs in patients with severe lung cancer

共识 9：抗肿瘤药物在重症肺癌患者中的应用

Drug treatment is not contraindicated in all patients with severe lung cancer, and the key consideration is how to precisely use the selected drugs to achieve high efficiency with low toxicity. Currently, the medications for lung cancer mainly include chemotherapy, targeted therapy, antiangiogenic therapy, and immunotherapy. For targeted therapy, clinical studies have been carried out in patients with PS 0–3; for chemotherapy, antiangiogenic therapy, and immunotherapy, clinical studies have been conducted mainly in patients with PS 0 or 1, with only a small amount of data from patients with PS 2.

药物治疗并不是所有重症肺癌患者的禁忌，关键是考虑如何精准使用所选药物，实现高效低毒。目前治疗肺癌的药物主要包括化疗、靶向治疗、抗血管生成治疗和免疫治疗。对于靶向治疗，已经在 PS 0-3 的患者中进行了临床研究；对于化疗、抗血管生成治疗和免疫治疗，临床研究主要在 PS 0 或 1 的患者中进行，仅有少量来自 PS 2 患者的数据。

Chemotherapy

化疗

Clinical evidence for the use of platinum-based double agents in advanced NSCLC with a PS score of 2 (recommendation category: A; level of evidence: 1a)

在 PS 评分为 2 的晚期 NSCLC 中使用铂基双药的临床证据（推荐类别：A；证据级别：1a）

In a meta-analysis of 12 randomized studies performed in NSCLC patients with PS 2 (4 dedicated to PS 2 and 8 stratified patients with PS 2), the platinum-based dual-agent combination group had a significantly higher survival benefit over the single-drug group [HR =0.71, 95% confidence interval (CI): 0.61–0.81]. Another meta-analysis also confirmed that dual-agent chemotherapy significantly improved OS (HR =0.72; 95% CI: 0.61–0.84; P<0.0001) and improved 1-year survival over single-drug chemotherapy, although the grade 3 to 4 hematologic toxicities also increased. An article summarizing 10 clinical studies reported a benefit of pemetrexed plus platinum in NSCLC patients with PS 2 over pemetrexed alone in both PFS (HR =0.46; P<0.001) and OS (HR =0.62; P=0.001). A recent study showed that carboplatin combined with albumin-bound paclitaxel also had good efficacy (median PFS: 5.2 months; median OS: 14 months). For advanced NSCLC patients with a PS of 2, platinum-containing dual-drug chemotherapy is an option, but patient tolerability needs to be considered.

在对 PS 2 的 NSCLC 患者（4 项专门针对 PS 2 和 8 项对 PS 2 患者进行的分层研究）进行的 12 项随机研究的 meta 分析中，铂基双药联合治疗组的生存获益显著高于单药治疗组[HR=0.71，95%置信区间(CI)：0.61－0.81]。另一项 meta 分析也证实，与单药化疗相比，双药化疗显著改善了 OS（HR=0.72；95%CI：0.61-0.84；P<0.0001）并提高了 1 年生存率，尽管 3-4 级血液学毒性也增加了。一篇总结 10 项临床研究的文章报道，在 PFS（HR=0.46；P<0.001）和 OS（HR=0.62；P=0.001）两方面，培美曲塞+铂治疗 PS 2 的 NSCLC 患者均优于单独使用培美曲塞。最近的一项研究表明，卡铂联合白蛋白结合型紫杉醇也具有良好的疗效（mPFS：5.2 个月；中位 OS：14 个月）。对于 PS 为 2 的晚期 NSCLC 患者，含铂双药化疗是一种选择，但需要考虑患者的耐受性。

Clinical evidence of chemotherapy for advanced NSCLC patients with a PS of 3 or 4 (recommendation category: B; level of evidence: 2b)

PS 为 3 或 4 的晚期 NSCLC 患者化疗的临床证据（推荐类别：B；证据级别：2b）

A phase II randomized controlled study comparing gemcitabine (1,250 mg/m2, days 1 and 8) vs. gemcitabine (200 mg/m2, day 1) plus cisplatin (60 mg/m2) in the treatment of advanced NSCLC with a PS of 2 or 3 (75.9% had a PS score of 3) found that the low-dose combination chemotherapy was more effective than the single-agent chemotherapy (median PFS: 3.8 vs. 5.6 months; median OS: 4.3 vs. 6.8 months) and had fewer adverse effects. A

retrospective study included 96 patients with advanced NSCLC with PS ≥2 who received chemotherapy, of whom 33.5% had a PS score of 3 or 4. The most common chemotherapy regimen used was a combination of weekly paclitaxel (60 mg/m2) and carboplatin (AUC 2) in 57.8%, followed by pemetrexed 500 mg/m2 plus carboplatin (AUC 5)/cisplatin every 3 weeks (16.8%) and paclitaxel alone (13.6%). Data analysis showed an overall response rate (ORR) of 20%, a disease control rate (DCR) of 48.42%, and a median PFS of 6.3 months; univariate analysis suggested that weekly paclitaxel plus carboplatin was associated with prolonged PFS, and 45.26% of the patients had an improved PS score during chemotherapy compared to baseline. However, there is little clinical evidence for chemotherapy application in NSCLC patients with a PS of 3 or 4 has been available. Most of these studies were retrospective studies, and there was a lack of prospective clinical research.

一项比较吉西他滨（1250mg/㎡，d1、8）与吉西他滨（200mg/㎡，d1）+顺铂（60mg/㎡）治疗 PS 评分为 2 或 3（75.9%的 PS 评分为 3）的晚期 NSCLC 的 II 期随机对照研究发现，低剂量联合化疗比单药化疗更有效（mPFS：3.8∶5.6 个月；mOS：4.3∶6.8 个月）并且不良反应少。一项回顾性研究纳入了 96 例接受化疗的 PS≥2 的晚期 NSCLC 患者，其中 33.5%的 PS 评分为 3 或 4。最常用的化疗方案是每周 1 次紫杉醇(60mg/㎡)联合卡铂(AUC2)为 57.8%，其次是培美曲塞 500mg/㎡+卡铂(AUC5)/顺铂每 3 周 1 次(16.8%)和单药紫杉醇(13.6%)。数据分析显示总缓解率(ORR)为 20%，疾病控制率(DCR)为 48.42%，mPFS 为 6.3 个月；单变量分析表明，每周 1 次紫杉醇+卡铂与 PFS 延长相关，45.26%的患者在化疗期间的 PS 评分与基线相比有所改善。然而，目前对于 PS 为 3 或 4 的 NSCLC 患者应用化疗的临床证据很少。这些研究多为回顾性研究，缺乏前瞻性临床研究。

Clinical evidence of chemotherapy for advanced SCLC patients with a PS of 3 or 4 (recommendation category: A; level of evidence: 1a)

PS 为 3 或 4 的晚期 SCLC 患者化疗的临床证据（推荐类别：A；证据级别：1a）

For extensive SCLC patients with a PS score of 3–4 caused by SCLC, the treatment recommended by the major guidelines is similar to that with a PS score of 0–2. However, it is necessary to combine various factors and carefully choose the chemotherapy regimen, such as choosing a single drug or a reduced dose combination treatment. For poor PS scores caused by non-SCLC, the guidelines recommend the best supportive treatment. However, a retrospective study showed that chemotherapy significantly prolonged the survival of SCLC patients with a PS of 3 or 4 compared with best supportive treatment. There are also relatively few clinical studies on these patients.

对于 SCLC 引起的 PS 评分为 3-4 的广泛期 SCLC 患者，主要指南推荐的治疗与 PS 评分为

0-2 者相似。但需要综合各种因素，慎重选择化疗方案，如选择单药或减量联合治疗等。对于不是 SCLC 导致的 PS 评分差，各指南推荐最佳支持治疗。然而，一项回顾性研究表明，与最佳支持治疗相比，化疗显著延长了 PS 为 3 或 4 分的 SCLC 患者的生存期。对这些患者的临床研究也相对很少。

Targeted therapy ***靶向治疗***

Clinical evidence for EGFR-TKIs in advanced NSCLC patients with a PS ≥2 (recommendation category: A; level of evidence: 1b)

EGFR-TKI 在 PS≥2 的晚期 NSCLC 患者中的临床证据（推荐类别：**A；证据级别：1b**）

One study demonstrated good efficacy and good tolerability of gefitinib in treating advanced NSCLC patients with EGFR mutation and PS ≥2. A retrospective study performed in super-elderly NSCLC patients (aged ≥85 years) with a PS score of 3–4 showed gefitinib had a greater OS benefit than best supportive care (4.6 vs. 2.3 months). In a retrospective analysis, in patients with first or second generation TKI resistance and EGFR T790M mutation-positive NSCLC with PS scores of 2–4 who were treated with osimertinib, the ORR was 53% (95% CI: 36–70%), the PS score improvement rate was 63%, and the median PFS was 8.2 months. In addition, the treatment was well tolerated. Similarly, osimertinib also appears to be effective (median PFS: 7.0 months; median OS: 12.7 months) in a recent phase II trial enrolling 18 patients with T790Mmutated NSCLC with PS ≥2, and it improved the PS score in 72% of the patients. For EGFR-positive patients with a PS ≥2, EGFR-TKI monotherapy remains the preferred regimen, and TKI combination therapy is currently less well documented.

在一项回顾性分析中，在接受奥希替尼治疗的第一或第二代 TKI 耐药且 EGFR T790M 突变阳性、PS 评分为 2-4 的 NSCLC 患者中，ORR 为 53%(95% CI：36-70%)，PS 评分改善率为 63%，mPFS 为 8.2 个月。此外，治疗耐受性良好。同样，在最近的一项Ⅱ期试验中，奥希替尼似乎也有效（mPFS：7.0 个月；mOS：12.7 个月），该试验招募了 18 名 PS≥2 的 T790M 突变 NSCLC 患者，72%的患者 PS 评分改善。对于 PS≥2 的 EGFR 阳性患者，EGFR-TKI 单药治疗仍然是首选方案，而 TKI 联合治疗目前鲜有证据。

Clinical evidence of ALK-TKIs for advanced NSCLC patients with PS ≥2 (recommendation category: A; level of evidence: 1b)

ALK-TKI 用于 PS≥2 的晚期 NSCLC 患者的临床证据（推荐类别：**A；证据级别：1b**）

A case report (n=5) suggested a promising efficacy for crizotinib in the treatment of advanced ALK rearrangement-positive NSCLC patients with a PS ≥2. In another study, patients with advanced ALK rearrangement-positive NSCLC and a PS of 2 to 4 received alectinib, which yielded an ORR of 72.2%, a PFS of

10.1 months, and a PS improvement rate of 83.3%. The updated data showed that the median PFS reached 16.2 months, the median OS reached 30.3 months, and the 3-year survival rate was 42%. A real-world study in Japan showed, after alectinib treatment, the OS was significantly shorter in patients with a PS score ≥2 than those with a PS score ≤1; however, the adverse reaction rates were similar, suggesting patients with poor PS scores could nonetheless tolerate alectinib.

最新数据显示，mPFS 达到 16.2 个月，mOS 达到 30.3 个月，3 年生存率为 42%。日本的一项真实世界研究表明，在接受阿来替尼治疗后，PS 评分≥2 的患者的 OS 明显短于 PS 评分≤1 的患者；然而，不良反应发生率相似，表明 PS 评分较差的患者仍然可以耐受阿来替尼。

Thus, ALK-TKIs may be a new option for ALK rearrangement-positive NSCLC patients with a PS ≥2, but is has only been explored in few clinical trials and deserves further verification in larger studies.

因此，ALK-TKI 可能是 PS≥2 的 ALK 重排阳性 NSCLC 患者的新选择，但仅在很少的临床试验中进行了探索，值得在更大的研究中进一步验证。

Angiogenesis inhibitors (recommendation category: B; level of evidence: 1b)

血管生成抑制剂（推荐类别：B；证据级别：1b）

A randomized phase II trial of pemetrexed, pemetrexed/ bevacizumab, and pemetrexed/carboplatin/bevacizumab in patients with advanced NSCLC and a PS of 2 showed that the PFS was 2.8, 4.0, and 4.8 months, respectively, and the ORR was 15%, 31%, and 44%, respectively, in these three groups. In a study with 92% of patients enrolled having PS of 2, the combination of erlotinib and bevacizumab also showed good efficacy and tolerability for recurrent NSCLC. A retrospective study showed that in the subgroup with a PS score of ≥2, the HR for both PFS and OS was 0.47 in the bevacizumab combined with carboplatin + paclitaxel group compared to the chemotherapy alone group, although the difference was not statistically significant. Recently, one of our studies showed that, for patients with advanced squamous lung cancer with a PS score between 2 and 3 after failed second-or later-line systemic therapy, anlotinib plus S-1 prolonged survival compared with anlotinib alone. Angiogenesis inhibitors have no specific PS score requirement and can be used as transitional options for patients with poor PS scores, and a new treatment regimen may be initiated after the PS score has improved.

一项关于培美曲塞、培美曲塞/贝伐珠单抗和培美曲塞/卡铂/贝伐珠单抗治疗 PS 为 2 的晚期 NSCLC 患者的随机Ⅱ期试验显示，这三组的 PFS 分别为 2.8、4.0 和 4.8 个月，ORR 分别为 15%、31%和 44%。在一项纳入 92%的患者 PS 为 2 的研究中，厄洛替尼和贝伐珠单抗的联合也显示出对复发性 NSCLC 的疗效和耐受性良好。一项回顾性研究表明，在 PS

评分≥2 的亚组中，贝伐珠单抗联合卡铂+紫杉醇组与单纯化疗组相比，PFS 和 OS 的 HR 均为 0.47，但差异无统计学意义。最近，我们的一项研究表明，对于二线或后线全身治疗失败后 PS 评分在 2 到 3 之间的晚期鳞型肺癌患者，与单独使用安罗替尼相比，安罗替尼加 S-1(替吉奥)延长了生存期。血管生成抑制剂没有特定的 PS 评分要求，可作为 PS 评分较差患者的过渡方案，在 PS 评分改善后可启动新的治疗方案。

Immunotherapy (recommendation category: B; level of evidence: 1b)

免疫疗法（推荐类别：B；证据级别：1b）

The OS was shorter in PS 2 patients compared with PS 0 or 1 patients in CheckMate 153 and CheckMate 171, which included patients with advanced NSCLC treated with nivolumab, although the incidence of toxicities was comparable. In a clinical trial on NSCLC patients treated with pembrolizumab, the efficacy was similar between patients with NSCLC of PS 2 and those with PS 0 or 1 (regardless of PD-L1 expression), and no novel AE was observed. However, there were also studies performed in patients with PS 2 in which immunotherapy was ineffective. Such data suggests that lung cancer patients with PS 2 are highly heterogeneous. It was found that patients with a PS of 2 as determined by comorbidities had significantly better outcomes compared with disease burden-induced PS 2. Friedlaender et al. also proposed that, for SCLC patients with a poor PS score, the cause of the poor PS should be evaluated; immunotherapy might also be applied in SCLC patients with a PS of 2 after efficacy prediction. This is well in line with our treatment strategy. A case of a patient with a PS score of 3 and recurrent pulmonary infections due to CAO. The patient received combination therapy including endoscopic recanalization of central airway followed by immunotherapy, which reduced tumor lesions and improved the PS score. Case reports have shown that immunotherapy was also effective in patients with a PS of 4. Nevertheless, the role of immunotherapy in patients with poor PS scores needs to be further investigated. Many studies of atezolizumab in treating elderly patients with advanced lung cancer have confirmed that the therapeutic benefits were similar between patients older than and younger than 65 years of age; meanwhile, no novel AE was noted, and the side effects were basically predictable and manageable. Furthermore, many studies evaluating the efficacy of immunotherapy in patients with PS scores ≥2 are in progress, with an attempt to further clarify the survival benefits and clinical value of immunotherapy in patients with severe lung cancer.

与 CheckMate 153 和 CheckMate 171 中的 PS 评分为 0 或 1 患者相比，PS 评分为 2 患者的 OS 更短，其中包括接受纳武利尤单抗治疗的晚期 NSCLC 患者，尽管毒性发生率相当。在一项针对接受帕博利珠单抗治疗的 NSCLC 患者的临床试验中，PS 评分为 2 和 PS 评分 0 或 1（无论 PD-L1 表达如何）的 NSCLC 患者的疗效相似，未观察到新的 AE。然而，也

有针对 PS 评分为 2 的患者进行的研究，免疫疗法无效。上述数据表明，PS 评分为 2 的肺癌患者具有高度异质性。结果发现，与疾病负荷引起的 PS 评分为 2 相比，由合并症决定的 PS 为 2 的患者具有显著更好的结果。Friedlaender 等也提出，对于 PS 评分较差的 SCLC 患者，应评估 PS 评分较差的原因；PS 评分为 2 的 SCLC 患者在疗效预测后也可应用免疫治疗。这完全符合我们的治疗策略。一例 PS 评分为 3 且因 CAO(中央气道阻塞)反复出现肺部感染的患者。患者接受了包括内镜下中央气道再通然后免疫治疗在内的综合治疗，缩小了肿瘤病变并改善了 PS 评分。病例报告显示，免疫疗法对 PS 评分为 4 的患者也有效。不过，免疫疗法在 PS 评分较差的患者中的地位需要进一步研究。许多关于阿替利珠单抗治疗老年晚期肺癌患者的研究证实，65 岁以上和 65 岁以下患者的治疗获益相似；同时，未发现新的 AE，副作用基本上是可预测和可控的。此外，许多评估免疫治疗在 PS 评分≥2 患者中的疗效的研究正在进行中，试图进一步阐明免疫治疗在重症肺癌患者中的生存获益和临床价值。

Consensus 10: application of life support techniques in patients with severe lung cancer

共识 10：生命支持技术在重症肺癌患者中的应用

Tumors originating in the lungs are often accompanied by other severe diseases. It is well known that the heart and lungs are the most important life-sustaining organs, and the failure of these two organs typically signals the end of life. While heart cancer is rare, lung cancer is one of the most common cancers worldwide. Therefore, life support including but not limited to the use of respiratory support techniques for patients with severe lung cancer is vital (recommendation category: B; level of evidence: 2a).

起源于肺部的肿瘤通常伴有其他严重的疾病。众所周知，心脏和肺是最重要的维持生命的器官，这两个器官的衰竭通常预示着生命的终结。虽然心脏癌症罕见，但肺癌是全球最常见的癌症之一。因此，生命支持包括但不限于对重症肺癌患者使用呼吸支持技术至关重要（推荐类别：B；证据级别：2a）。

Appropriate respiratory support

适当的呼吸支持

The appropriate respiratory support techniques should be selected based on the patients' respective conditions. Patients with severe lung cancer have a poor systemic status, and most of them also have poor lung compliance and are prone to hypoxemia or even respiratory failure. The main causes are diverse, mainly including: severe pneumonia, cardiogenic or non-cardiogenic pulmonary edema, lung injury caused by anti-tumor therapy (radiotherapy, targeted therapy, immunotherapy, etc.), aggravation of underlying diseases (e.g., COPD and ILD),

and tumor complications (pulmonary embolism, airway obstruction, pleural effusion, pericardial effusion, etc.). Respiratory failure may also occur postoperatively as a result of conditions such as atelectasis, pneumonia, pulmonary edema, and bronchopleural fistula. At admission, patients with severe lung cancer should receive routine blood gas tests, assessment of respiratory function, and aggressive oxygen therapy with a nasal cannula or face mask to maintain an oxygen saturation level of 94–98%. Based on the results of blood gas analysis and oxygenation monitoring, patients should be promptly judged to have respiratory failure (or not), and the timing of noninvasive and invasive ventilation should be carefully evaluated. The non-invasive ventilator ensures the quality of ventilation and can also set a balanced ratio of the spontaneous breaths according to the actual physical condition. It is better than the conventional oxygen inhalation in relieving dyspnea and can reduce the probability of intubation and the incidence of complications.

应根据患者的具体情况选择适当的呼吸支持技术。重症肺癌患者全身状况较差，且多数肺顺应性也差，易发生低氧血症甚至呼吸衰竭。主要病因多种多样，主要包括：重症肺炎、心源性或非心源性肺水肿、抗肿瘤治疗（放疗、靶向治疗、免疫治疗等）所致肺损伤、基础疾病（如 COPD 和 ILD）加重，以及肿瘤并发症（肺栓塞、气道阻塞、胸腔积液、心包积液等）。由于肺不张、肺炎、肺水肿和支气管胸膜瘘等情况，术后也可能发生呼吸衰竭。重症肺癌患者入院时应接受常规血气分析、呼吸功能评估，并通过鼻导管或面罩进行积极氧疗，以维持 94-98%的氧饱和度水平。应根据血气分析和氧合监测结果，及时判断患者有无呼吸衰竭，仔细评估无创和有创通气时机。无创呼吸机在保证通气质量的同时，还可以根据实际身体状况设定平衡的自主呼吸比例。在缓解呼吸困难方面优于常规的氧气吸入，可降低插管概率和并发症发生率。

Supportive treatment of other vital organs

其他重要器官的支持治疗

Severe lung cancer can be associated with various types of organ dysfunction or even multi-organ failure. It is important to assess organ function in a timely manner, monitor intake/output, natriuretic peptide, cardiac enzyme profile, electrolytes and liver and kidney function, and perform electrocardiography and cardiac ultrasound in patients with severe lung cancer. Possible causes and triggers should be actively removed or mitigated and symptomatic supportive treatment of vital organs provided (e.g., heart, liver, kidney and brain) as soon as possible to prevent further deterioration. It is also necessary to correct electrolyte disorders and enhance fluid management to prevent hypovolemia or fluid overload. Supportive therapy with multiple devices (e.g., intra-aortic balloon counterpulsation, liver replacement therapy, renal replacement therapy, etc.) or tubes (nasogastric tube, urinary

catheter, central venous catheter, etc.) may be considered in critically ill patients.

重症肺癌可能与各种类型的器官功能障碍甚至多器官功能衰竭有关。重要的是及时评估器官功能，监测出入量、钠尿肽、心肌酶谱、电解质和肝肾功能，并对重症肺癌患者进行心电图和心脏超声检查。应积极去除或缓解可能的病因和诱因，尽快对重要器官（如心、肝、肾、脑）进行对症支持治疗，防止病情进一步恶化。还有必要纠正电解质紊乱并加强液体管理，以防止血容量不足或输液过量。危重患者可考虑采用多种器械（如主动脉内球囊反搏、肝脏替代治疗、肾脏替代治疗等）或导管（鼻胃管、导尿管、中心静脉导管等）的支持治疗。

Appropriate local therapy

适当的局部治疗

Malignant pleural effusion and pericardial effusion should be effectively drained. Tumor-induced tracheal obstruction can be relieved by interventional techniques. Body position can be adjusted so as to promote the drainage of respiratory secretions. Bedridden patients should be regularly turned and patted to avoid choking and mis-aspiration. Sputum can be aspirated at the bedside using a fiberoptic bronchoscope.

恶性胸腔积液和心包积液应有效引流。肿瘤引起的气管阻塞可以通过介入技术来缓解。可调整体位，促进呼吸道分泌物的排出。卧床不起的患者应定期翻身和拍背，以免窒息和误吸。可以在床边使用纤维支气管镜吸痰。

Appropriate nutritional support therapy

适当的营养支持疗法

Nutritional support is essential to optimize the health status of lung cancer patients and maximize their ability to complete long-term cancer treatment. Studies have shown that 34.5–56.4% of lung cancer patients have malnutrition. Malnourished cancer patients have a reduced quality of life, a poorer prognosis, and a higher incidence of postoperative complications than well-nourished patients. Patients with severe lung cancer should be screened regularly for the risk for the presence of malnutrition. According to the ESPEN guidelines, patients should firstly be counseled on diet, and those who can eat should be encouraged to consume adequate energy (target energy intake: 25–30 cal/kg; protein intake is recommended to be 1.0–1.5 g/kg/d), and nutritional supplements can be added; for patients with feeding difficulties, enteral nutrition is preferred; and when nutritional needs cannot be met or enteral nutrition is contraindicated, parenteral nutrition can be selected. Supplementation of micronutrients can also be helpful, and an individualized nutrition regimen is recommended.

营养支持对于优化肺癌患者的健康状况和最大限度地提高他们完成癌症长期治疗的能

力至关重要。研究表明，34.5-56.4%的肺癌患者存在营养不良。与营养良好的患者相比，营养不良的癌症患者生活质量下降，预后较差，术后并发症发生率更高。应定期筛查重症肺癌患者是否存在营养不良的风险。根据 ESPEN(欧洲肠外肠内营养学会)指南，应首先对患者进行饮食指导，鼓励能进食者摄入足够的能量(目标能量摄入量：25 - 30 cal/kg；蛋白质摄入量推荐为 1.0-1.5g/kg/d)，可以添加营养补充剂；对于进食困难的患者，首选肠内营养；当不能满足营养需要或有肠内营养禁忌时，可选择肠外营养。补充微量营养素也有帮助，推荐采用个体化的营养方案。

Active anti-infective treatment ***积极抗感染治疗***

Most lung cancer patients have chronic underlying diseases (e.g., COPD and bronchiectasis) and poor nutritional status and are affected by anti-tumor treatments (e.g., chemotherapy, radiotherapy, immunotherapy, and surgery), which lead to decreased immunity and/or damaged lung structure. As a result, these patients are more likely to suffer from respiratory tract infections. In immunocompromised lung cancer patients, delayed anti-infective therapy increases the risks of secondary complications and infection-related death. Therefore, patients with severe lung cancer with co-existing infection should be given proper initial empirical antimicrobial therapy immediately. Specimens for culture must be collected prior to the administration of antimicrobials. Based on the clinical and epidemiological features, the antimicrobial regimen should be tailored to cover all of the likely pathogens. When the causative organism is not identified, broad-spectrum antibacterials (e.g., β-lactams/enzyme inhibitors, third-generation cephalosporins/enzyme inhibitors, and carbapenems) are recommended. If there are obstructive cavity and poor drainage, which are more likely to be accompanied by anaerobic infection, the antibiotics selected should cover anaerobic bacteria; if routine antibiotic therapy fails, empirical antifungal therapy should be used as soon as possible, while also paying attention to the presence of any possible viral infection.

大多数肺癌患者有慢性基础疾病（如慢阻肺和支气管扩张）和营养状况不佳，并受到抗肿瘤治疗（如化疗、放疗、免疫治疗和手术）的影响，导致免疫力下降和/或肺组织受损。因此，这些患者更易患呼吸道感染。在免疫功能低下的肺癌患者中，延迟抗感染治疗会增加继发性并发症和感染相关死亡的风险。因此，合并感染的重症肺癌患者应立即给予适当的初步经验性抗菌治疗。在给予抗菌剂之前，必须采集用于培养的标本。根据临床和流行病学特征，应调整抗菌方案以涵盖所有可能的病原体。在致病微生物未确定时，推荐使用广谱抗菌药（如β-内酰胺类/酶抑制剂、第三代头孢菌素/酶抑制剂和碳青霉烯类）。如果有管腔阻塞、引流不畅，很可能伴有厌氧菌感染，选用的抗生素应覆盖厌氧菌；如果常规抗生素治疗失败，应尽快使用经验性抗真菌治疗，同时还要注意是

否存在任何可能的病毒感染。

Timely anticoagulation therapy

及时抗凝治疗

Research has shown that patients with lung cancer combined with pulmonary embolism who do not undergo anticoagulation have a higher mortality rate than those treated with anticoagulants. The ASCO guidelines have recommended prophylactic anticoagulation in patients with malignancies who are at risk of VTE with a low risk of bleeding. Therefore, we recommend aggressive anticoagulation for patients with a confirmed VTE or risk of VTE. Based on the recommendations proposed by the International Society on Thrombosis and Haemostasis (ISTH), the British Committee for the Standards in Haematology (BCSH), and the ASCO, our anticoagulation strategies in lung cancer patients are as follows: for patients with cancer-related VTE with platelet counts above 50×109/L, full-dose anticoagulation is recommended; for patients with platelet counts between 25×109/L and 50×109/L, half-dose anticoagulation is acceptable; and for patients with platelet counts below 25×109/L, anticoagulation is not recommended.

研究表明，未接受抗凝治疗的合并肺栓塞的肺癌患者的死亡率高于接受抗凝治疗的患者。ASCO指南推荐对有VTE(静脉血栓栓塞症)风险且出血风险低的恶性肿瘤患者进行预防性抗凝治疗。因此，我们推荐对已确诊VTE(静脉血栓栓塞症)或VTE风险的患者进行积极抗凝治疗。根据国际血栓与止血学会(ISTH)、英国血液学标准委员会(BCSH)和ASCO提出的建议，我们对肺癌患者的抗凝策略如下：对于血小板计数大于50×10^9/L的癌症相关VTE(静脉血栓栓塞症)患者，推荐全剂量抗凝治疗；对于血小板计数在25×10^9/L～50×10^9/L的患者，可接受半量抗凝；对于血小板计数低于25×10^9/L的患者，不推荐抗凝治疗。

Pulmonary rehabilitation *肺康复*

In patients with lung cancer combined with COPD, preoperative pulmonary rehabilitation training can improve postoperative lung re-expansion and reduce postoperative complications. Postsurgical rehabilitation programs in patients surgically treated for lung cancer are also beneficial to improve the quality of life. Multidimensional exercise intervention can also improve physical and functional capacity, anxiety, and depression in patients with advanced-stage lung cancer. Pulmonary rehabilitation includes exercise, education, nutritional support, and psychological support. Therefore, pulmonary rehabilitation requires multidisciplinary collaboration and joint efforts. In conclusion, with the help of supportive care and antitumor treatment on the basis of dynamic clinical patients' assessment and precise molecular testing, patients with severe lung cancer are likely to achieve survival

benefit, and improve PS score and their quality of life. Clinicians should pay close attention to severe lung cancer, search for its cause, and combine the results of precise detection and multidisciplinary opinions to provide individualized and comprehensive treatment for patients with severe lung cancer. We hope that this consensus will help in the treatment of severe lung cancer and encourage further research in this field.

对于合并 COPD(慢阻肺)的肺癌患者，术前肺康复训练可改善术后肺复张，减少术后并发症。对于接受肺癌手术治疗的患者，术后康复计划也有利于提高生活质量。多方面运动干预还可以改善晚期肺癌患者的体能和机能、焦虑和抑郁。肺康复包括锻炼、教育、营养支持和心理支持。因此，肺康复需要多学科协作和共同努力。综上所述，在对患者临床动态评估和精准分子检测的基础上，在支持治疗和抗肿瘤治疗的帮助下，重症肺癌患者有可能获得生存获益，并改善 PS 评分和生活质量。临床医生应密切关注重症肺癌，寻找病因，结合精准检测结果和多学科意见，为重症肺癌患者提供个体化综合治疗。我们希望该共识有助于重症肺癌的治疗，并鼓励该领域的进一步研究。