NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

非小细胞肺癌

Version 3.2014

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翻译人员

蔡文杰：福建医科大学附属泉州第一医院放疗科

肿瘤学硕士

福建省抗癌协会放射肿瘤专业委员会青年委员会副主任委员

《Chinese Journal of Cancer Research》沙龙委员（CSCD源，SCI）

丁香园肿瘤版版主

一直有个愿望，就是把全套 NCCN 指南翻译出来并维护下去。这个想法从 2010 年已经开始付诸实施，在丁香园肿瘤版开展 NCCN 指南草根汉化版活动。很荣幸地得到近千位战友响应。在多位精英战友的同心协力下做出了 20 多本“草根汉化版 NCCN 指南”。但因为任务太繁重，这个活动已经冷下来一段时间了。近日与天天超版联系，打算与 NCCN 官方接触，争取获得授权并招募团队长期维护指南。希望这个任务能有机会早日启动。

说起指南，那句“成也指南、败也指南”是最经典的。但要解决国内不规范治疗及疗效欠佳的问题，个人认为拿来主义也许是最快。翻译 NCCN 指南并推广是提高国内肿瘤诊疗水平的捷径，对于基层单位尤为如此。也是广大肿瘤患者的福音。

从 2011 年的 NCCN 指南 NSCLC 中国版至今虽然只有 3 年，但更新确实很多。本人利用业余时间，在学习过程中参考 2011 年中国版 NCCN 指南把她翻译成中文。除值班、加班外的每天晚上 8 点到 12 点都贡献给她。但因水平有限、时间太少，估计错误连篇，特别是每次上完夜班隔天的翻译错误会更多。希望各位同道指正，发现问题麻烦您发到我的邮箱 caiwj2001@126.com。

2014 第三版在第二版翻译的基础上更新完成，这个过程中也修改部份第二版翻译的错误。

NCCN Guidelines Version 3.2014 Panel Members
Non-Small Cell Lung Cancer

* David S. Ettinger, MD/Chair †
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Douglas E. Wood, MD/Vice Chair ¶ Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance
Wallace Akerley, MD † Huntsman Cancer Institute at the University of Utah
Lyudmila A. Bazhenova, MD † ‡
UC San Diego Moores Cancer Center
Hossein Borghaei, DO, MS † ‡ Fox Chase Cancer Center
D. Ross Camidge, MD, PhD † University of Colorado Cancer Center
Andrew C. Chang, MD ¶ University of Michigan Comprehensive Cancer Center
Richard T. Cheney, MD ≠
Roswell Park Cancer Institute
Lucian R. Chirieac, MD ≠
Dana-Farber/Brigham and Women's Cancer Center
Thomas A. D'Amico, MD ¶ Duke Cancer Institute
Todd L. Demmy, MD ¶ Roswell Park Cancer Institute
Ramaswamy Govindan, MD † Siteman Cancer Center at Barnes- Jewish Hospital and Washington University School of Medicine
Frederic W. Grannis, Jr., MD ¶
City of Hope Comprehensive Cancer Center
Stefan C. Grant, MD, JD † ‡ University of Alabama at Birmingham Comprehensive Cancer Center
Leora Horn, MD, MSc † Vanderbilt-Ingram Cancer Center
Thierry M. Jahan, MD † ‡ UCSF Helen Diller Family Comprehensive Cancer Center
Ritsuko Komaki, MD § The University of Texas MD Anderson Cancer Center
Mark G. Kris, MD †
Memorial Sloan-Kettering Cancer Center
Lee M. Krug, MD †
Memorial Sloan-Kettering Cancer Center
Rudy P. Lackner, MD
Fred & Pamela Buffett Cancer Center at The Nebraska Medical Center
Inga T. Lennes, MD †
Massachusetts General Hospital Cancer Center
Jules Lin, MD ¶
University of Michigan Comprehensive Cancer Center
Billy W. Loo, Jr., MD, PhD § Stanford Cancer Institute
Renato Martins, MD, MPH †
Fred Hutchinson Cancer Research Center/ Seattle Cancer Care Alliance
Gregory A. Otterson, MD †
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute
Jyoti D. Patel, MD ‡
Robert H. Lurie Comprehensive Cancer Center of Northwestern University
Mary C. Pinder-Schenck, MD †
Moffitt Cancer Center
Katherine M. Pisters, MD † The University of Texas MD Anderson Cancer Center
Karen Reckamp, MD, MS † ‡
City of Hope Comprehensive Cancer Center
Gregory J. Riely, MD, PhD †
Memorial Sloan-Kettering Cancer Center
Eric Rohren, MD, PhD ф
The University of Texas MD Anderson Cancer Center
Theresa A. Shapiro, MD, PhD ¥
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Scott J. Swanson, MD ¶
Dana-Farber/Brigham and Women's Cancer Center
Kurt Tauer, MD
University of Tennessee Health Science Center
Stephen C. Yang, MD ¶
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

NCCN
Kristina Gregory, RN, MSN Miranda Hughes, PhD

† Medical oncology
¶ Surgery/Surgical oncology
§ Radiation oncology/Radiotherapy Pathology
‡ Hematology/Hematology oncology
ф Diagnostic/Interventional radiology
¥ Patient advocate
* Writing committee member

NCCN Guidelines Panel Disclosures

Continue

NCCN Guidelines Version 3.2014 Table of Contents
Non-Small Cell Lung Cancer

临床试验：NCCN认为任何肿瘤患者都可以在临床试验中得到最佳处理，因此特别鼓励肿瘤患者参加临床试验研究。

查找NCCN成员机构的在线临床研究可点击以下链接: nccn.org/clinical_trials/physician.html.

NCCN对证据和共识的分类：除非特别指出，NCCN对所有建议均达成2A类共识。

见 NCCN Categories of Evidence and Consensus

非小细胞肺癌指南 2014 年第 3 版与 2014 年第 2 版 相比，更新的内容包括:

MS-1 – 讨论部份进行更新以反应流程图的改变。

非小细胞肺癌指南2014年第2版与2014年第1版相比，主要更新内容包括:

NSCL-3
IB, IIA期, 切缘阴性: 对于高危患者，辅助化疗的推荐从2B类改为2A类.

非小细胞肺癌指南2014年第1版与2013年第2版相比，主要更新内容包括:

DIAG-2
>10 mm非实性或部份实性结节, LDCT检查后的选项更改: 肿瘤增大或实性成分增加。

NSCL-1
基线评估: “支持治疗” 改成 “整合姑息治疗.” 添加一个到NCCN姑息治疗指南的链接.

NSCL-2
IA期, 对于因医学原因不能手术治疗者的推荐更改：根治性RT包括SABR.
IB, I, II, IIB期, 因医学原因不能手术治疗者的推荐更改.
增加了淋巴结状态
N0 者推荐接受根治性RT包括SABR, 接着行辅助性化疗(2B类) 对于高危的IB-II期. N1 推荐接受根治性化放疗.
NSCL-3中加入高危的脚注: 高危因素的例子可能包括低分化肿瘤（包括肺神经内分泌肿瘤【除外高分化神经内分泌肿瘤】），血管受侵，楔形切除，肿瘤大于4cm，脏层胸膜受侵，和不完全的淋巴结采样(Nx). 这些独立因素可能不是适应症，但在决定辅助化疗的同时应该考虑。

NSCL-3
IIA, IIB期的辅助治疗推荐, 切缘阳性的修改。
R1 切除分列出来，而且其后的推荐：再切除+化疗或化放疗（序贯或同步）。
R2 切除分列出来，而且其后的推荐：再切除+化疗或同步化放疗.
对于IIIA 期辅助治疗推荐的更改.
R0 切除阐明为化疗*(1类)* 或序贯化疗 + RT *(只对于N2)*.
R1 切除分列出来，而且其后的推荐： 化放疗（序贯或同步）。
R2 切除分列出来，而且其后的推荐： 同步化放疗.
删除了以前的脚注 “j” : 有可能接受辅助化疗的患者应该用诱导化疗代替。
脚注“l” 更改: 高危~~病人~~因素的例子可能包括 ~~被定义为~~ 低分化肿瘤（包括肺神经内分泌肿瘤【除外高分化神经内分泌肿瘤】），血管受侵，楔形切除，肿瘤大于4cm，脏层胸膜受侵，和不完全的淋巴结采样(Nx). 这些独立因素可能不是适应症，但在决定辅助化疗的同时应该考虑。
以前的脚注 “p” 删除: 专家组推荐R2切除同步化放疗，R1切除序贯化放疗.这个信息现在已经写入流程图中 (NSCL-5, NSCL-6, NSCL-8, NSCL-9中也是一样的)

NSCL-5
肺上沟瘤 (T4 extension, N0-1): 临界可切除改变成可能可切除.
脚注“q” 的更改:如果在初始治疗中，放疗时没有给予足够剂量的同步化疗，应再给予~~1~~ 2个周期足够剂量的化疗。(NSCL-6, NSCL-12也是这样)

NCCN Guidelines Version 3.2014 Updates
Non-Small Cell Lung Cancer

非小细胞肺癌指南2014年第1版与2013年第2版相比，主要更新内容包括:

NSCL-6

胸壁,近端气道, 或纵隔: T4界定为 “可切除”

手术作为初始治疗, 切缘阳性:

R1 切除分列出来，而且其后的推荐：再切除+化疗或化放疗（序贯或同步）。

R2 切除分列出来，而且其后的推荐：再切除+化疗或同步化放疗.

NSCL-8

T1-3, N0-1: 不可切除更改为医学原因不可手术.

手术作为初始治疗, 切缘阳性:

R1 切除分列出来，而且其后的推荐：化放疗（序贯或同步）。

R2 切除分列出来，而且其后的推荐：同步化放疗.

脚注 “s”是这一页新增加的: 可能需要辅助化疗的患者也许应该采用诱导化疗作为一种替代方法.

NSCL-9

手术作为初始治疗, 切缘阳性:

R1 切除分列出来，而且其后的推荐：化放疗（序贯或同步）。

R2 切除分列出来，而且其后的推荐：同步化放疗.

NSCL-10

脚注 “v”修改: 导致症状危险性低的病灶可能观察 *(如，生长缓慢的半实性的小结节)*。然而，当病灶变得有症状或变成导致症状的危险性高时*(如，既使很小时，半实性的结节加速生长或实性成份增加或FDG摄取增加)*, 应该考虑治疗。

NSCL-13

T1-2, N0-1; T3, N0: 针对肺部病灶的SABR增加做为一种化疗后的治疗选择

NSCL-14

病史和体格检查以及胸部CT推荐做为随访手段，从2B类改变成2A类证据。

NSCL-15

纵隔淋巴结复发：按先前RT推荐治疗选择，如果患者先前接受过RT，增加了系统化疗这个推荐。

NSCL-16

对合适的组织进行分子检测确定组织学亚型:增加了“如果合适考虑活检” 。

“整合到姑息治疗” 增加了脚注 “b”. 增加了一个到NCCN姑息治疗的链接。

腺癌，大细胞，NSCLC非特指型; 增加了以下部份:

ALK检测增加了1类证据.

EGFR ± ALK检测应该作为多通道/下一代测序的一部份。

鳞状细胞癌;进行了以下修改/增加：

EGFR变异和ALK检测除不吸烟患者和小活检标本外不常规推荐检测，修改为考虑EGFR变异和ALK检测除不吸烟患者或小活检标本或混合组织类型。

EGFR ± ALK检测应该作为多通道/下一代测序的一部份。

脚注 “cc” 直接增加为一个新的页面, 其他遗传学改变患者的靶向药物(NSCL-H)。

EGFR 变异和ALK 阴性:增加了 “或未明”。

非小细胞肺癌指南2014年第1版与2013年第2版相比，主要更新内容包括:

NSCL-16

脚注 "dd" 修改:鳞状细胞癌患者，研究表明EGFR变异发生率2.7%，结合置信区间，其真实突变率小于3.6% ~~在鳞状细胞癌患者中~~. 这个EGFR变异的概率不支持对所有肿瘤标本进行常规检测.

Forbes SA, Bharma G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.

脚注 "ff"修改: *考虑 ROS1检测, 如果阳性* ~~如果ROS1变异状态未明和阳性~~,可以选用克唑替尼。http:// www.nccn.org/disclosures/panel_list.asp?ID=40 Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 2012;30:863-870. (NSCL-18也做了这样的修改)

NSCL-17

一线治疗, 一线化疗前检测EGFR变异情况:阿法替尼增加作为一类证据推荐。

一线治疗，一线化疗期间检测EGFR变异情况:推荐治疗选项修改成 "中断或完成计划的化疗，开始厄罗替尼或阿法替尼或可能在当前的化疗中加入厄罗替尼或阿法替尼 *(2B类证据)*"

二线治疗: 增加了阿法替尼治疗选项.

二线治疗, 有脑的症状: 脚注 "ll" 增加: 对脑膜转移癌考虑脉冲剂量的厄罗替尼.

二线治疗,全身多发病灶: 考虑系统治疗修改成考虑含铂双药± *贝伐单抗*±厄罗替尼.

增加脚注"mm": 阿法替尼对于EGFR治疗进展后的患者显然有些疗效。Miller VA, Hirsh V, Cadrenal J,et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;13:528-38.

NSCL-18

ALK阳性治疗推荐修改到与EGFR变异阳性一致.

NSCL-19

一线治疗: 顺铂/培美曲赛联合方案从本页删除，这是因为它已经包括在两药化疗方案里了。

维持治疗:

- 删除了继续当前方案直至疾病进展的选项。
- 用吉西他滨继续维持从2A类推荐更改为2B类推荐。
- 用培美曲赛或厄罗替尼转换维持，从2A类推荐更改为2B类推荐。

增加脚注 "nn" : 考虑其它变异检测，如果只有检测过EGFR和ALK. 参加其他遗传学改变患者的靶向药物 (NSCL-H).

删除以前的脚注"ii": 对于非鳞癌患者有证据表明培美曲赛/顺铂与吉西他滨/顺铂方案比较疗效更好而且毒性减轻。Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage NSCLC.J Clin Oncol 2008;26:3543-3551.

删除以前的脚注"jj": Pirker R, Periera JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small- cell lung cancer (FLEX): an open label randomised phase III trial. Lancet 2009;373:1525-1531. (NSCL-20也做相同的改变)

删除以前的脚注"ll": Pérol M, Chouaid C, Pérol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non- small-cell lung cancer. J Clin Oncol 2012;30:3516-3524. (NSCL-20也做相同的改变)

二线治疗:

- 界定状态增加了 "如果不是已经用过"。
- 增加了吉西他滨选项。

NCCN Guidelines Version 3.2014 Updates
Non-Small Cell Lung Cancer

非小细胞肺癌指南2014年第1版与2013年第2版相比，主要更新内容包括:

NSCL-20

维持治疗:

删除了“继续当前方案直到疾病进展”这个选项.
继续用吉西他滨维持从2A类推荐更改为2B类推荐.
用多西他赛或厄罗替尼转换维持从2A类推荐更改为2B类推荐.

二线治疗

界定状态增加了 “如果不是已经用过”
增加了吉西他滨选项。

NSCL-21

三线治疗: 增加了吉西他滨选项。

本页增加了脚注“ss”: 如果在一线和二线治疗中没有接受过厄罗替尼或克唑替尼，培美曲赛，多西他赛和吉西他滨是2B类.

NSCL-A (1 of 4)

删除了先前的第5项:虽然福尔马林固定，石蜡包埋肿瘤可以应用于大多数分子分析，为先进的分子研究应该考虑获取新鲜的冷冻标本 。

当前的第5项修改: 强烈推荐限制IHC研究在小组织标本中的应用, 从而为分子研究保存关键的肿瘤组织，特别是病变处于晚期的病人。一个鳞癌标志（如P63）和一个腺癌标志（如TTF-1）的有限组合对于解决多数诊断问题应该是充足的了。

NSCL-A (3 of 4)

EGFR 和KRAS, 对子项目2和7的修改:

21外显子中加入L861而 18外显子中加入G719

对TKI治疗原发耐药与KRAS变异相关 。获得性耐药与EGFR激酶结构域（如T790M）内的第二个位点变异、alternative kinases 扩增(如MET)、从非小细胞肺癌组织学转化成小细胞肺癌以及上皮间质化(EMT)等因素相关.

ALK, 对于子项目 2 和 3 的修改:

ALK NSCLC 最常发生在一类独特的NSCLC患者中，这些患者包含多个NSCLC患者的临床特征，可能也包括了EGFR变异。然而，通常ALK转位与EGFR变异是互相排斥的。~~ALK转位倾向于发生在年轻病人和较晚期的NSCLC中，然而这个相关性在EGFR变异的NSCLC中没有报导.~~
当前检测ALK NSCLC的标准方法是荧光原位杂交 (FISH), 而其他方法目前仍在研究阶段。包括聚合酶链反应(PCR) 和IHC。IFSH的一个很大的优势在于存在商业化的探针，用于ALK重排的间变大细胞淋巴瘤(ALCL)诊断方面的进展，也能应用于ALK重排的肺腺癌的诊断。全世界范围内临床实验室广泛应用的IHC检测诊断ALK重排的ALCL，不适合用于检测多数ALK重排的肺腺癌癌。其原因在于与ALK重排的ALCL相比ALK重排的NSCLC的ALK表达水平 较低。近期FDA进行的分子诊断学检测证实，应用FISH法可确定哪些肺腺癌病人是ALK阳性肺癌患者。

NCCN Guidelines Version 3.2014 Updates
Non-Small Cell Lung Cancer

非小细胞肺癌指南2014年第1版与2013年第2版相比，主要更新内容包括:

NSCL-B (1 of 4)

评估

删除以前的第6项: 当前戒烟的嗜烟患者，考虑手术前等待4周，以达到手术疗效最大化。

切除

修改第5项: 对于没有解剖学和外科学方面禁忌症的病人，如果没有触犯肿瘤学标准和胸外科切除原则，强烈推荐VATS *或微创手术~~是一种合理的和可接受的方式~~*。

NSCL-C (1 of 9)

早期 NSCLC (I期)

对第2项的修改是删除了以下句子: 一个亚肺叶切除术与SABR比较的前瞻性协作组研究正在进行中。

NSCL-C (3 of 9)

局部晚期/常规分割放疗

对第2 项的修改: RTOG 0617的最终结果,60Gy与74Gy放疗同步化疗比较仍未定论，但有初步结果，74 Gy~~与1年总生存的提高无相关~~ *并不提高总生存. 一个meta分析证实了超分割放疗方案能提高生存, 而一个随机研究(RTOG 1106)正在评估超分割放疗的个体化增加剂量.*

NSCL-E

化疗后同步化疗/RT: 每周紫杉醇/卡铂方案从2B类推荐修改成2A类推荐。

删除了以前的脚注 "*": 有数据支持足够剂量的顺铂优于卡铂为基础的方案。卡铂方案没有经过足够的检验。

NSCL-F (1 of 3)

一线治疗

第3 项修改: 厄罗替尼推荐作为EGFR敏感突变患者的一线治疗，不能用于EGFR突变阴性或EGFR状态未明患者的一线治疗。

第 4项增加了: Afatinib对于EGFR敏感突变的特定患者是有指征。

NSCL-F (2 of 3)

维持治疗:在吉西他滨继续维持治疗和厄罗替尼或培美曲赛转换维持治疗中加入2B类证据.

二线治疗:在第4亚项目中增加：阿法替尼在EGFR敏感突变的选择性病人中有适应症。

三线治疗: 用"如果没用过，PS0-2分的患者的选项包括多西他赛，培美曲赛（非鳞癌），厄罗替尼，或吉西他滨（所有选项都是2B证据）"代替原有的"厄罗替尼优于最佳支持治疗"。

NSCL-F (3 of 3)

阿法替尼加入系统性治疗及引文。

NSCL-G

删除了宫颈癌NCCN指南的链接。

NSCL-H

在新增加的页面中列举了遗传学改变患者的靶向治疗药物.

肺癌的预防与筛查

肺癌是一种独特的疾病，主要的致病因素是工业产生的成瘾性产物。大约 85%- 90%的肺癌是由于主动吸烟或被动吸 “二手” 烟所致。如果要降低肺癌的死亡率，就需要采取有效的公共卫生措施以避免吸烟的开始，美国食管和药品管理局(FDA)监管烟草的生产以及其他烟草监管措施。
长期吸烟容易导致第二原发癌、 治疗并发症、 药物相互作用、 其它吸烟相关疾病、 生活质量降低和生存期缩短。
根据美国医事总署 （Surgeon General） 的报告， 主动吸烟 (http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/executivesummary.pdf) 和被动吸烟都可以导致肺癌。 有证据表明， 和吸烟者生活在一起从而吸二手烟的人群罹患肺癌的风险上升20%~30% (http://surgeongeneral.gov/library/reports/smokeexposure/fullreport.pdf)。 每个公民都应被告知吸烟和曝露于烟雾环境可对健康产生危害、 导致成瘾并可威胁生命，政府需要采取恰当的、 有效的措施如立法、 行政、 管理或其他手段以保护所有的公民免于烟草的危害 (www.who.int/tobacco/framework/final_text/en/).
肺的致癌物中还含有高度成瘾性物质尼古丁， 这使问题进一步复杂化。 为了降低肺癌死亡率， 需要深入贯彻卫生保健研究和质量机构 （AHRQ）指南 (www.ahrq.gov/path/tobacco.htm#Clinic) ， 以发现、 劝告和治疗尼古丁成瘾患者。
吸烟者或有吸烟史的人发生肺癌的风险明显增高。 对于这些人， 尚无可用的化学预防药物。 如有可能， 应该鼓励这些人参加化学预防研究。
推荐对选择性的高危嗜烟者和有嗜烟者应用低剂量CT (LDCT) 进行肺癌筛查 (见 NCCN Guidelines for Lung Cancer Screening).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

临床表面

可疑肺癌结节 → 多学科评估[a]
戒烟辅导 →

危险评估[b]

病人因素
- 年龄
- 嗜烟史
- 既往肿瘤病史
- 家族史
- 职业暴露
- 其他肺部疾病 (慢性阻塞性肺部疾病 [COPD], 肺纤维化)
- 病原体暴露 (如, 霉菌、结核病疫区) 或感症状病史或高危因素(如, 免疫抑制, 误吸,传染性呼吸道症状)

影像学因素[c]
- 大小,形状,以及肺部结节的密度
- 相关的肺实质异常(如, 疤痕或可疑炎症改变)
- PET影像中的氟脱氧葡萄糖 (FDG)活性

→ 见临床表现和随访(DIAG-2)

[a]多学科评估包括胸外科医生，胸部放射学家，和肺科医生共同决定癌症诊断的可能性以及最佳诊断或随访策略。
[b]Risk 危险评估可以用于对患者个体和放射学因素进行量化，但不能代替在肺癌诊断有丰富经验的多学科诊断团队。
[c]见诊断评估原则 (DIAG-A 1 of 2).

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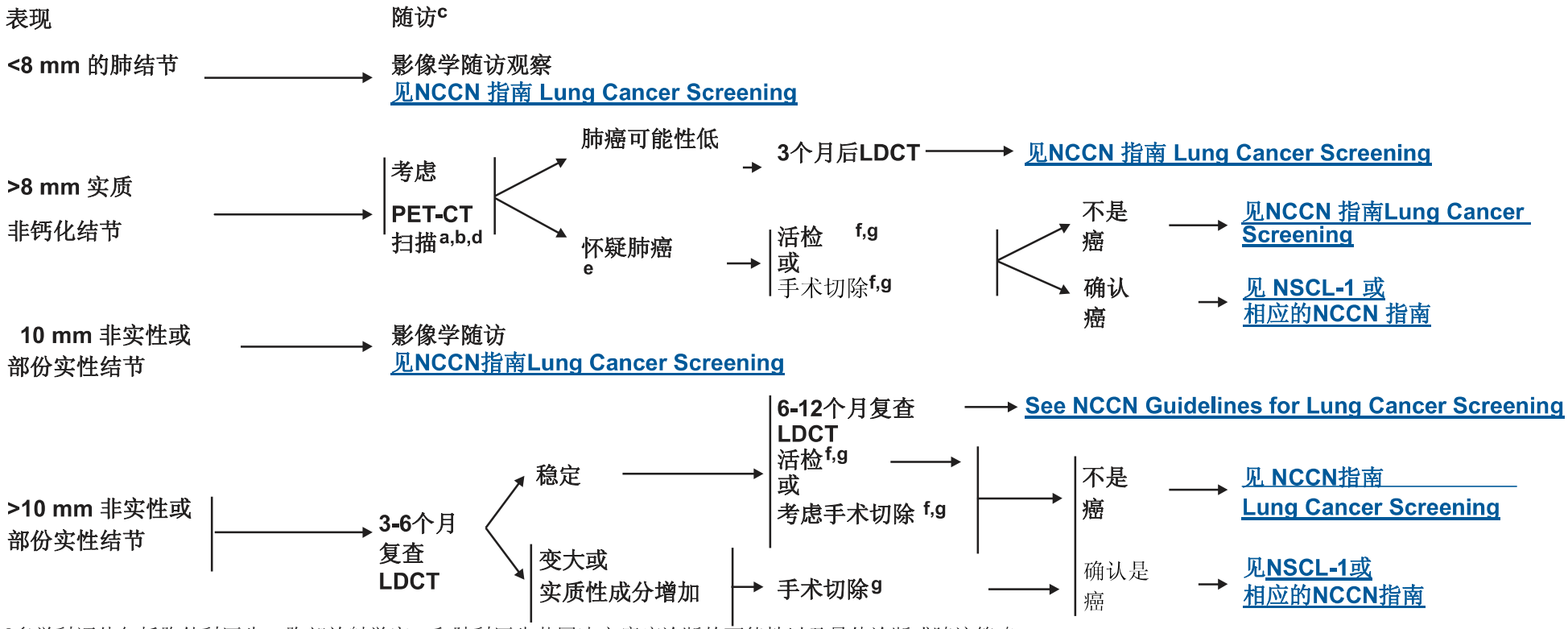

[a]多学科评估包括胸外科医生，胸部放射学家，和肺科医生共同决定癌症诊断的可能性以及最佳诊断或随访策略。
[b]Risk 危险评估可以用于对患者个体和放射学因素进行量化，但不能代替在肺癌诊断有丰富经验的多学科诊断团队。
[c]见诊断评估原则 (DIAG-A 1 of 2).
[d]PET阳性结果定义为肺部结节的标准摄值(SUV) 大于纵隔血池基线。阳性PET扫描结果可以是感染或炎症所致，包括无肺癌的局部感染和肺癌合并相关的（如阻塞性）感染,以及与肺癌相关的炎症（淋巴结、肺实质、胸膜）。PET扫描假阴性可以是小结节、低细胞密度（非实质性结节或毛玻璃样征[GGO]）、或肿瘤的FDG亲合力低 (如, 原位腺癌 [以前称为支气管肺泡腺癌], 类癌).
[e]经PET-CT检查后怀疑肺癌的患者在任何非手术治疗前均要求有组织学证实.
[f]应该在临床怀疑肺癌, 病灶定位 (术中识别和电视辅助胸腔镜[VATS]微创手术是可行的), 和患者偏好这三个前提下选择活检或手术切除。
[g]临床高度怀疑I期或II期肺癌的病人（按危险因素和影像学表现）手术前不需要活检.

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诊断评估原则

临床高度怀疑I期或II期肺癌的病人（按危险因素和影像学表现）手术前不需要活检.
- 活检费时间、增加费用和程序危险，可能对治疗决策没有影响。
- 如果不是强烈怀疑肺癌可以在手术前用FNA活检诊断可能性合适的.
- 如果术中诊断明显很困难或很危险，进行术前活检应该是合适的。
- 如果在术前无有获得组织诊断，在肺叶切除、双肺叶切除或全肺切前行术中诊断(如,楔形切除或针吸活检)是必需的。
- 支气管镜检查应该是外科手术计划中的，而不是一个单独的操作。
- 支气管镜检查应该在外科手术前进行 (见 NSCL-2).
- 手术前单独的支气管镜检查费时间、增加费用和程序危险，对治疗决策来说是不需要的。
- 如果是中央型肺癌需要对活检、手术计划（如，潜在袖状切除）或术前气道准备（如，取出阻塞的病灶）进行手术前评估，术前气管镜检查可能是合适的。

对于多数临床I 或 II期肺癌, 推荐手术前行侵入性纵隔分期 (见 NSCL-2).
- 患者应该在计划性手术前的起始步骤就进行侵入性纵隔分期（在同一麻醉程序中），而不是作为一个单独的操作。
- 单独的分期操作增加了时间、费用、护理协调、困难，并且增加了麻醉风险。
- 对于临床分期中高度怀疑淋巴结为N2或N3或无法获得术中细胞学或冰冻切片时，需要行术前侵入性纵隔分期。

对于怀疑NSCLC的患者，多种技术可以获得组织诊断。
- 常规获得的诊断工具包括:
  - 痰细胞学
  - 支气管镜检查并活检和经气管针吸活检(TBNA)
  - 影像引导下经胸壁针吸活检(TTNA)
  - 胸腔穿刺术
  - 纵隔镜
  - 电视辅助胸腔镜手术 (VATS) 和开放手术活检
- 诊断工具提供了重要的活检补充策略包括:
  - 气管腔内超声 (EBUS)–引导活检
  - 导航气管镜

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诊断评估原则

对于患者个体最佳诊断策略依肿瘤大小及位置， 病灶位于肺或纵隔，病人特征（如肺的病理改变和/或其他重要并发症），以及本地经验和专家意见而定。

选择最优诊断步骤应考虑的因素包括:

- 预期的诊断效率 (敏感性)
- 诊断的准确率，包括特异性和阴性诊断研究的可信度显著性（如真阴性率）
- 组织标本的大小足够用于诊断和分子检测
- 操作的侵入性和风险
- 评估的效率
  - 操作的路径和时序
  - 同步分期是有益的,因为它可以避免额外的活检或操作，一般更倾向于活检可以得到更高分期的病理组织 (如, 活检可疑的转移灶或纵隔淋巴结，而不是活检肺部病灶)。
- 有用的技术和专家意见

对于可疑I至 III期肺癌的最佳诊断步骤应该由绝大多数工作都放在胸部肿瘤的胸部放射学家、介入放射学家和专业认证的胸外科医生来做决定。

纳入有先进支气管镜诊断技术经验的肺科医生和依靠当地专家，也可能会使多学科评价获益.

最小创伤而效率最高的活检应该优先作为首选的诊断确究。

- 中央型肿块和可疑气管内受侵的患者应该 行气管镜检查。
- 外周型(外1/3) 结节的患者应该行导航气管镜, 放射腔内超声（EBUS）, 或影像引导下经胸壁针吸活检（TTNA）。
- 可疑淋巴结病变的病人应该通过EBUS、导航气管镜或纵隔镜活检。
  - 如果临床上怀疑5、7、8、9区淋巴结转移，食管超声 (EUS)–引导提供了另一种活检途径。
  - 如果临床上怀疑前纵隔淋巴结转移，TTNA 和前纵隔切开术 (如, Chamberlain术式) 提供了另一种进入前纵隔(5 区和6区)的途径。
- 肺癌相关的胸腔积液患者应该行胸腔穿刺术和细胞学检查。初次细胞学结果阴性不能排除胸膜受侵。在根治性治疗前应该考虑再行胸腔穿刺和/或胸腔镜评估胸膜情况.
- 对于可疑有孤立转移灶的患者，如果可能的话最好对这个部位进行组织确认.
- 对于可疑有转移灶的患者，如果可能的话最好对这些部位的其中一个部位进行组织学确认。
- 如果临床高度怀疑有多个转移灶，而对这些转移灶的活检在技术上有困难或非常危险，就应该行原发肺部病灶或纵隔淋巴结活检。

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NSCLC的病理诊断

非小细胞肺癌 (NSCLC)

初始评估

病理学回顾[a]
病史与体检 (包括行为能力状态 + 体重下降)
胸部和上腹部CT, 包括肾上腺，全血细胞计数, 血小板，生化,
戒烟建议, 咨询, 和药物疗法
应用5A模式:
问Ask, 建议Advise, 评估Assess, 帮助Assist, 处理Arrange
http://www.ahrq.gov/clinic/tobacco/5steps.htm
综合姑息疗法[b] (见 NCCN 指南 Palliative Care)

临床分期

IA期, 周围型[c] (T1ab, N0) 纵隔CT 阴性 (淋巴结 <1 cm)	见治疗前评价 (NSCL-2)
I期, 周围型[c] (T2a, N0); 中央型[c] (T1ab-T2a, N0); II 期 (T1ab-T2ab, N1; T2b, N0); IIB 期(T3, N0)[d] 纵隔CT 阴性 (淋巴结<1 cm)	见治疗前评价 (NSCL-2)
IIB期[e] (T3, N0); IIIA期[e] (T4, N0-1; T3, N1)	见治疗前评价 (NSCL-4)
IIIA期[e] (T1-3, N2)	见治疗前评价 (NSCL-7)
单个的肺结节(s) (IIB, IIIA, IV期)	见治疗前评价 (NSCL-7)
多发肺癌	见治疗前评价 (NSCL-9)
IIIB期[e] (T1-3, N3) 纵隔 CT 阳性 对侧 (淋巴结 1 cm) 或可触及的锁骨上淋巴结	见治疗前评价 (NSCL-11)
IIIB期[e] (T4, N2-3) on CT	见治疗前评价 (NSCL-12)
IV期 (M1a)[b] (胸腔积液或心包积液)	见治疗前评价 (NSCL-12)
IV 期(M1b)[b] 可切除的肺结节伴孤立的转移	见治疗前评价 (NSCL-13)
IV期 (M1b)[b] 播散性转移	见治疗前评价 (NSCL-16)

[a] 见病理回顾原则 (NSCL-A).
[b] Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small cell lung cancer. N Engl J Med 2010;363:733-742.
[c] 按胸部CT分: 周围型 =肺的外1/3. 中央型 =肺的内2/3.
[d] 因为大小或卫星结节分期的T3, N0。
[E] 对于 IIB 和III 期患者, 通常存在一种以上的治疗模式(手术, 放疗,或化疗), 应该行多学科综合评价.

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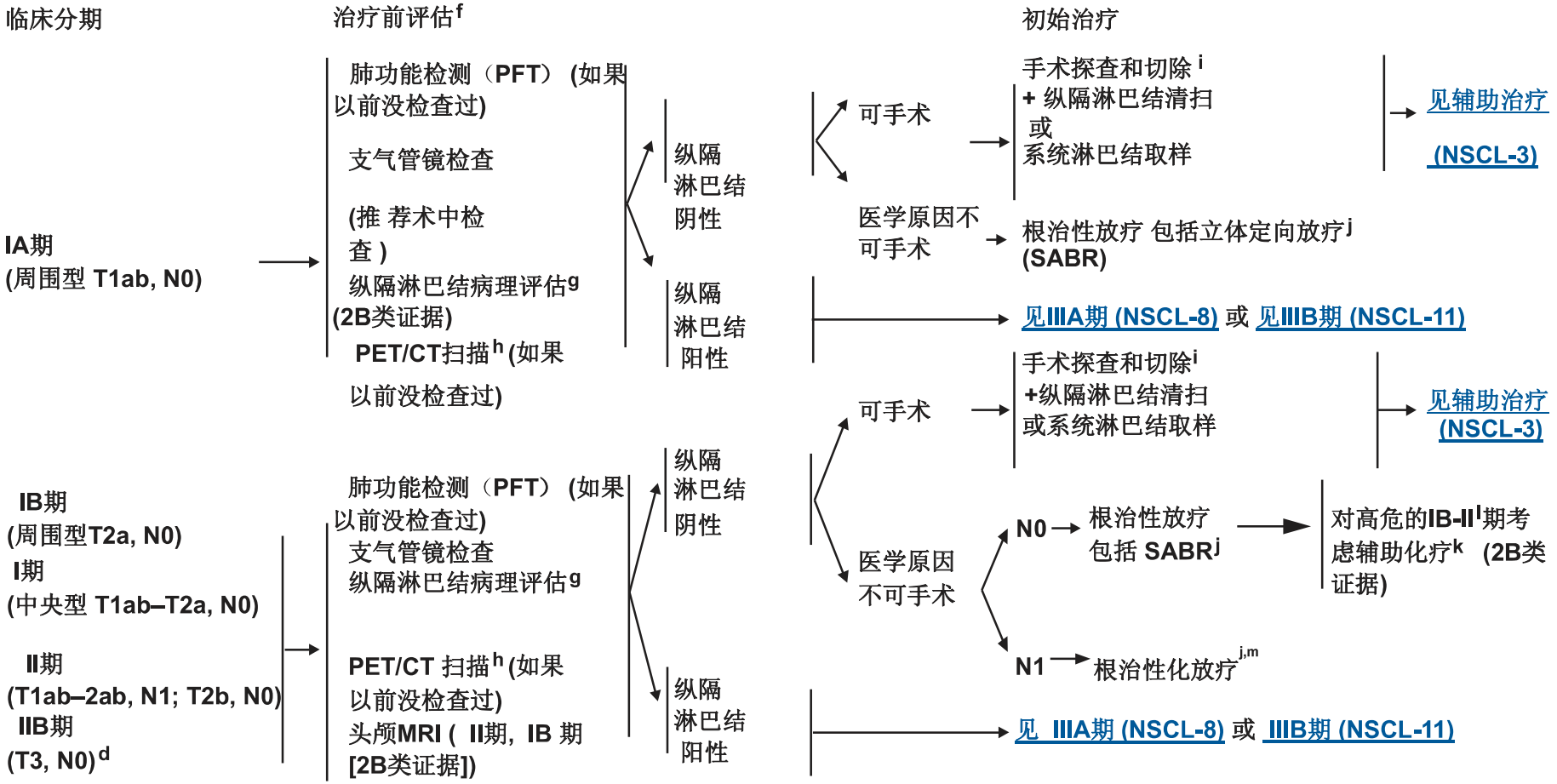

d 与大小或卫星结节相关的T3, N0 。
f 检查的列举不按优先程度排列，而是按临床情况，机构程序和审慎使用资源而定.
g 评估方法包括纵隔镜，纵隔切开术, EBUS, EUS, and CT引导下活检。
h 远处转移的PET/CT 扫描阳性表现需要病理学或其他影像学确认。如果PET/CT 扫描纵隔、淋巴结阳性需要病理学确认.
i 见外科治疗原则(NSCL-B).
j 见放射治疗原则(NSCL-C).
k 见新辅助及辅助治疗的化疗方案 (NSCL-D).
l 高危因素可能包括 低分化肿瘤(包括肺神经内分泌肿瘤 [除外高分化神经内分泌肿瘤]), 脉管受侵, 楔形切除, 肿瘤 >4 cm, 脏层胸膜受侵,和不完全的淋巴结取样(Nx)。这些独立因素可能不是适应症但在决定辅助化疗时应该考虑。
m 见与放疗联合应用的方案 (NSCL-E).

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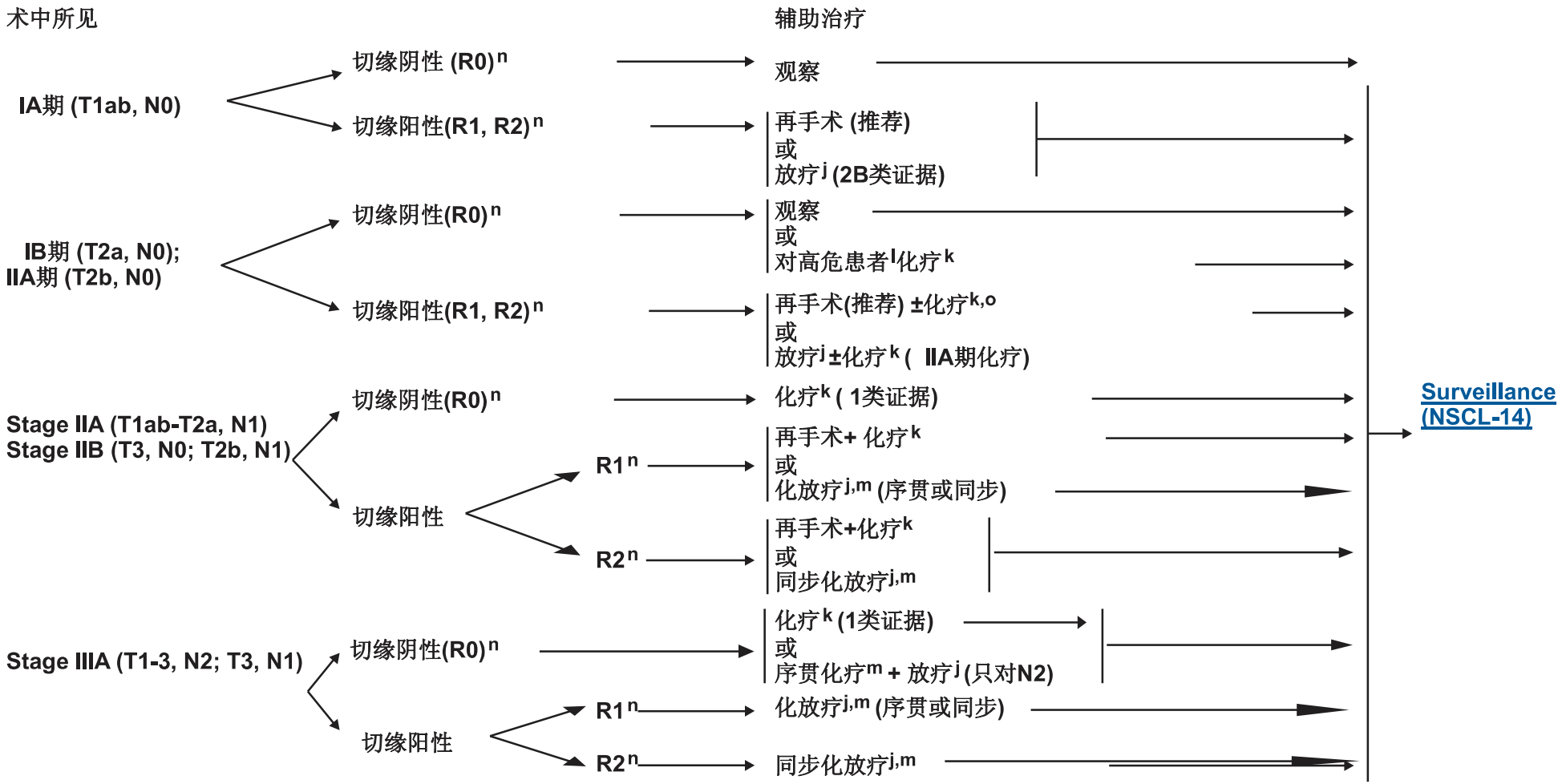

j 见放射治疗原则(NSCL-C).
k 见新辅助及辅助治疗的化疗方案(NSCL-D).
l 高危因素可能包括 低分化肿瘤(包括肺神经内分泌肿瘤 [除外高分化神经内分泌肿瘤]), 脉管受侵, 楔形切除, 肿瘤 >4 cm, 脏层胸膜受侵,和不完全的淋巴结取样(Nx)。这些独立因素可能不是适应症但在决定辅助化疗时应该考虑。

m 见与放射治疗联用的化疗方案(NSCL-E).
n R0 = 无残存肿瘤, R1 = 镜下残存肿瘤, R2 = 肉眼残存肿瘤

o 大肿瘤是考虑是否需要辅助化疗的重要因素

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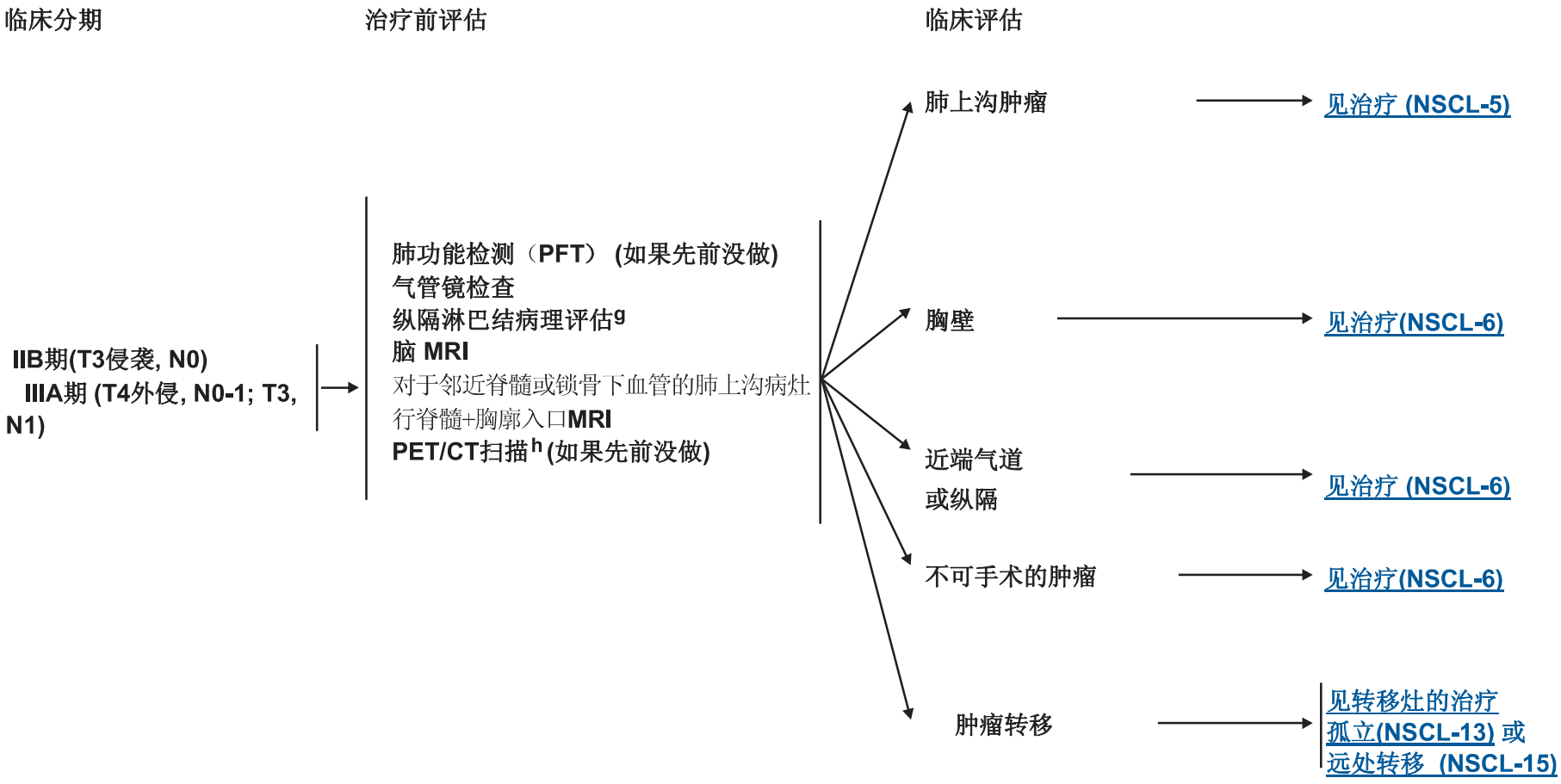

g评估方法包括纵隔镜，纵隔切开术, EBUS, EUS, and CT引导下活检.
h远处转移的PET/CT 扫描阳性表现需要病理学或其他影像学确认。如果 PET/CT 扫描纵隔、淋巴结阳性需要病理学确认.

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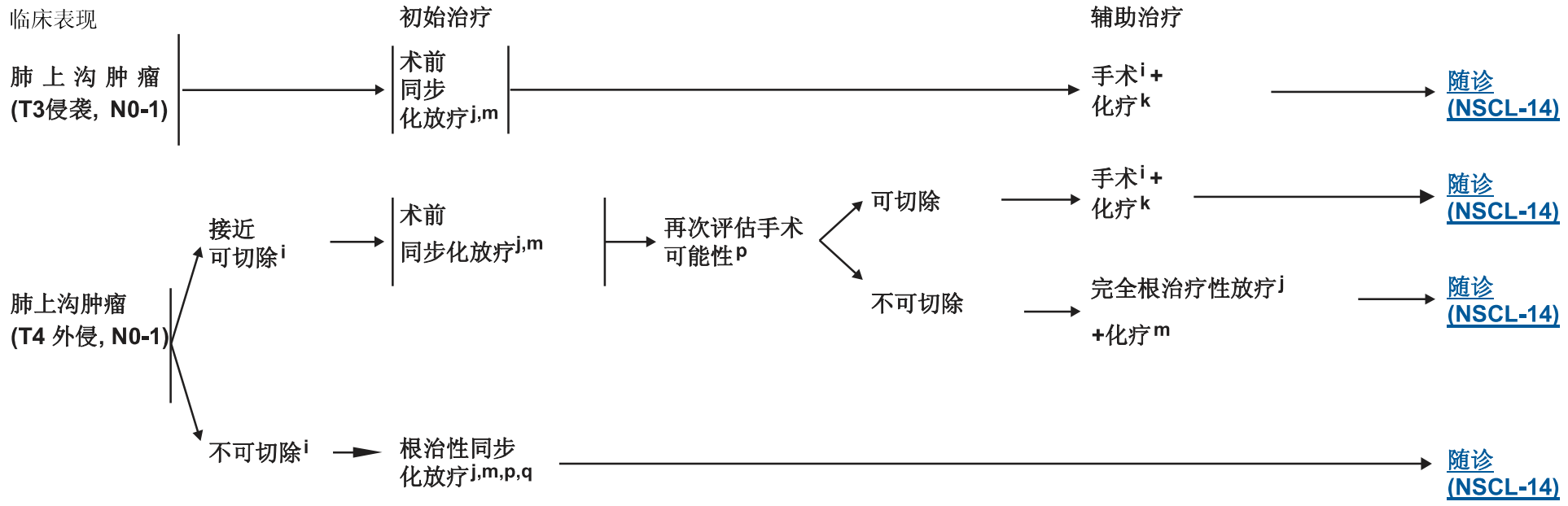

i 见手术治疗原则 (NSCL-B).
j 见放射治疗原则 (NSCL-C).
k 见新辅助和辅助治疗的化疗方案(NSCL-D).
m 见与放射治疗联用的化疗方案(NSCL-E).

p 如果病人不适合手术，放疗应该给到根治剂量，不能间断。
q如果在初始同步放化疗中的化疗没有给足剂量, 应该再给2个周期 的足量化疗.

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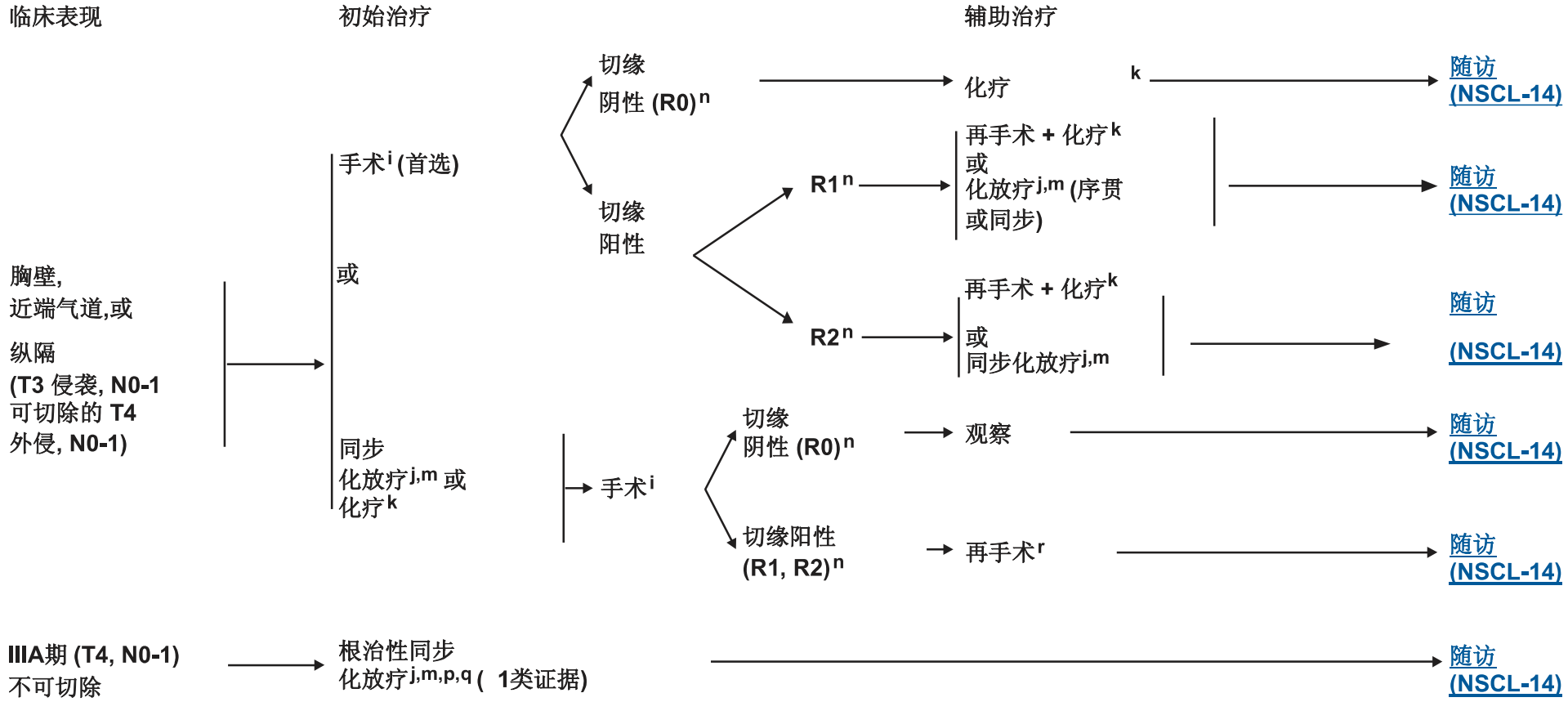


[i] 见手术治疗原则(NSCL-B).
[j] 见放射治疗原则(NSCL-C).
[k] 见新辅助和辅助治疗的化疗方案(NSCL-D).
[m] 见与放射治疗联用的化疗方案(NSCL-E).
[n] R0 = 无残存肿瘤, R1 = 镜下残存肿瘤, R2 = 肉眼残存肿瘤

[p] 如果病人不适合手术，放疗应该给到根治剂量，不能间断。
[q] 如果在初始同步放化疗中的化疗没有给足剂量, 应该再给2个周期 的足量化疗.
[r] 如果化放疗已经作为初始治疗，可以考虑放疗推量.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

临床分期 | 治疗前评估 | 纵隔活检结果和可切除性

IIIA期 (T1–3, N2) →

肺功能检测（PFT） (如果以前没检查过)
支气管镜检查
纵隔淋巴结病理评估[g]
PET/CT扫描[h] (如果以前没检查过)
脑 MRI

- N2, N3 淋巴结阴性 → 见治疗 T 1-3, N0-1 (NSCL-8)
- N2淋巴结阳性 → 见治疗(NSCL-8)
- N3淋巴结阳性 → 见 IIIB期 (NSCL-11)
- 转移病灶 → 见转移灶的治疗 孤立(NSCL-13) 或远处转移 (NSCL-15)

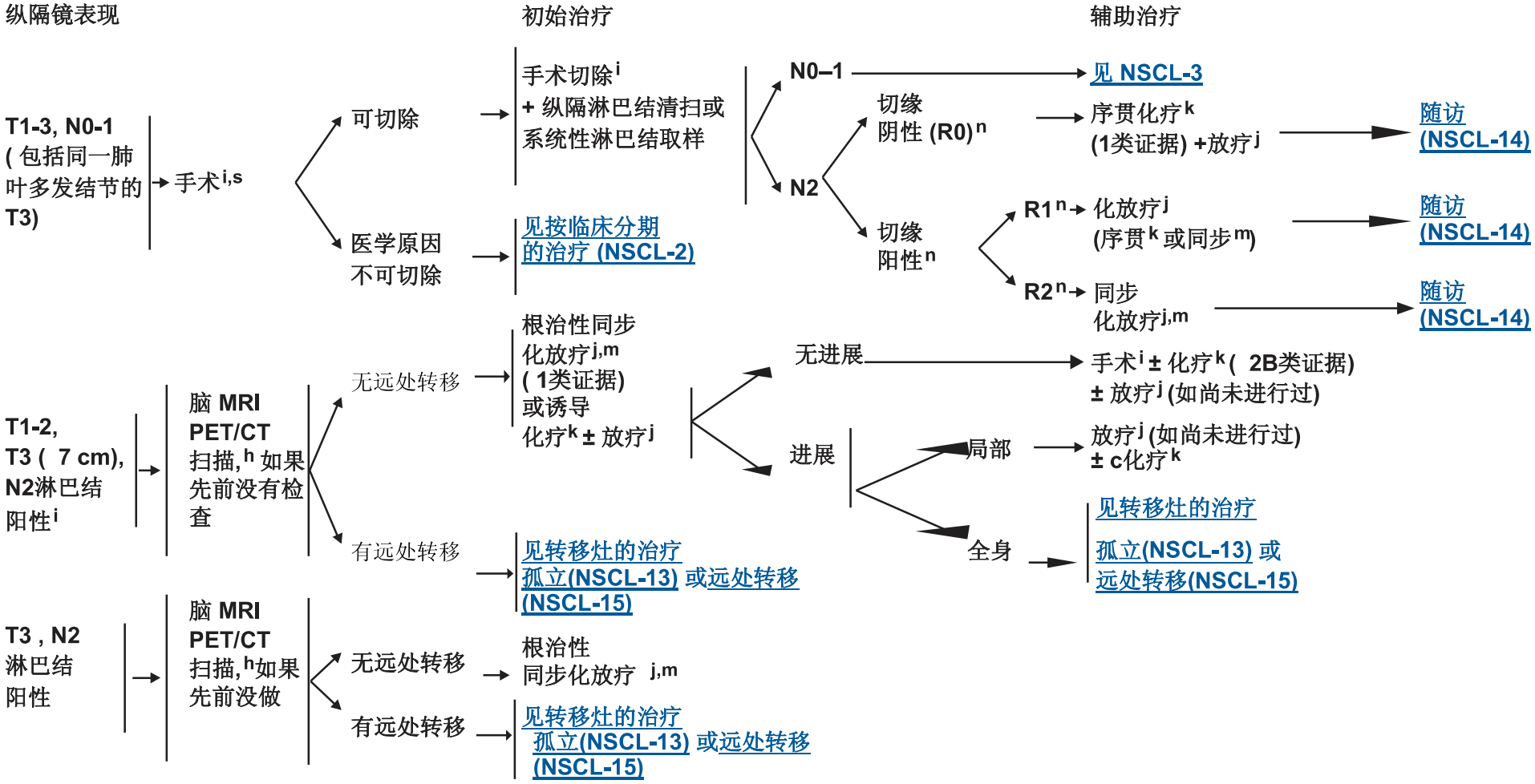
分散的肺结节 (IIB, IIIA, IV期) →

肺功能检测（PFT） (如果先前没做)
气管镜检查
纵隔淋巴结病理评估[g]
脑 MRI
PET/CT扫描[h] (如果先前没做)

- 分散的肺结节,同一肺叶 (T3, N0) 或同侧非原发肺叶 (T4, N0) → 见治疗 (NSCL-9)
- IV期 (N0, M1a): 对侧肺 (孤立结节) → 见治疗 (NSCL-9)
- 胸外转移灶 → 见转移灶的治疗 孤立(NSCL-13) 或 远处转移 (NSCL-15)

[g]评估方法包括纵隔镜，纵隔切开术, EBUS, EUS,和 CT引导下活检.
[h]远处转移的PET/CT 扫描阳性表现需要病理学或其他影像学确认。如果 PET/CT 扫描纵隔、淋巴结阳性需要病理学确认.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[h]远处转移的PET/CT 扫描阳性表现需要病理学或其他影像学确认。如果 PET/CT 扫描纵隔、淋巴结阳性需要病理学确认.
[i]见外科治疗原则(NSCL-B).
[j]见放射治疗原则(NSCL-C).
[k]见新辅助及辅助治疗的化疗方案(NSCL-D).
[m]见与放疗联合应用的方案(NSCL-E).
[n]R0 = 无残存肿瘤, R1 = 镜下残存肿瘤, R2 = 肉眼残存肿瘤
[s]可能接受辅助化疗的患者可以用诱导化疗代替.

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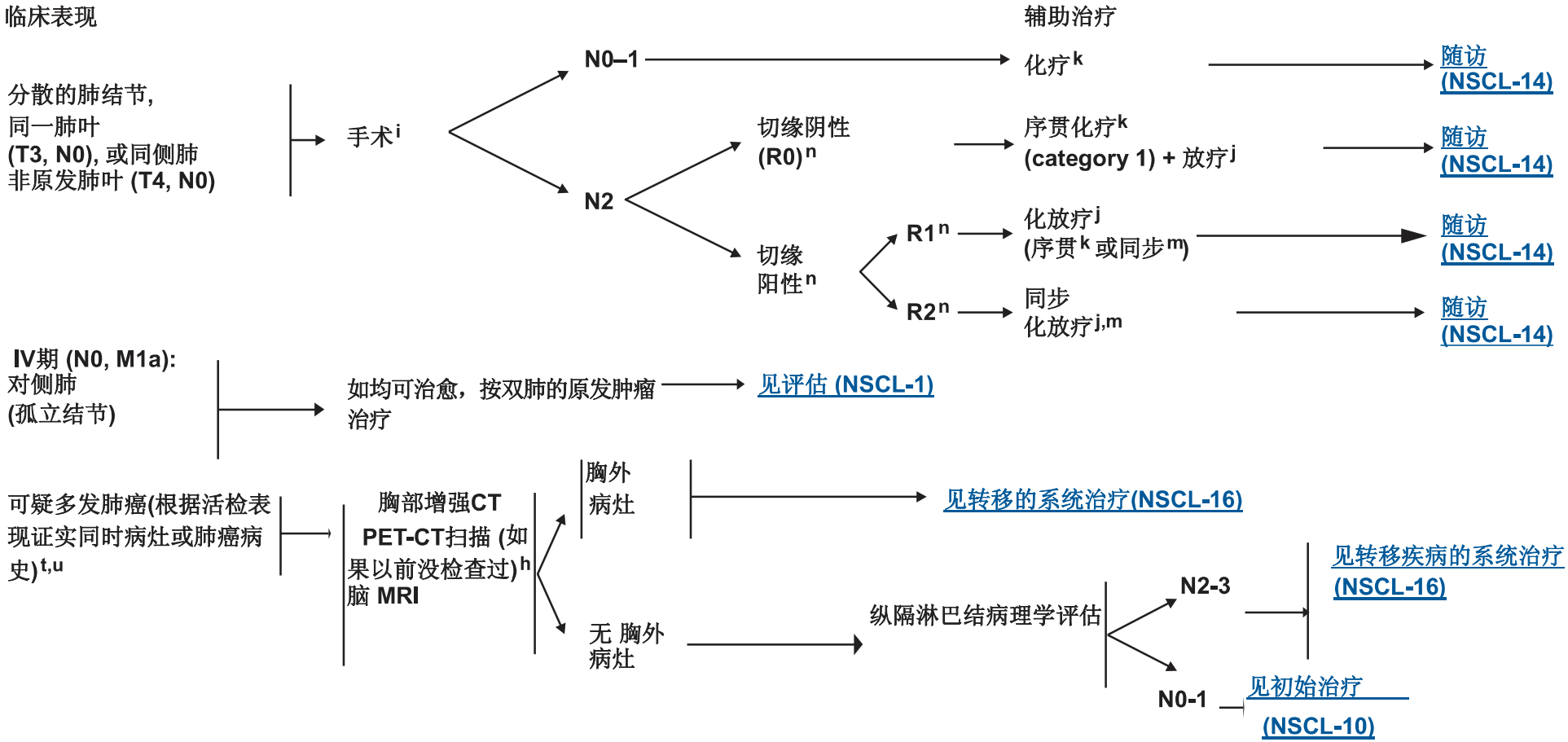

[g]评估方法包括纵隔镜，纵隔切开术, EBUS, EUS, and CT引导下活检。
[h]远处转移的PET/CT 扫描阳性表现需要病理学或其他影像学确认。如果 PET/CT 扫描纵隔、淋巴结阳性需要病理学确认.
[i]见外科治疗原则(NSCL-B).
[j]见放射治疗原则(NSCL-C).
[k]见新辅助及辅助治疗的化疗方案(NSCL-D).
[m]见与放疗联合应用的方案(NSCL-E).

[n]R0 = 无残存肿瘤, R1 = 镜下残存肿瘤, R2 = 肉眼残存肿瘤
[t]不同细胞型的病灶 (如,鳞状细胞癌，腺癌) 可能是不同原发肿瘤，这个分析对于小活检标本可能是局限的.但是同一细胞类型的病灶并不必然是转移灶.
[u]关于半实性肺结节的评价、工作和管理指南，见可疑肺结节的诊断评价(DIAG-1).

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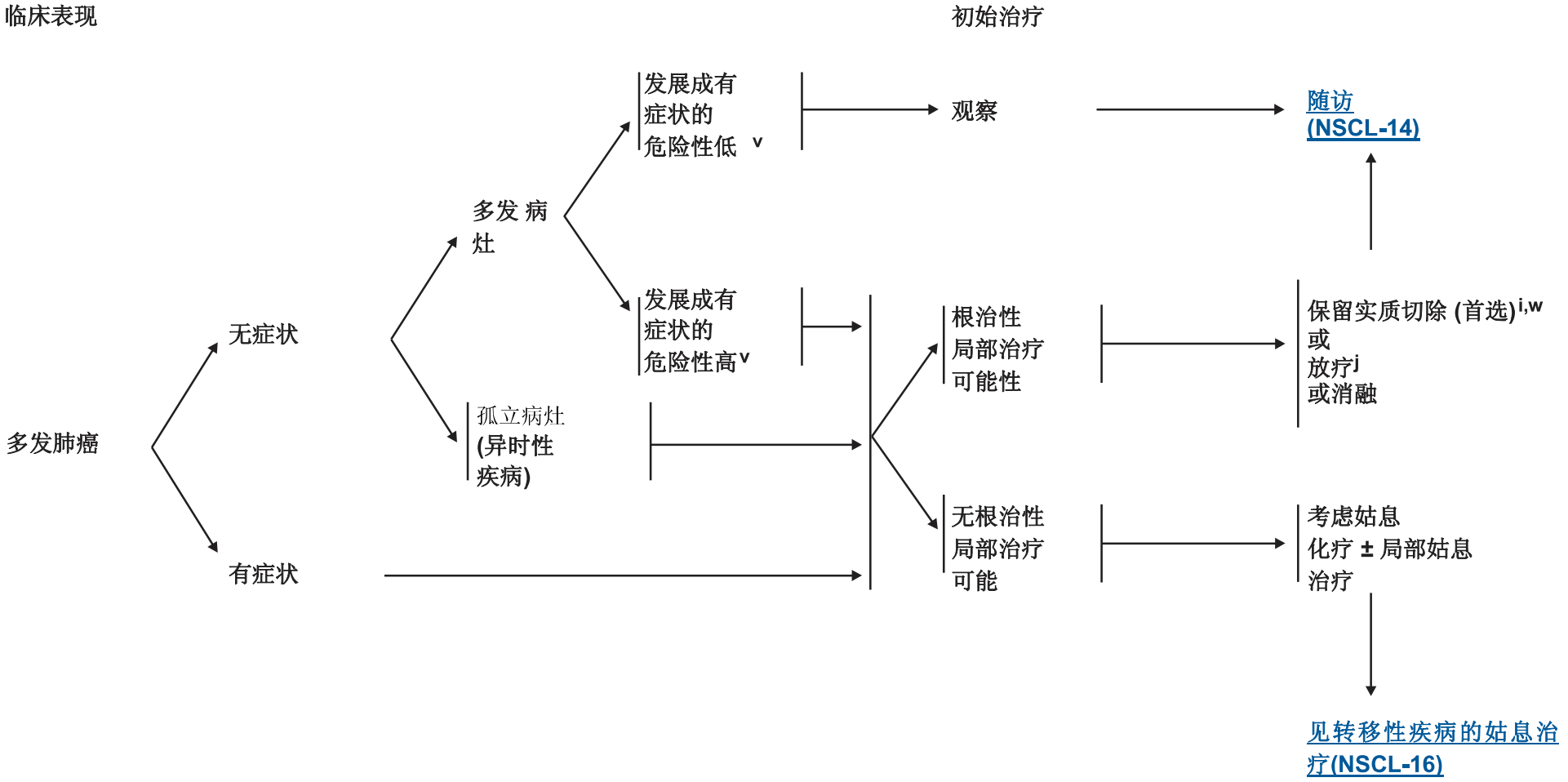
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[i] 见外科治疗原则(NSCL-B).
[j] 见放射治疗原则(NSCL-C).
[v] 有症状危险性低的病灶可以观察 (如，小而生长慢的半实性结节)。但是如果病灶发展到有症状或出现症状的风险变高 (如,半实性结节，就算是很小，但加速生长或实性成分增加或FDG的摄取增加), 就应该考虑治疗.
[w] 应该行保留肺的手术, 但是肿瘤的分布和机构专家应该影响个体化疗治疗计划.

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

临床分期 | 治疗前评估 | 初始治疗

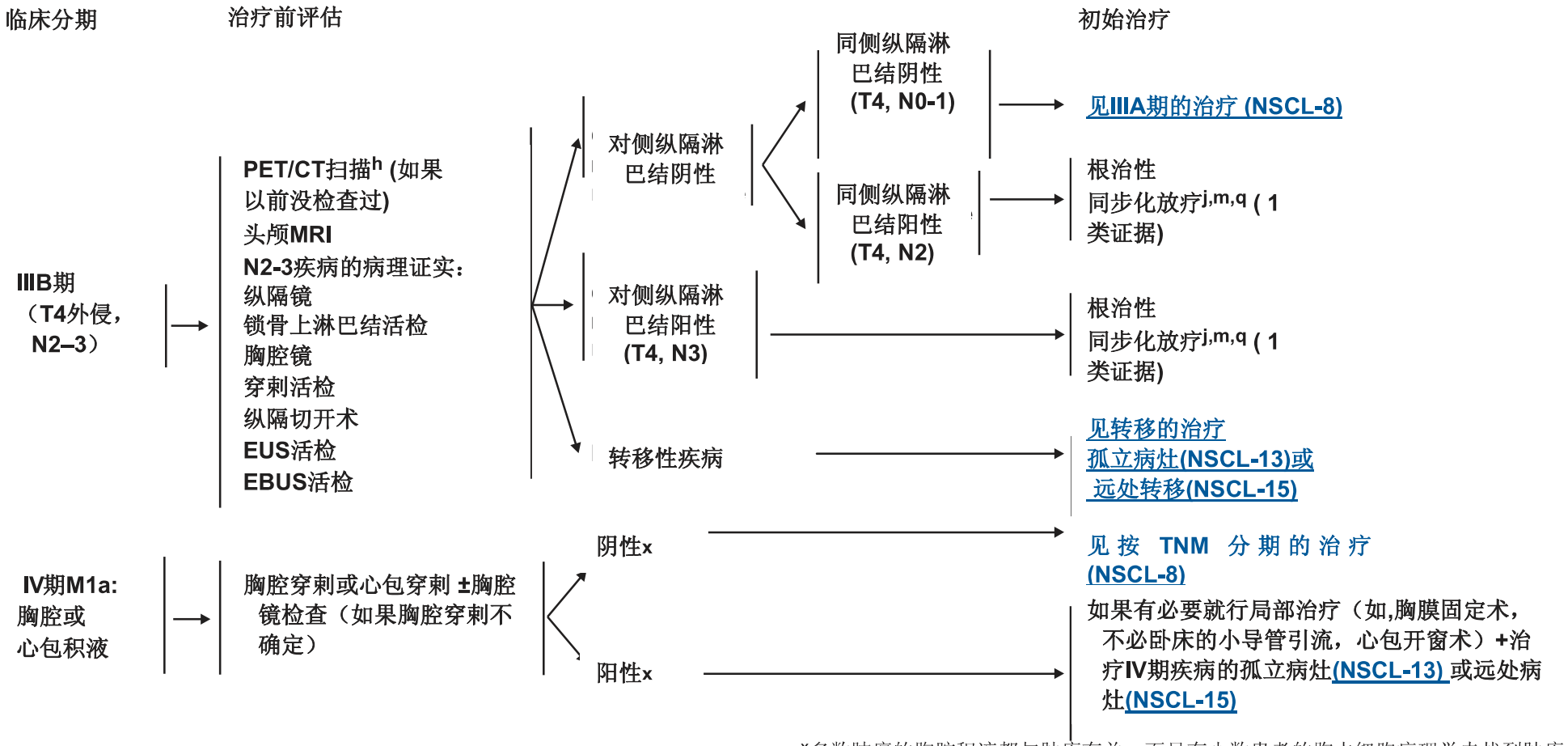
IIIB期(T1–3, N3) →

肺功能检测（PFT）
(如果
以前没检查过)
头颅MRI
N3疾病的病理证实：
纵隔镜
锁骨上淋巴结活检
胸腔镜
穿刺活检
纵隔切开术
EUS活检
EBUS活检

- N3阴性 → 见I–IIIA期的初始治疗 (NSCL-8)
- N3阳性 → 根治性同步化放疗(1类证据) [j,m,q]
- 转移性疾病 → 见转移的治疗
  孤立病灶(NSCL-13)或
  远处转移(NSCL-15)

[h]远处转移的PET/CT 扫描阳性表现需要病理学或其他影像学确认。如果 PET/CT 扫描纵隔、淋巴结阳性需要病理学确认。
[j]见放射治疗原则(NSCL-C)。
[m]见与放疗联合应用的方案 (NSCL-E)。
[q]如果在初始同步放化疗中的化疗没有给足剂量, 应该再给2个周期 的足量化疗。

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[h]远处转移的PET/CT 扫描阳性表现需要病理学或其他影像学确认。如果 PET/CT 扫描纵隔、淋巴结阳性需要病理学确认。

[j]见放射治疗原则(NSCL-C)。

[m]见与放疗联合应用的方案 (NSCL-E)。

[q]如果在初始同步放化疗中的化疗没有给足剂量, 应该再给2个周期 的足量化疗。

[x]多数肺癌的胸腔积液都与肿瘤有关，而只有少数患者的胸水细胞病理学未找到肿瘤且非血性、非渗出液。当这些因素和临床判断显示积液与肿瘤无关时，积液不做为分期因素。心包积液的分期也按同一标准。

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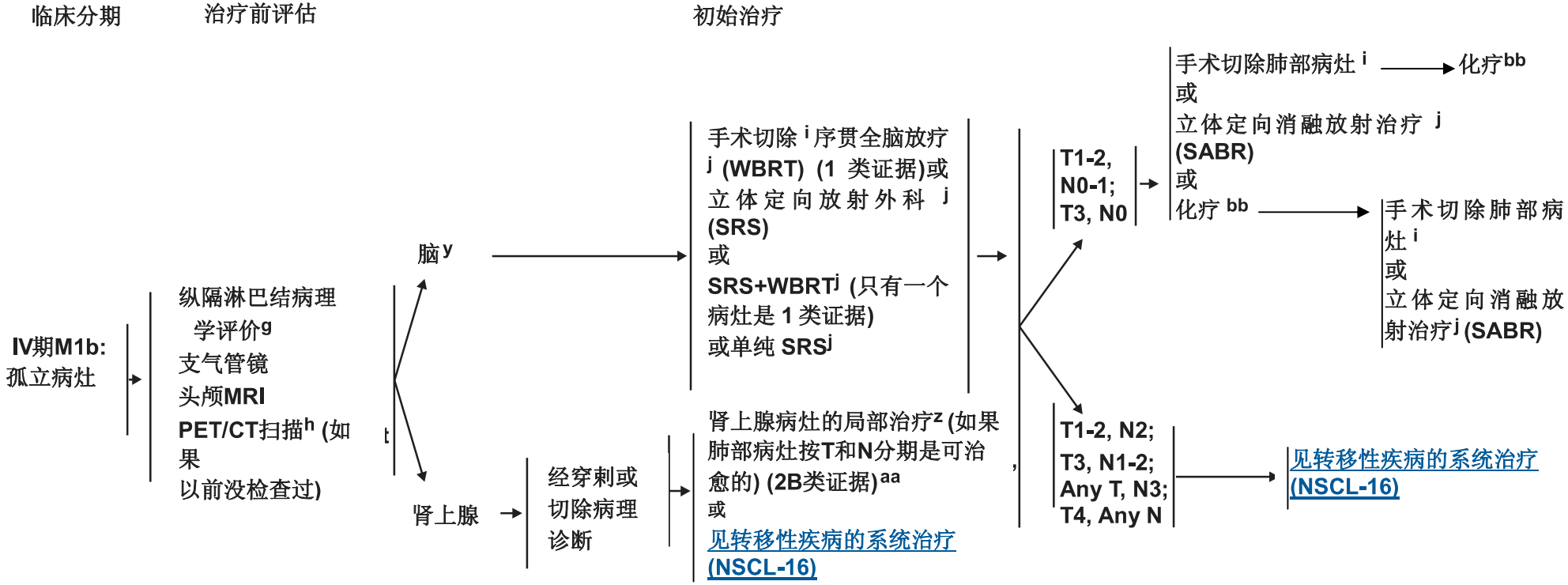
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



g评估方法包括纵隔镜，纵隔切开术, EBUS, EUS, and CT引导下活检。
h远处转移的PET/CT 扫描阳性表现需要病理学或其他影像学确认。如果 PET/CT 扫描纵隔、淋巴结阳性需要病理学确认。
i见外科治疗原则(NSCL-B)。
j见放射治疗原则(NSCL-C)。
y见NCCN中枢神经系统肿瘤指南 。
z可以包括肾上腺切除或放疗(包括SABR)。
aa疾病的患者的预后差，系统治疗应该考虑。
bb 见晚期或转移疾病的系统治疗 (NSCL-F)。

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

随访

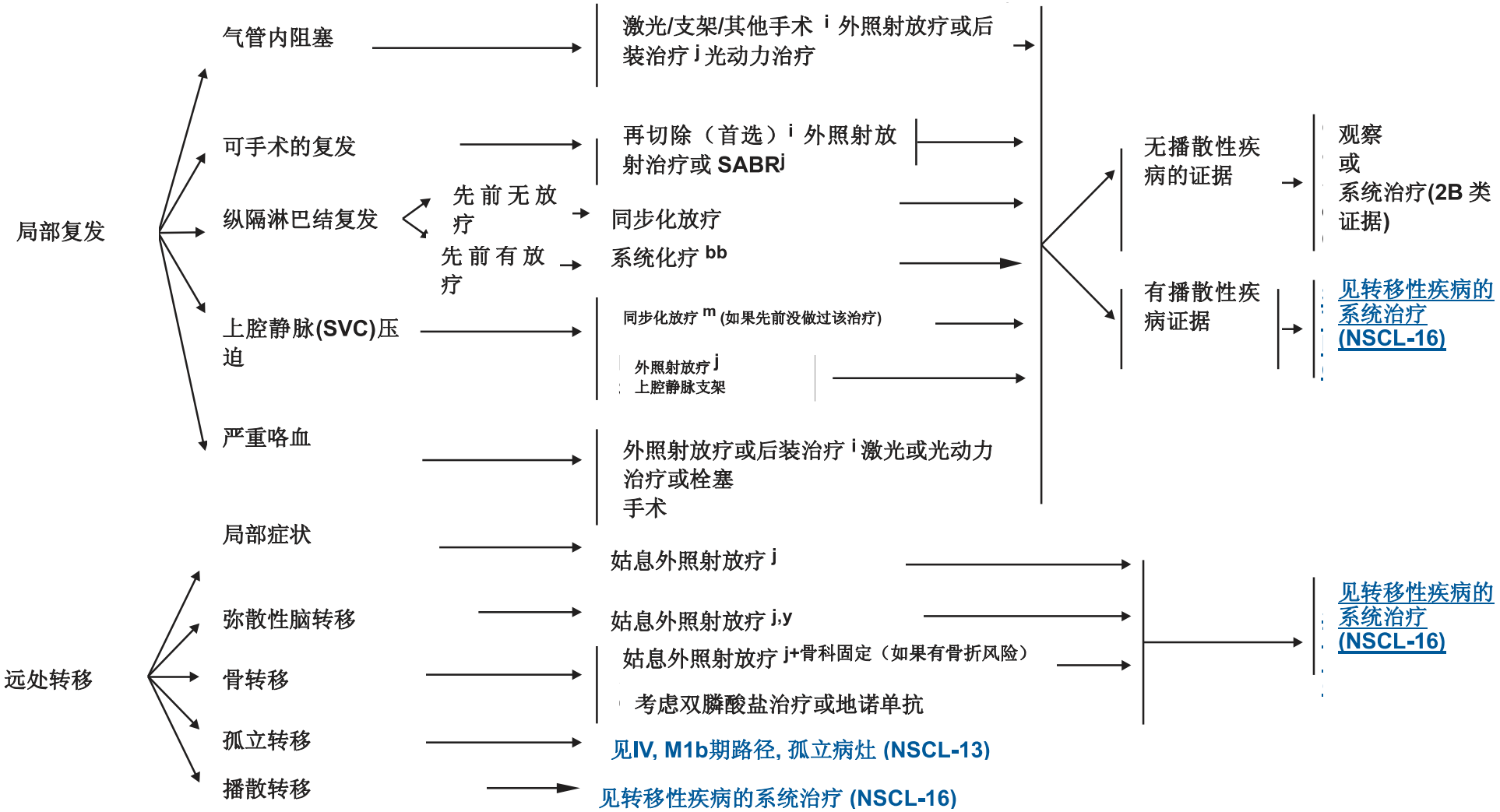
无临床或影像学证据的疾病, I-IV期:
前 2 年每 6-12 个月随访病史、体检和胸部 CT **±增强**
以后每年随访病史、体检和非增强的胸部 CT
戒烟建议，个别辅导和药物治疗
PET 或脑 MRI 无指征
见癌症幸存者护理 (NSCL-G)

局部复发 → 见复发和转移性疾病的治疗 (NSCL-15)

远处转移 → 见复发和转移性疾病的治疗 (NSCL-15)

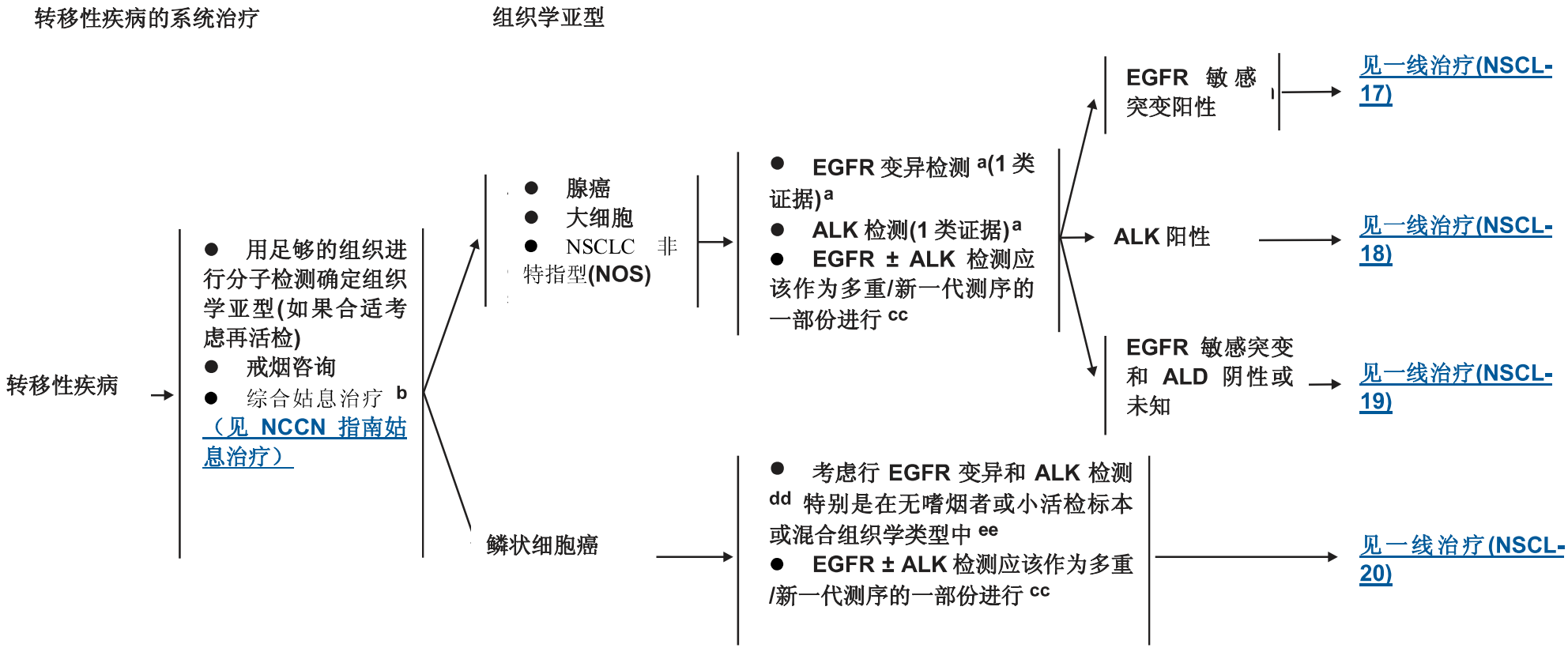
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

THERAPY FOR RECURRENCE AND METASTASIS



[i] 见外科治疗原则(NSCL-B)。
[j] 见放射治疗原则(NSCL-C)。
[m] 见与放疗联合应用的方案 (NSCL-E)。
[y] 见NCCN中枢神经系统肿瘤指南 。
[bb] 见晚期或转移疾病的系统治疗 (NSCL-F)。

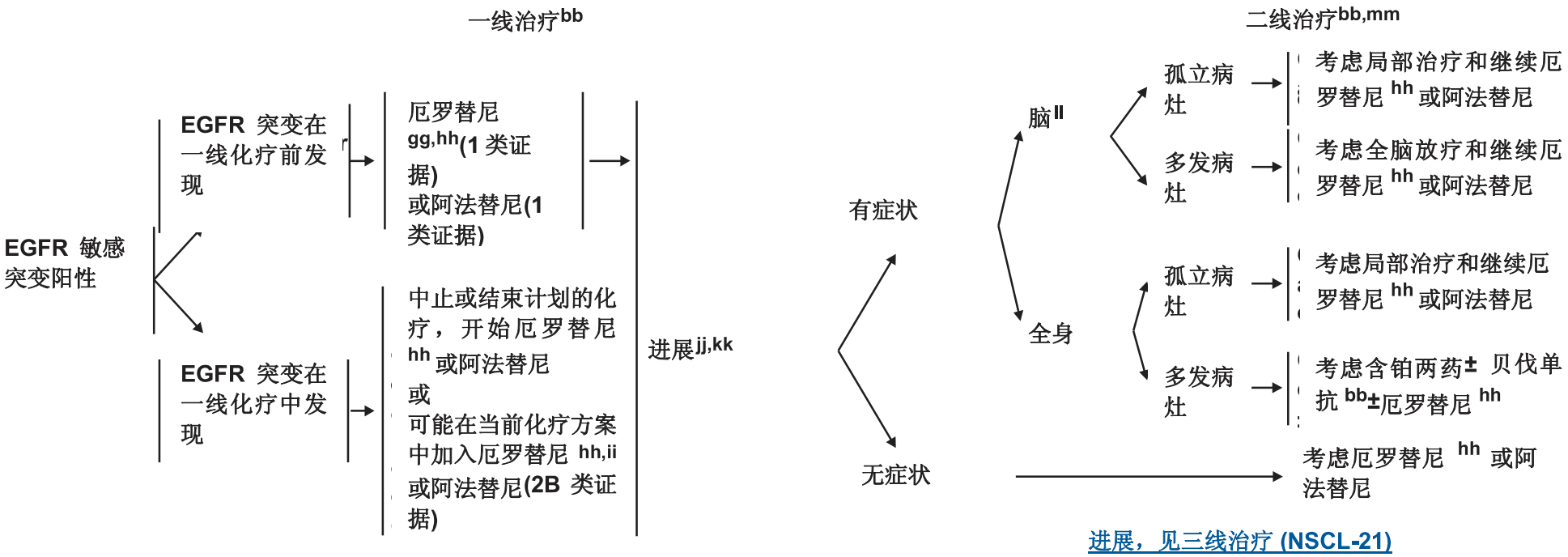
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[a] 见病理学评估原则(NSCL-A)。
[b] Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.
[cc] 见其他基因改变患者的靶向药物 (NSCL-H).
[dd] 鳞状细胞癌患者的EGFR变异率2.7%，真变异率的可信区间小于3.6%。这个EGFR变异频率不支持对所有肿瘤标本进行常规检测。Forbes SA, Bharma G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.
[ee] Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with EGFR mutant advanced non-small cell lung cancers with a squamous or squamous-like component. Mol Cancer Ther 2012;11:2535-2540.
[ff] 考虑ROS1检测; 如果阳性，可用克唑替尼治疗。Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 2012;30:863-870.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

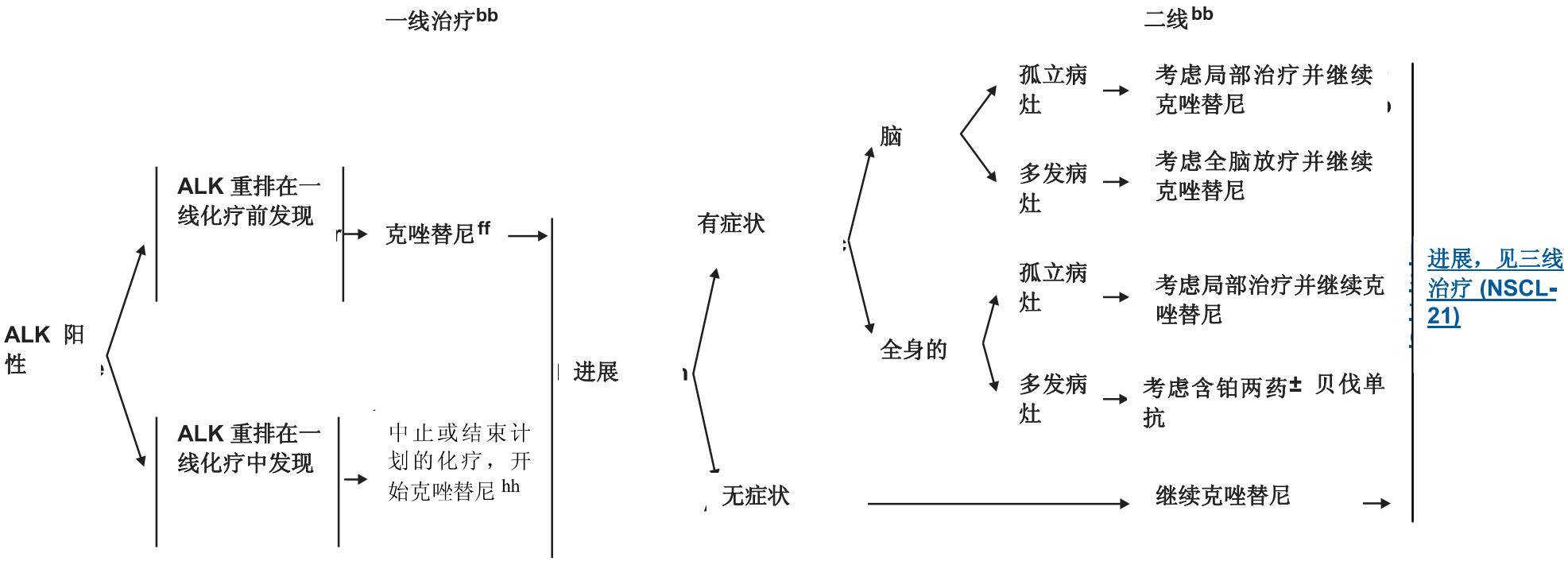
腺癌,大细胞, NSCLC非特指型: EGFR敏感突变阳性[a]



[a]见病理学评估原则(NSCL-A)。
[bb]见晚期或转移疾病的系统治疗 (NSCL-F)。
[gg]对于行为能力状态 0-4。
[hh]在可以获得吉非替尼的地区, 可以用它来代替厄罗替尼。
[ii]Janne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who are never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial.J Clin Oncol 2012;30:2063-2069.
[jj]进展时行活检以确定获得性耐药机制, 因为部份病人在进展时转化成SCLC。
[Kk]当心在亚组病人中停止EGFR TKI出现复燃现象。如果发生复燃，重新启用EGFR TKI。
[ll]对癌性脑膜炎者考虑加用厄罗替尼。
[mm]EGFR治疗进展的患者中阿法替尼有一些疗效。Miller VA, Hirsh V, Cadrenal J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;13:528-38.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

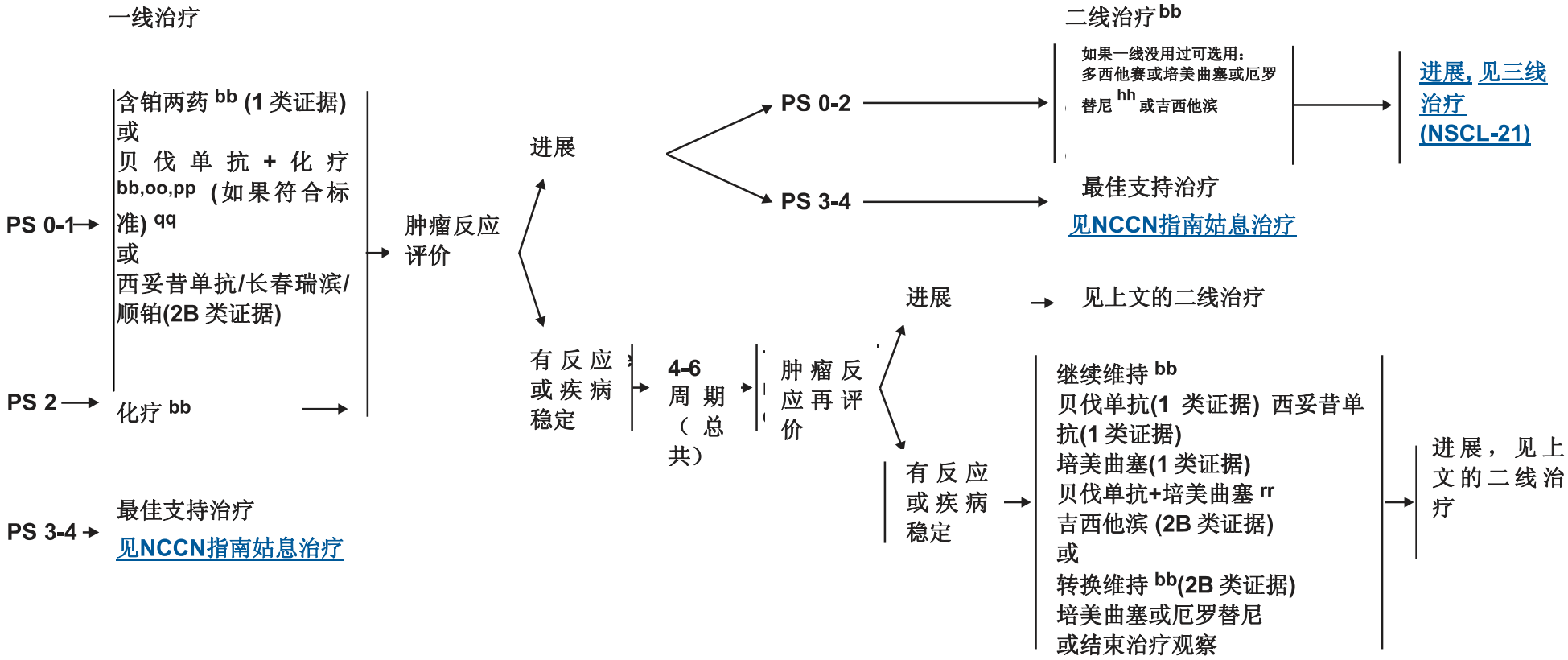
腺癌,大细胞, NSCLC非特指型: ALK阳性[a]



[a] 见病理学评估原则(NSCL-A)。
[bb] 见晚期或转移疾病的系统治疗 (NSCL-F)。
[ff] 考虑ROS1检测; 如果阳性，可用克唑替尼治疗。Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 2012;30:863-870.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

腺癌,大细胞, NSCLC非特指型: EGFR 变异和 ALK阳性阴性或未明[nn]



bb 见晚期或转移疾病的系统治疗 (NSCL-F)。
hh 在可以获得吉非替尼的地区, 可以用它来代替厄罗替尼。
nn 如果只检测过EGFR 和ALK，考虑额外的变异检测。见其他基因改变患者的靶向药物 (NSCL-H).
oo 继续给予贝伐单抗直到进展。
pp 任何血小板减少危险性高和有潜在出血危险的方案与贝伐单抗联用时应慎重。
qq 贝伐单抗+化疗的应用标准: 非鳞的NSCLC, 最近无咯血史。贝伐单抗不能单独给药, 除非在初始治疗与化疗联用后的维持治疗。
rr 如果贝伐单抗在一线治疗中与培美曲赛/顺铂化疗方案联用。

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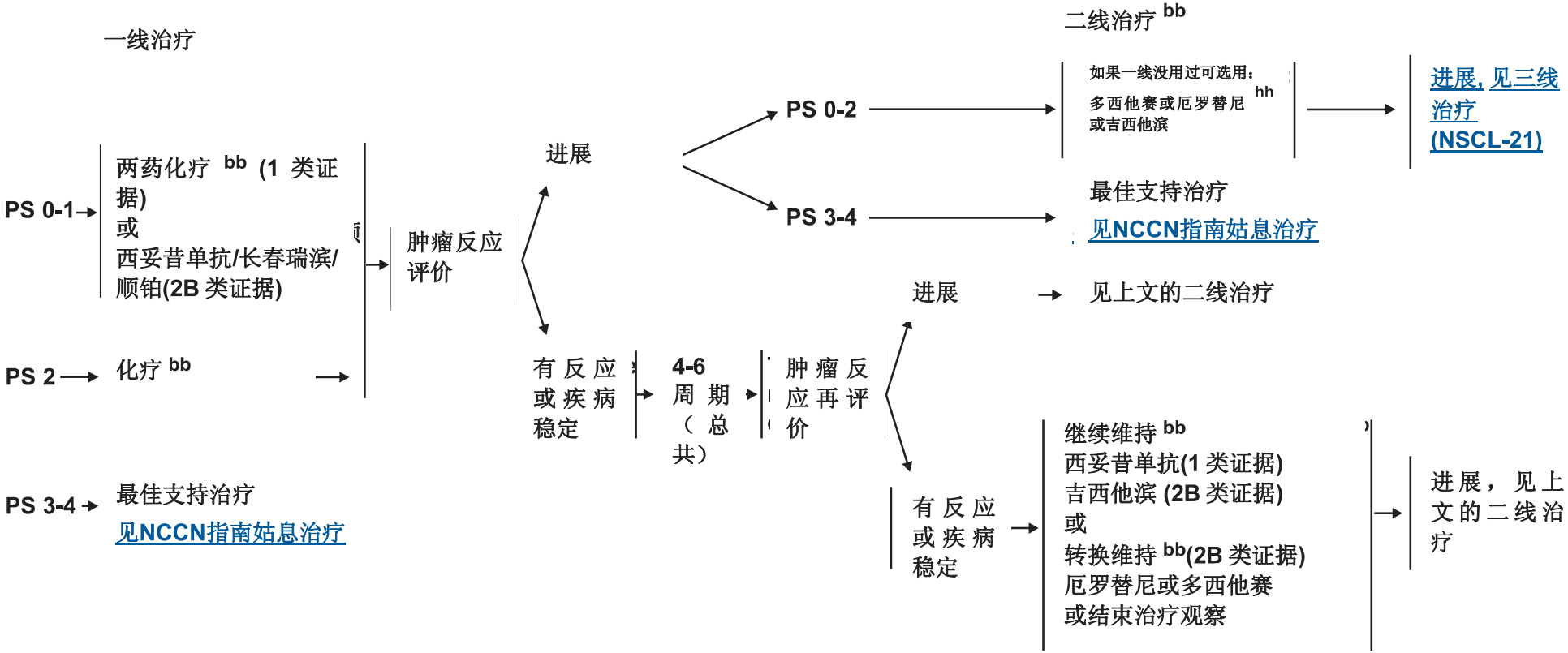
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

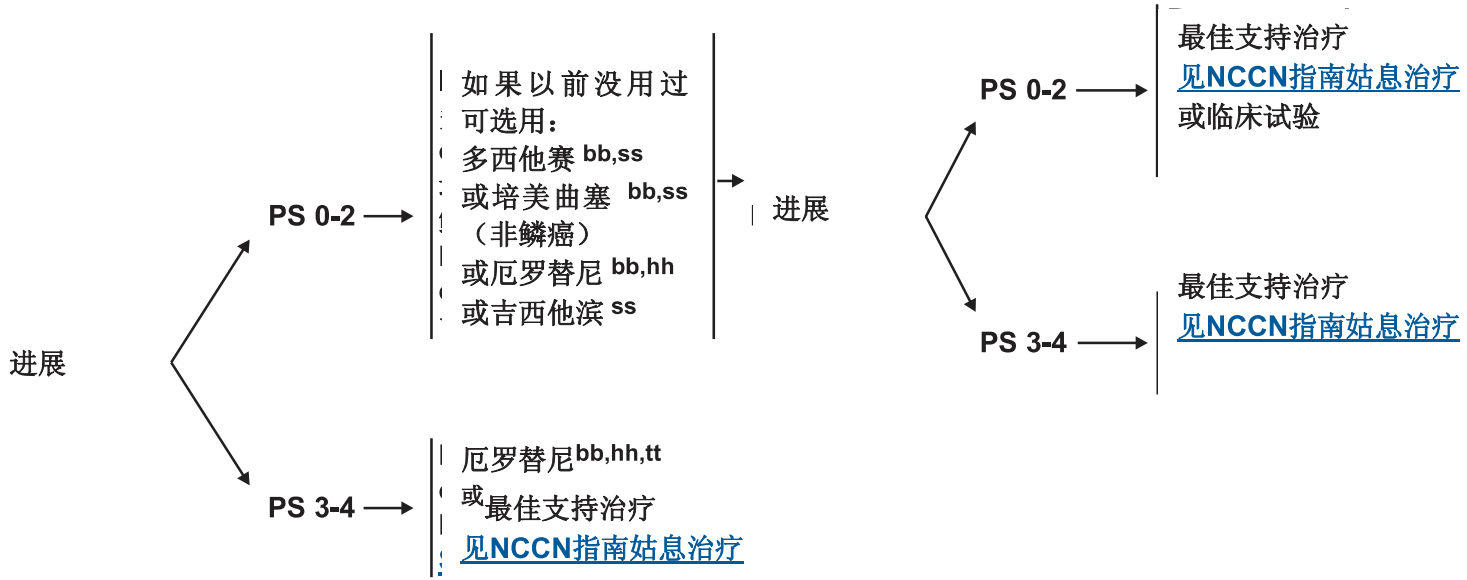
鳞状细胞癌



bb 见晚期或转移疾病的系统治疗 (NSCL-F)。
hh 在可以获得吉非替尼的地区，可以用它来代替厄罗替尼。

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

腺癌,大细胞, NSCLC非特指型, 或鳞状细胞癌三线治疗



bb 见晚期或转移疾病的系统治疗 (NSCL-F)。
hh 在可以获得吉非替尼的地区, 可以用它来代替厄罗替尼。
ss 如果患者在一线或二线治疗中没有接受受厄罗替尼或克唑替尼，培美曲塞，多西他赛和吉西他滨都是2B类证据。
tt 厄罗替尼可以考虑在EGFR变异，PS3-4分的患者中使用。

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

病理学评估原理 (1 of 4)

病理学评估

病理学评估的目的在于对肺癌组织学类型进行分类并确定所有AJCC[1]推荐的分期参数，包括肿瘤大小，包侵（胸膜和支气管），足够的手术切缘，以及是否有淋巴结转移。[2,3]进而, 确定肿瘤特定的分子异常，这对于预测肿瘤对越来越多的药物靶点是敏感或抗拒是很重要的，这些靶点中最早的是酪氨酸激酶抑制剂(TKIs) (见本节中的分子诊断研究).[4,5]

WHO 肿瘤分类系统一直以来都在提供肺癌分类的基础，包括肺癌的组织学类型，临床特征，分期因素，和分子、基因，以及流行病学表现。[6,7]

病理诊断报告应该包括WHO描述的肺肿瘤组织学分类，鳞状形态、神经内分泌分化和其他不同癌。在切除的标本和小活检标本中，最近出版的腺癌分类应该应用于这些肿瘤亚类。[8] 应用支气管肺泡腺癌(BAC) 命名是绝不允许的。

尽量避免统称为 “非小细胞肺癌 (NSCLC)”做为一个单独的诊断命名。在进行免疫组织化学染色后的小活检标本中的低分化癌，以下命名是可接受的：“非小细胞肺癌倾向于腺癌” 或 “非小细胞肺癌倾向于鳞癌” [8]这一系列中应该进行变异检测 (如，表皮生长因子受体 [EGFR]) 。

虽然福尔马林固定石蜡包埋的肿瘤可以用于大多数分子分析，但是为进一步分子研究应该考虑获得新鲜冷冻肿瘤组织

强烈建议限制免疫组化研究在小组织标本中的应用，从而为分子研究保瘤关键的肿瘤组织,特别是病变处于晚期的病人。一个鳞癌标志（如P63）和一个腺癌标志（如TTF-1）的有限组合对于解决多数诊断问题应该是充足的了。[8]

腺癌分类[8]

原位腺癌 (AIS; 以前称为 BAC): ≤3 cm 结节, 鳞状生长, 粘液性, 非粘液性或混合粘液/非粘液型。

微浸润腺癌 (MIA): ≤3 cm 结节，≤5 mm外侵, 鳞状生长, 粘液性, 非粘液性或混合粘液/非粘液型。

侵袭性腺癌, 主要生长方式: 鳞屑状 浸润 >5 mm， 腺泡状, 乳头状, 微乳头状,或实性伴粘蛋白产生

浸润性腺癌变异型: 粘液型腺癌, 胶样型, 胎儿型, 和肠型。

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病理学评估原理(2 of 4)

免疫组化染色

虽然在小活检标本与外科切除标本相似，组织学亚型和免疫表型的一致性普遍来说是好的，对材料有限的小活检标本和免疫表型模糊的案例进行亚型分类时建议应该谨慎。

IHC应该用于区分肺原发腺癌与以下肿瘤的区别：鳞状细胞癌、大细胞癌、转移癌和恶性胸膜间皮瘤并决定是否有出现神经内分泌分化。[9-11]

原发肺腺癌

推荐应用一个合适的免疫组化染色组合以排除肺转移癌。[12]

TTF-1是Nkx-2基因家族一个包含同源结构域核的转录蛋白，表达在肺和甲状腺的胚胎和成熟上皮细胞.TTF-1免疫反应性见于原发肺腺癌中的绝大多数(70%-100%)非粘液性腺癌亚型[13] 。肺转移性腺癌除转移性甲状腺癌恶性肿瘤外TTF-1通常是阴性的。转移性甲状腺癌恶性肿瘤中甲状腺球蛋白也是阳性的。

Napsin A 是正常肺泡壁II型细胞和近端及远端肾小管表达的一种天冬氨酸蛋白酶。>80% 的肺腺癌表达，与TTF-1联合检测是有用的。[12]

TTF-1 和 p63 (或p40代替)的组合可能对于确诊小活检标本中的腺癌或鳞癌是有用的，以前分类为非小细胞肺癌及非特指型 (NOS).[8]

神经内分泌分化

CD56, 嗜铬粒蛋白, 和突触囊泡蛋白应用于确定神经内分泌肿瘤.

恶性间皮细胞瘤与肺腺癌比较

应用一组标志物区别肺腺癌与恶性胸膜间皮瘤（上皮型）,包括2个间皮瘤的免疫反应性（但在腺癌中是阴性的）和2个在腺癌中是阳性（而间皮瘤中是阴性的）。[11]

间皮瘤相对敏感性和特异性的免疫染色包括WT-1, calretinin, D2-40, HMBE-1, and cytokeratin 5/6 (腺癌中阴性).[14,15]

腺癌中的抗体免疫反应性包括CEA, B72.3, Ber-EP4, MOC31, CD15, and TTF-1 (间皮瘤中阴性).[8,11]

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病理学评估原理(3 of 4)

肺癌的分子诊断研究

EGFR 和KRAS

EGFR正常可出现在上皮细胞的表面，在一系列人类恶性肿瘤中经常过表达。EGFR活化突变的出现对肺癌病人的治疗选择来说，代表着一个重要的生物学决定因素。

EGFR 突变[特别是 19外显子缺失和21外显子 (L858R, L861) 和 18外显子(G719X, G719) 突变]与TKIs敏感之间存在显著相关。[16-19]

20外显子插入突变可能预测了对TKIs临床获得水平耐药。[20,21]

EGFR和 KRAS变异在肺癌病人中是相互排斥的。[22]

KRAS变异与固有的TKI耐药相关，KRAS基因测序对于选择TKI治疗患者是有用的。[23]

普遍认为 EGFR突变在西方腺癌中占10%而在亚洲腺癌患者中高达50%，而在不吸烟、女性和非粘液癌患者中的EGFR突变率更高。 KRAS突变在非亚裔、吸烟和粘液腺癌中最常见。[24] 最常见的EGFR变异导致21外显子第858位氨基酸由亮氨酸变为精氨酸（L858R）和19外显子框架内缺失。突变更常出现在肺非粘液腺癌的鳞屑型（以前的支气管肺泡腺癌）和乳头状型（和/或微乳头状型）肺腺癌。

TKI治疗原发耐药与KRAS突变相关。获得性耐药与EGFR激酶结构域 第二位点突变(如 T790M), 另一种激酶扩增 (如MET), NSCLC组织学转化成SCLC,和上皮-间质转化(EMT) 有关.

ALK

间变性淋巴瘤酶(ALK) 基因重排表现为ALK与各种伴侣基因融合, 包括棘皮动物微管相关蛋白样-4 (EML4)。[25] ALK融合已经在NSCLC患者亚类中得到确认，表现为一个独特的NSCLC亚类，这类病人中ALK抑制剂的应用是一种非常有效的策略。[26] Crizotinib是一种口服的ALK抑制剂，FDA已批准用于局部晚期或转移性ALK基因重排（也就是ALK阳性）的NSCLC患者。

ALK NSCLC 最常出现在一个独特的NSCLC患者亚群中，这个亚群的患者具有很多伴EGFR突变NSCLC患者的共同临床特征。[27,28]。但EML4-ALK融合和EGFR突变大多数情况下不同时存在[27, 29-31]

当前检测ALK NSCLC 的标准方法是荧光原位杂交 (FISH), 而其他方法目前仍在研究阶段。包括聚合酶链反应(PCR)和 IHC。FISH的一个很大的优势在于存在商业化的探针，用于ALK重排的间变大细胞淋巴瘤(ALCL)诊断方面的进展，也能应用于ALK重排的肺腺癌的诊断。全世界范围内临床实验室广泛应用的IHC检测诊断ALK重排的ALCL，不适合用于检测多数ALK重排的肺癌[32,33]。其原因在于与ALK重排的ALCL相比ALK重排的NSCLC的ALK表达水平 较低。近期FDA进行的分子诊断学检测证实，应用FISH法可确定哪些病人是ALK阳性肺癌患者。

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病理学评估原理(4 of 4) – 引文

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外科治疗原则 (1 of 4)

评估

可治愈性、外科分期和肺切除的决定，应该由具有胸外科专业认证的，且在实践中以做肺癌外科为主的外科医生执行。

外科评价前60天前的CT 和 PET才能用于分期。

手术切除是首选的局部治疗方式 (其他方式包括射频消融、冷冻和SABR)。对于每个考虑根治性局部治疗病人，胸部肿瘤外科会诊应该是评价的一部份。对于高危病人考虑行SABR的情况下，推荐行多学科（包括放射肿瘤学家）评估。

包括必要的影像学研究在内的所有治疗计划应该在任何非急诊治疗开始前做决定。

胸外科医生应该积极参与关于肺癌患者的多学科讨论和会议（如多学科临床和/或肿瘤委员会）。

手术

对于大多数NSCLC患者解剖性肺切除是首选的.

亚肺叶切除 – 节段切除和楔形切除可以获得实质切除边界≥2cm或≥该结节的大小。

在没有增加外科危险性时，亚肺叶切除也应该适当地对N1和N2淋巴结进行活检，除非在技术上不可行。

节段切除(首选) 或楔形切除基于下列原因可适用于部分特定患者:

- 可保留肺组织很少或因其他主要合并症而不能接受肺叶切除
- 周围型结节[1] ≤2 cm，并至少符合以下标准中的一项:
  - 组织学类型为单纯原位腺癌
  - CT显示结节≥50%表现为毛玻璃样
  - 影像学随访证实肿瘤倍增时间较长(≥400 days)

如果患者没有解剖学和外科禁忌，只要不违反肿瘤学标准和胸部手术切除原则，强烈推荐考虑行电视辅助胸腔镜外科手术（VATS）或微创手术。

在有丰富VATS经验的高流量医学中心里, 在特定病人中行VATS肺叶切除可提高近期疗效。 (如，减少疼痛、减少住院日、功能恢复更快、并发症更少) 且不降低癌症疗效。

如果解剖位置合适且可以做到切缘阴性，保留肺组织的解剖性肺切除（袖状叶切除术）优于全肺切除术。

T3 (浸润)和T4 局部外侵肿瘤要求整块切除受侵结构且切缘阴性。如果一个外科医生或中心不能确定是否可能完全切除，应该从一个高流量专科中心获得额外的手术意见。

切缘和 淋巴结评估 (见 NSCL-B 2 of 4)

[1]外周定义为肺实质的外1/3.

对于 IIIA (N2) NSCLC患者，手术的作用 (见 NSCL-B 2 of 4 至 NSCL-B 4 of 4)

Note: All recommendations are category 2A unless otherwise indicated.
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手术治疗原则 (2 of 4)

切缘与淋巴结评价

手术病理的关系对于评价明显靠近或切缘阳性很重要，这是因为这些并不表现为真的边界或可能没有真正代表局部复发危险的区域(如，当行隆突下淋巴结清扫时的纵隔内侧面或中间段支气管，或无胸膜与主动脉粘连表现时胸膜与主动脉相邻).

N1 和 N2 淋巴结清扫并标明位置，这应该作为肺癌切除术的常规组成—至少3个N2淋巴结区取样或完全淋巴结清扫。

IIIA期（N2）患者在接受切除术时应行正规同侧纵隔淋巴结清扫术。

完全切除要求切缘阴性、系统地淋巴结清扫或取样和最上纵隔淋巴结阴性。不完全切除的定义是以下一项切缘阳性，不可切除的阳性淋巴结或或胸膜腔积液或心包积液阳性。完全切除称为R0，镜下阳性残留R1而肉眼肿瘤残留R2。

病理分期II 期或以上的患者应该进行肿瘤内科评价，IIIA 期应考虑介绍给放射肿瘤医师治疗。

IIIA 期(N2) NSCLC患者中手术的地位

病理学确认N2的患者中手术的地位仍有争议。[1] 两个随机研究评价了手术在这个人群中的作用，但是两者都没有显示手术有总生存获益。[2,3]尽管如此， 我们认为这些研究都没有对伴随N2患者异质性而存在的差异以及手术在特定临床情况下的益处进行充分评估。

由于纵隔淋巴结转移对预后以及治疗决策的制定具有重要的影响， N2期疾病的诊断需要在治疗前严格由影像学分期和有创分期两种方法决定(NSCL-1, NSCL-2, and NSCL-6)

在肺切除手术中发现隐匿性N2阳性的患者应该按照既定方案行肺切除， 并行正规纵隔淋巴结清扫。如果在VATS过程中发现N2疾病,外科医生应该考虑中止这个操作并在手术前行诱导治疗; 但是继续操作也是一种选择。

对N2淋巴结阳性的患者是否需要手术治疗应在进行任何治疗前由多学科小组决定， 小组应包括经过资质认证的、 大部分时间从事胸外科肿瘤治疗的胸外科医生。[4]

N2淋巴结阳性的存在极大地增加了N3淋巴结阳性的可能。 对纵隔淋巴结的病理评估应包括隆突下淋巴结以及对侧淋巴结。 EBUS +/- EUS为微创纵隔病理分期提供了技术补充， 但不能代替纵隔镜。 即使使用了这些方法， 在最终治疗决定制定前还需要对侵犯的站数进行足够的评估， 对对侧淋巴结是否侵犯进行活检和记录。

IIIA期 (N2) NSCLC患者中手术的作用在NSCL-B 3 of 4至 NSCL-B 4 of 4继续

Note: All recommendations are category 2A unless otherwise indicated.
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手术治疗原则(3 of 4)

IIIA期 (N2) NSCLC患者中手术的作用

与首次纵隔镜相比， 可行的再次纵隔镜在技术上更困难， 准确性也更低。 一种可行的方法是在治疗前评估中使用EBUS (+/- EUS)， 将纵隔镜保留至新辅助治疗后重新行淋巴结分期时使用[5]。

患者单个淋巴结小于3 cm可以考虑多学科治疗， 包括手术切除[1,6,7]

诱导治疗后的再分期难以解读，但应该行CT +/- PET以除外疾病进展或转移灶在间歇期增大。

新辅助治疗后纵隔阴性的患者预后较好[7,8]

新辅助放化疗在50%的NCCN机构中使用， 另外50%使用新辅助化疗。 考虑到放疗如未术前使用则在术后也会使用， 两种方法的总生存期相似。[5,9]接受新辅助放化疗的患者病理完全缓解率以及纵隔淋巴结阴性率更高[10]。 但其代价是急性毒性反应发生率更高， 成本也有增加。

当新辅助放化疗的使用剂量低于标准根治性治疗剂量时， 应尽量缩短放疗与外科评估之间的时间差， 时间差不能超过一周。 如果不能及时进行外科评估， 则不应该进行新辅助放化疗。 在个别患者中， 在得到胸外科医生认可的情况下， 另一个可选方案是在重新评估和考虑手术前完成新辅助放化疗[11,12] 。

如果一位外科医生或中心对根治剂量放疗后的手术切除可行性或安全性不确定，可以考虑从高容量的专科中心获取额外的手术选项。这些操作也可能从在放射野中手术时对软组织覆盖的额外考虑中受益

来自大样本多中心研究的数据表明新辅助化放疗后行肺切除术存在不可接受的并发症和死亡率。[2]但是单纯新辅助化疗是不是也这样还不清楚。另外， 很多研究小组都对这一协作组的研究结果提出疑问， 他们的单中心研究显示诱导治疗后的肺切除是安全的。[13-16]另外，并没有证据支持在可手术的IIIA (N2)患者的诱导方案加入RT与诱导化疗比较能提高疗效[17]

我们在2010年向NCCN成员机构发放了一份关于他们如何治疗N2疾病的问卷调查。他们的反馈结果显示了在处理这一临床难题时的思路。

a) 只有一站N2淋巴结侵犯且小于3 cm时将考虑手术治疗： (90.5%)
b) 超过一站N2淋巴结侵犯且没有淋巴结大于3 cm时将考虑手术治疗：(47.6%)
c) 在初步评估纵隔时使用EBUS (+/- EUS): (80%)
d) 新辅助化疗后，使用病理评估，在手术前最后做决定：(40.5%)
e) 当患者在初步评估后需要行全肺切除时考虑新辅助治疗： (54.8%)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

手术治疗原则 (4 of 4)

手术在IIIA 期(N2) NSCLC患者中的作用 – 引文

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放射治疗原则 (1 of 9)

一般原则 (见表1. 放射治疗常用缩略词)

合适的放疗(RT)应该由以肺癌放疗为主要工作的专业认证放射肿瘤学家决定。

对各期NSCLC放疗都可能有作用, 包括根治性或姑息性治疗。在所有NSCLC患者中都应该把放射肿瘤作为多学科评价或讨论的一部份。

现代放疗的重要目标是最大程度的肿瘤控制和最小的治疗毒性。最低技术标准是CT计划的三维适形放疗（3D-CRT）。[1]

当需要安全地给予根治性放疗时可以选用更先进的放疗技术。这些技术包括(但不局限于)4D-CT 和/或 PET-CT 模拟, IMRT/VMAT, IGRT, 运动解决方案，和质子治疗。非随机比较了先进的技术与旧技术，证实了先进技术可以减少毒性和提高生存。[2-4]

应用先进技术的中心应该使用并记录特定模式的质量保证测量。就像是参与采用先进的技术RTOG临床试验的要求那样，这是治疗计划和执行治疗共同的外部资格认证目标。放射肿瘤学ACR-ASTRO实践指南等是有用的参考资料。(http://www.acr.org/~/media/ACR/Documents/PGTS/toc.pdf)。

早期 NSCLC (I期)

SABR (也称为 SBRT) 推荐用于医学上不适合手术和经胸外科评价后拒绝手术的病人。在因医学原因不能手术或老年患者中，非随机和以人群为基础的研究中， SABR取得的原发肿瘤控制率和总生存与肺叶切除相似，优于3D-CRT。[5-10]

SABR也是手术高危患者的合适选择(能耐受亚肺叶切除，但不能耐受肺叶切除，如，年龄≥75岁，肺功能差)。 SABR和亚肺叶切除获得相似的癌症特异生存和原发肿瘤控制。[10-12]

对于没有SABR的机构，可以谨慎地采用大分割或剂量增强的常规分割3D-CRT治疗方案替代[13-14]

对于手术治疗的患者, 除非切缘阳性或升期到N2，否则不推荐应用术后放疗 (PORT) (见下文的局部晚期*NSCLC*)。

局部晚期NSCLC (Stage II-III)

不可手术的 II期和III 期NSCLC患者的标准治疗是同步化放疗。[15-17] (http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/NonsurgicalTreatmentForNSCLCGoodPerformanceStatusDefinitiveIntent.pdf)通过支持治疗，避免因可控制的急性毒性反应所致的放疗中止和减少剂量。

对于不能耐受同步化放疗的虚弱患者序贯化放疗或单纯放疗是合适的.[18,19] (http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/NonsurgicalTreatmentForNSCLCPoorPerformanceStatusOrPalliativeIntent.pdf)

Note: All recommendations are category 2A unless otherwise indicated.
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放射治疗原则 (2 of 9)

局部晚期NSCLC (II-III期) (续)

加速放疗方案可能是有益的,特别是在没有与化疗同步时(如, 在序贯或单纯放疗)。[20,21]
放疗在手术前和手术后都有作用。
http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/InductionAndAdjuvantTherapyForN2NSCLC.pdf
术前同步化放疗是IIIA期可手术患者的治疗选择 (最小N2和可行肺叶切除治疗) [22]，也推荐用于可手术肺上沟肿瘤的治疗。[23-24]
可手术IIIA期患者可选择术前化疗或术后放疗.[25,26]
应该在所有治疗开始前就做好三种模式可治愈性的决定
在非随机分析中，临床分期为 I/II期的患者在手术后升期到N2+者，术后放疗与术后化疗相比，显著提高生存。[27,28] 虽然就佳顺序尚未确定,术后放疗通常在术后化疗之后执行。在条件允许的患者中术后放疗可以安全地与化疗同步进行，[29-31]推荐用于术后切缘阳性的患者。
术后放疗不推荐用于病理分期N0-1的患者，因为在这种情况下术后放疗与死亡率相关，至少在旧放疗技术条件下是这样的。[32]

晚期/转移性NSCLC (IV期)

放疗推荐用于局部姑息或防止症状出现（如，疼痛、出血或阻塞）。
在小部份仔细选择过的行为能力评份好的，且接受胸内病灶根治性治疗的患者中，对孤立或局限转移灶（寡转移）的根治性局部治疗（包括脑、肺和肾上腺及以外的转移） 获得了生存期的延长。在可以安全地对受累部位照射的病例中，寡转移的根治性放疗，特别是采用SABR，是一个合适的选择。[33-35]
见 NCCN 中枢神经系统癌指南关于脑转移的放疗。

靶区,处方剂量和正常组织剂量限制 (见NSCL-B 6 of 9和NSCLB 7 of 9中的表 2-5)

ICRU 62 号文件和 83号文件详细地定义了当前3D-RT和IMRT的靶区。GTV包含了已知影像和病理评估中的病变范围(原发灶和淋巴结), CTV包括推测的微浸润或播散区域, 而 PTV包括ITV（包括靶区运动）加上摆位和机械误差所致的摆位边界。
http://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx
PTV 边界可以通过固定装置、运动控制和IGRT技术来缩小。
勾画正常组织的一致性对评价计划的安全性很重要。RTOG肺勾画共识图谱是有用的资源。
http://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx
基于发表的经验、正常进行的试验、历史数据、模型和经验判断[37,38]的常用处方剂量和正常组织受量限制列在表2-5。有用的参考文献包括最近QUANTEC项目关于正常组织剂量反应的综述。[39-43]

Note: All recommendations are category 2A unless otherwise indicated.
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放射治疗原则 (3 of 9)

淋巴结阴性早期NSCLC的 SABR

SABR的高剂量强度和适形性要求PTV最小化。

在SABR治疗中,剂量强度BED ≥100 Gy 的方案与较低强度的方案相比局部控制和生存都显著提高。[44]在美国,只有5分次的方案符合SBRT的强制帐单代码，但是稍微延长的方案同样是合适的。[44,45]对于中央型肿瘤而主 (定义为近端气管树2 cm范围内), 4 至10 分次的风险适应SABR方案显然是有效和安全的,[45,46]而3分次54 至 60 Gy 的方案是不安全的，应该避免。[47] RTOG0813前瞻性研究了5分次方案。 SABR常见用于大小不超过5 cm的肿瘤，如果正常组织限量满足的话可以安全地治疗经选择的较大孤立肿瘤。[48]

处方剂量并不完全描述实际给予的剂量，这也极大地依赖于剂量是如何规定的（以等中心还是以等剂量体积覆盖PTV的比例），剂量不均匀性的程度，是否使用组织密度不均匀性校正，以及剂量计算算法类型。[49,50]所有这些因素在解读或模仿先前的研究方案时必须加以考虑。

局部晚期/常规分割放疗

不考虑选择性淋巴结照射（ENI）的受累野照射（IFI）允许增加肿瘤剂量，与孤立的淋巴结复发风险下降相关，特别是在PET-CT分期的患者中。[51-55]

一个随机研究发现IFI与ENI比较改善了生存, 可能与它的剂量增加有关。[56]为了优化肿瘤的根治性剂量，受累野照射（IFI）是合理的。

最常见的根治性放疗的处方剂量是60 至70 Gy ， 2 Gy/次。最小的处方剂量是60 Gy。[57]在非随机研究中，单纯放疗、[58]序贯化放疗、[59]或同步化放疗[60]的剂量递增与生存改善相关。当满足正常组织受量限制时，同步化放疗剂量高达74 Gy也是安全的 。[61-64]来自RTOG 0617的最终结果, 60 与 74 Gy同步化疗比较结果仍未明确，但初步认为，74Gy这个剂量并不改善总生存。[65]meta分析证明加速分割放疗方案改善生存,[66]而一项随机研究（RTOG1106）正在进行以评价个体化剂量增强的加速放疗 (RTOG 1106)。

术前放疗的标准剂量是45 -50 Gy ，1.8 -2 Gy/次。术前放化疗中给予根治性放疗剂量是安全的，可以获得预期的淋巴结清扫和生存率,[67-70]但需要丰富的胸外科技术经验，以减少高剂量放疗后的手术并发症风险。

在术后放疗中，CTV包括支气管残端和高危引流淋巴结区。完全切除后的标准剂量是50-54 Gy，1.8−2.0 Gy/次，但可以对包括结外受侵或镜下阳性的区域在内的高危区推量。[29,30]因为手术后肺的耐受剂量明显下降，所以肺的正常组织受量限制应该更严格。正在进行的欧洲肺ART研究为术后放疗技术提供了有用的指南。[72]

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

放射治疗原则 (4 of 9)

晚期/姑息放疗

姑息放疗的剂量和分次应根据治疗目的，症状，行为能力状态和逻辑因素个体化给予。短程方案放疗与长疗程方案比较疼痛缓解率相似，但是需要再治疗的机会大，[73-76]首选用于行为能力评分低和/或预期寿命短的患者中。当需要给予高剂量时 (>30 Gy), 应该应用3D-CRT以减少正常组织的照射。

放射治疗模拟、计划和执行

应该用合适的固定装置获取放射治疗体位的CT模拟定位。只要有可能，对于中央型肿瘤或淋巴结转移患者推荐静脉造影同时口服或不口服造影剂，可以更好地勾画靶区/器官。因为静脉造影会影响组织的异质性校正计算，当存在强化时，可能需要密度屏蔽或静脉造影前扫描。

PET/CT 明显提高靶区勾画的准确性,[77]特别是存在明显肺不张或有静脉增强禁忌的患者。 PET / CT与单纯CT的放疗计划比较的随机研究，证实PET/CT放疗计划改善无益根治放疗的优先权，减少复发并且有改善总生存的趋势。[77]考虑到NSCLC的快速进展能力,[79,80] PET/CT应该最好在治疗前4周内获得。最理想的是在治疗体位下行PET/CT 检查。

肿瘤和器官的运动，特别是呼吸，应在模拟时进行评估或计算。评估选项包括透视，吸气/呼气CT或慢扫描CT，或最好是4D-CT检查。 光子束的能量应根据肿瘤的解剖部位和光束路径进行个体化选择。在一般情况下，被为光束在进入肿瘤之前通过低密度的肺组织，推荐的光子能量为4−10 MV。当光束入射到肿瘤之前没有空气间隙（如用于一些大纵隔肿瘤或肿瘤与胸壁粘连），更高的能量可以改善剂量分布，特别是应用少量固定角度照射野时尤其如此。

在密度不均匀组织中因为剂量建成和横向电子散射效应，建议采用组织的异质性校正和精确的剂量计算算法。不建议用简单的笔形束算法进行异质性校正。[50]

如果呼吸运动明显的话应该控制呼吸运动，这些方法包括（但不局限于）腹部压迫强迫浅呼吸，加速器射线束呼吸周期门控，实时肿瘤跟踪，主动呼吸控制（ABC），或辅导/生物反馈技术。一种有用的呼吸控制方法是AAPM任务组76号文件。[81]

当应用SABR和3D-CRT/IMRT这些靶区周围剂量梯度陡峭的技术，危及器官（OARs）非常靠近高剂量区时，或应用复杂的运动管理技术，以上三种情况推荐使用IGRT—包括 (但不局限于)正交对平面影像和容积影像(如 CBCT 或导轨CT) 。

Note: All recommendations are category 2A unless otherwise indicated.
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放射治疗原则 (5 of 9)

表 1. 放射治疗常用缩略辞

RT	放射治疗
2D-RT	2-维放射治疗
3D-CRT	3-维适形放射治疗
4D-CT	4-维计算机断层摄影
AAPM	美国医学物理师协会
ABC	主动呼吸控制
ACR	美国放射学会
ASTRO	美国放射肿瘤协会
BED	生物有效剂量
CBCT	锥形束 CT
CTV*	临床靶区
DVH	剂量体积直方图
ENI	选择性淋巴结照射
GTV*	大体肿瘤体积
ICRU	国际辐射单位和测量委员会
IFI	受累野照射
IGRT	影像引导放射治疗
IMRT	调强放射治疗
ITV*	内靶区
MLD	平均肺受量
OAR	危及器官
OBI	即时影像
PORT	术后放射治疗
PTV*	计划靶区
QUANTEC	临床正常组织效应定量分析
RTOG	肿瘤放射治疗协作组
SABR	立体定向消融放射治疗，也称为立体定向体部放射治疗(SBRT)
V20	危及器官受到20Gy照射体积百分比
VMAT	容积调强旋转放射治疗

*参考ICRU83号文件详细定义 。

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

放射治疗原则 (6 of 9)

表 2. SABR常用剂量

总剂量	# 分次	适应症例子
25-34 Gy	1	周围型, 小肿瘤 (<2 cm), 特别是离胸壁 >1 cm
45-60 Gy	3	周围型, 且离胸壁 >1 cm
48-50 Gy	4	中央型或周围型肿瘤 <4-5 cm, 特别是离胸壁< 1 cm
50-55 Gy	5	中央型或周围型肿瘤, 特别是离胸壁< 1 cm
60-70 Gy	8-10	中央型肿瘤

表 3. SABR的最大剂量限制*

危及器官/方案	1 分次	3 分次	4 分次	5 分次
脊髓	14 Gy	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	30 Gy (6 Gy/fx)
食管	15.4 Gy	30 Gy (10 Gy/fx)	30 Gy (7.5 Gy/fx)	32.5 Gy (6.5 Gy/fx)
臂从	17.5 Gy	21 Gy (7 Gy/fx)	27.2 Gy (6.8 Gy/fx)	30 Gy (6 Gy/fx)
心脏/ 心包	22 Gy	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	35 Gy (7 Gy/fx)
大血管	37 Gy	39 Gy (13 Gy/fx)	49 Gy (12.25 Gy/fx)	55 Gy (11 Gy/fx)
气管 & 近端支气管	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	32.5 Gy (6.5 Gy/fx)
肋骨	30 Gy	30 Gy (10 Gy/fx)	30 Gy (7.5 Gy/fx)	32.5 Gy (6.5 Gy/fx)
皮肤	26 Gy	30 Gy (10 Gy/fx)	36 Gy (9 Gy/fx)	40 Gy (8 Gy/fx)
胃	12.4 Gy	27 Gy (9 Gy/fx)	30 Gy (7.5 Gy/fx)	35 Gy (7 Gy/fx)

*根据近期或正在进行的 RTOG SABR研究的限量 (RTOG 0618, 0813, & 0915)。

Note: All recommendations are category 2A unless otherwise indicated.
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放射治疗原则 (7 of 9)

表4. 常规分割和姑息放疗常用剂量

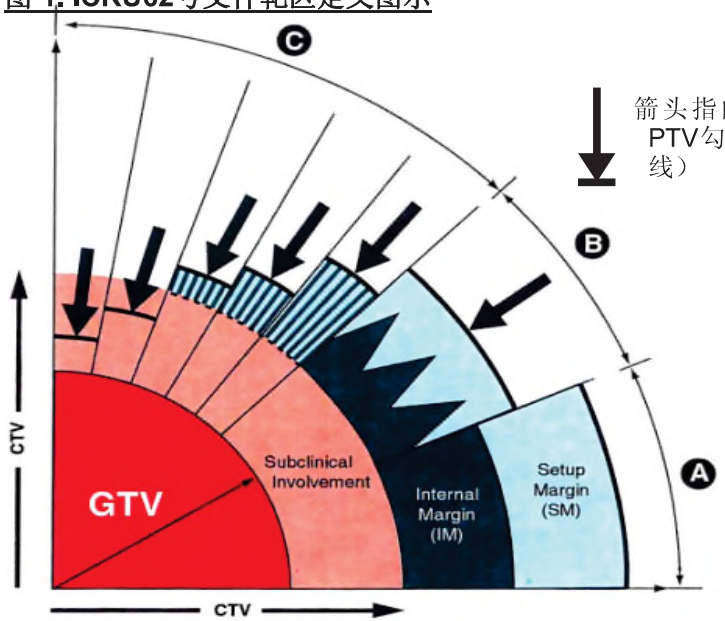
治疗类型	总剂量	分割量	治疗时间
联合或不联合化疗的根治性放疗	60-74 Gy	2 Gy	6-7.5 周
术前放疗	45-50 Gy	1.8-2 Gy	5 周
术后放射治疗			
切缘阴性	50-54 Gy	1.8-2 Gy	5-6 周
淋巴结包膜外受侵或镜下切缘阳性	54-60 Gy	1.8-2 Gy	6 周
肉眼肿瘤残留	60-70 Gy	2 Gy	6-7 周
姑息放射治疗			
阻塞性疾病(上腔静脉压迫综合征或阻塞性肺炎)	30-45 Gy	3 Gy	2-3 周
骨转移并软组织肿块	20-30 Gy	4-3 Gy	1-2 周
骨转移不伴软组织肿块	8-30 Gy	8-3 Gy	1 天-2 周
脑转移	CNS GLs	CNS GLs	CNS GLs
PS评分低且有胸部症状的患者	17 Gy	8.5 Gy	1-2 周
任何部位转移PS评分低患者	8-20 Gy	8-4 Gy	1 天-1 周

表5. 常规分割放疗的正常组织剂量-体积限量

危及器官	30-35 分次的限量
脊髓	最大≤50 Gy
肺	V20≤35%; V5≤65%; MLD ≤20 Gy
心脏	V40≤80%; V45≤60%; V60≤30%; 平均≤35 Gy
食管	Mean≤34 Gy; Max≤105%处方剂量
臂丛	Max≤66 Gy

Vxx =全危及器官接受≥xx Gy的百分比。

图 1. ICRU62号文件靶区定义图示



Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinic

PRINCIPLES OF RADIATION THERAPY - References (8 of 9)

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新辅助和辅助化疗的化疗方案

顺铂 50 mg/m^2 days 1 and 8; 长春瑞滨 25 mg/m^2 days 1, 8, 15, 22, 每 28 天 为一周期，共 4周期[a]
顺铂 100 mg/m^2 day 1; 长春瑞滨 30 mg/m^2 days 1, 8, 15, 22; 每28天为一周期 共4周期[b,c]
顺铂 75-80 mg/m^2 day 1; 长春瑞滨 25-30 mg/m^2 days 1 + 8, 每21天为一周期 共4周期
顺铂 100 mg/m^2 day 1; 伊托泊甙 100 mg/m^2 days 1-3, 每28天为一周期 共4周期[b]
顺铂 80 mg/m^2 days 1, 22, 43, 64; 长春碱 4 mg/m^2 days 1, 8, 15, 22, 29 接着从第43天开始每2周给药, 每21天为一周期 共4周期[b]
顺铂 75 mg/m^2 day 1; 吉西他滨 1250 mg/m^2 days 1, 8, 每21天为一周期 共4周期
顺铂 75 mg/m^2 day 1; 多西紫杉醇 75 mg/m^2 day 1 每21天为一周期 共4周期[d]
顺铂 75 mg/m^2 day 1, 培美曲塞 500 mg/m^2 day 1 用于腺癌和大细胞癌或NSCLC非特指型 (无特殊组织学亚型) 每21天为一周期 共4周期

有并发症或无法耐受顺铂患者的化疗方案
紫杉醇 200 mg/m^2 day 1, 卡铂 AUC 6 day 1, 每21天为一周期[e]

[a]Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-lung cancer. N Engl J Med 2005;352:2589-2597.
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与放疗联用的化疗方案

同步化疗/放疗方案

顺铂 50 mg/m^2 on days 1, 8, 29, and 36; 伊托泊甙 50 mg/m^2 days 1-5, 29-33; 同步胸部放疗[a] (首选)*
顺铂 100 mg/m^2 days 1 and 29; 长春碱 5 mg/m^2/每周 x 5; 同步胸部放疗[b] (首选)
卡铂AUC 5 on day 1, 培美曲塞 500 mg/m^2 on day 1 每21天为一周期 共4周期; 同步胸部放疗[c] (非鳞癌)
顺铂 75 mg/m^2 on day 1, 培美曲塞 500 mg/m^2 on day 1 每21天为一周期 ,共3周期; 同步胸部放疗[d] (非鳞癌)

序贯化疗/放疗方案

顺铂 100 mg/m^2 on days 1 and 29; 长春碱 5 mg/m^2/每周 on days 1, 8, 15, 22, and 29; 接着行放疗[b]
紫杉醇 200 mg/m^2 静滴超过3小时on day 1; 卡铂 AUC 6静滴超过60 分钟on day 1 ，每周为一周期，共2周期，接着行胸部放疗[e]

同步化疗/放疗后化疗方案

紫杉醇 45-50 mg/m^{2}每周; 卡铂 AUC 2, 同步胸部放疗后紫杉醇 200 mg/m^{2}联合 卡铂 AUC 6[e] 2周期。
顺铂 50 mg/m^2 on days 1, 8, 29, and 36; 伊托泊甙 50 mg/m^2 days 1-5, 29-33; 同步胸部放疗后再2周期 顺铂 50 mg/m^{2}联合伊托泊甙 50 mg/m^2 (2B类证据)[a]

*这个方案可以用于新辅助化放疗。顺铂 和伊托泊甙是首选方案。如果因为患者无法耐受同步足量的顺铂和放疗，而已经用过每周的卡铂联合紫杉醇 ，治疗医师应该考虑在局部治疗结束后予2周期足够剂量的含铂治疗。

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进展期或转移性疾病的系统性治疗 (1 OF 3)

进展期疾病:

在进展期肺癌中，可能获益最高，同时医师和病人都评价毒性可以接受的药物方案应该在初治时给予。

分期、体重下降、行为能力状态和性别预测生存。

与最佳支持相比，以含铂方案延长生存、改善症状控制和得到好的生活质量。

NSCLC的组织学类型在选择系统治疗时很重要。

在合适的病人中，新药联合铂类的效率达到平台，总有效率(≈25%-35%)、疾病进展时间(4-6 个月)、中位生存 (8-10 个月)、1年生存率(30%-40%)。

任何年龄的不合适病人（PS评分3-4分）不能从细胞毒治疗中获益，除了EGFR突变阳性患者应用厄罗替尼外。

一线治疗

贝伐单抗 +化疗或单纯化疗的适应症是PS0-1分晚期或复发NSCLC患者。

贝伐单抗应该连续应用到疾病进展。

西妥昔单抗+ 长春瑞滨/顺铂 是PS评分0-1分患者的治疗选择(2B类证据)。

厄罗替尼推荐用于EGFR敏感突变患者的一线治疗，而不应该用于EGFR突变阴性或EGFR突变状态未明的患者的一线治疗。

阿法替尼的适应症是EGFR敏感突变的特定病人。

克唑替尼的适应症是有ALK重排的特定患者。

与顺铂/吉西他滨比较，在组织学类型非鳞癌的患者中顺铂/培美曲塞有更好的疗效和减少的毒性。

与顺铂/培美曲塞比较，鳞癌患者中顺铂/吉西他滨有更好的疗效。

首选两药方案;第三种药增加有效率但不改善生存。

对于PS为2或老年患者， 单药治疗或含铂的联合治疗是合理的选择。

顺铂或卡铂与以下任何一种药物联合都是有效的：紫杉醇, 多西紫杉醇, 吉西他滨,伊托泊甙, 长春碱, 长春瑞滨, 培美曲塞, 或白蛋白结合紫杉醇。

新药/非铂类联合方案在现有数据显示有效和毒性可耐受的情况下， 可视为替代方案(如,吉西他滨/多西紫杉醇, 吉西他滨/长春瑞滨)。

见维持化疗,二线和三线治疗NSCL-F (2 of 3)

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进展期或转移性疾病的系统性治疗(2 OF 3)

维持治疗

继续维持指的是应用一线治疗中至少一种药物继续维持治疗是指在一线治疗4~6个周期之后， 如果没有出现疾病进展， 使用至少一种在一线治疗中使用过的药物进行治疗。 换药维持治疗是指在一线治疗4~6个周期之后， 如果没有出现疾病进展， 开始使用另一种不包含在一线方案中的药物进行治疗。

继续维持:与化疗联用的贝伐单抗和西妥昔单抗应该继续应用，直到出现疾病进展证据或不可接受的毒性, 根据临床研究设计支持继续使用这些药物。

- 4-6周期含铂两药化疗联合贝伐单抗后贝伐单抗维持 (1类证据)。
- 4-6周期顺铂, 长春瑞滨,联合西妥昔单抗后西妥昔单抗维持 (1类证据)。
- 组织学类型非鳞状细胞癌的患者， 4-6周期顺铂+培美曲塞化疗后培美曲塞维持 (1类证据)。
- 组织学类型非鳞状细胞癌的患者， 4-6周期贝伐单抗+顺铂+培美曲塞后贝伐单抗+培美曲塞维持。
- 4-6周期含铂两药化疗后吉西他滨维持 (2B类证据)。

换药维持治疗: 两个研究表明在一线化疗4-6周期后无疾病进展，应用培美曲塞或厄罗替尼，在无进展生存和总生存方面有获益。

- 组织学类型非鳞状细胞癌的患者，一线含铂两药化疗4-6周期后，应用培美曲塞维持(2B类证据)。
- 一线含铂两药化疗4-6周期后，应用厄罗替尼维持(2B类证据)。
- 鳞状细胞癌的患者，一线含铂两药化疗4-6周期后，应用多西紫杉醇维持(2B类证据)。

密切随访是没有维持治疗患者的合理替代方案。

二线治疗

在一线化疗中或化疗后出现疾病进展的患者, 单药多西紫杉醇, 培美曲塞, 或厄罗替尼是确定的二线药物。

- 多西紫杉醇 优于 长春瑞滨 或异环磷酰胺
- 在腺癌或大细胞癌患者中，培美曲塞 与 多西紫杉醇相似而毒性低 。厄罗替尼优于最佳支持治疗。
- 阿法替尼适用于EGFR敏感突变的特定病人。

三线治疗

PS 0-2患者，如果先前未用过，可选用多西紫杉醇, 培美曲塞 (非鳞癌), 厄罗替尼,或吉西他滨 (所有选项都是2B类证据)。

疾病进展后的维持

除了应用靶向药物（厄罗替尼、吉非替尼、阿法替尼、克唑替尼）有客观消退的EGFR敏感突变或ALK重排的患者外，其他药物在确定疾病进展后不能继续应用（除选择性情况）。(参考讨论部份)

见NSCL-F 中的特殊系统药物(3 of 3)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

进展期或转移性疾病的系统性治疗(3 OF 3)
下列药物用于治疗NSCLC患者，多为联合应用，有些为单药使用（如，维持治疗或二线治疗）

顺铂[1-9]
卡铂[4,6-11]
紫杉醇[1,4,6,8-11]
多西紫杉醇[5,7,8,12,13]
长春瑞滨[7,9,10]
吉西他滨[3,5,6,8,9,13]
伊托泊甙[4]
伊立替康[9]
长春碱
丝裂霉素
异环磷酰胺[12]
培美曲塞[14,15]
厄罗替尼[16]
贝伐单抗[17]
西妥昔单抗[18]
白蛋白结合紫杉醇[19-21] †
克唑替尼[22]
阿法替尼[23]

[1]Bonomi P, Kim K, Fairclough D, et al. Comparison of survival and quality of life in advanced non-small cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin:results of an Eastern Cooperative Oncology Group trial. J Clin Oncol 2000;18:623-631.
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† Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (dexamethasone, H2 blockers, H1 blockers) are contraindicated.

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癌症幸存者护理

NSCLC长期随访

癌症随访

前两年每6-12个月，病史、体检和胸部CT扫描±增强，接着每年病史、体检和不增强的胸部CT扫描±增强
每次随访的吸烟状态评估；需要进行戒烟咨询和指导。

免疫接种

每年流感疫苗、带状疱疹疫苗接种
必要时行肺炎球菌疫苗接种和复种

促进健康的建议[1]

保持健康的体重
养成积极运动的生活方式 （规律的体育运动： 一周中几乎每天都应进行30分钟中等强度的体育运动）
健康饮食， 以蔬菜类为主
如果饮用酒精类饮料， 应限制酒精的摄入

其他健康监测

常规血压、 血脂、 血糖监测
骨健康： 适当时行骨密度检测
口腔健康： 常规口腔检查
日常防晒

资源

National Cancer Institute Facing Forward: Life After Cancer Treatment
http://www.cancer.gov/cancertopics/life-after-treatment/allpages

癌症筛查推荐[2,3]

以下推荐适用于标危人群，高危患者应予个体化处理。

结直肠癌:
See NCCN Guidelines for Colorectal Cancer Screening
前列腺癌:
See NCCN Guidelines for Prostate Cancer Early Detection
乳腺癌:
See NCCN Guidelines for Breast Cancer Screening

[1] ACS Guidelines on Nutrition and Physical Activity for Cancer Prevention: http://www.cancer.org/docroot/PED/content/PED_3_2X_Diet_and_Activity_Factors_That_Affect_Risks.asp?sitearea=PED (Accessed November 30, 2012)
[2] Memorial Sloan-Kettering Cancer Center Screening Guidelines: http://www.mskcc.org/mskcc/html/65279.cfm (Accessed November 30, 2012)
[3] American Cancer Society Guidelines for Early Detection of Cancer: http://www.cancer.org/docroot/PED/content/PED_2_3X_ACS_Cancer_Detection_Guidelines_36.asp?sitearea=PED (Accessed November 30, 2012)

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其他基因改变患者的靶向药物

基因改变 (如,驱动事件)	肺癌中可用的抗驱动事件活性靶向药物
EGFR突变	厄罗替尼,[1] 吉非替尼,[2] 阿法替尼[3]
ALK 重排	克唑替尼[4]
HER2 突变	曲妥珠单抗,[5]阿法替尼[6]
BRAF 突变	**vemurafenib,[7] dabrafenib[8]**
MET 扩增	克唑替尼[9]
ROS1 重排	克唑替尼[10]
RET重排	**cabozantinib[11]**

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表 1. TNM定义*

T　原发肿瘤

T　原发肿瘤

TX 原发肿瘤不能评估， 或痰、 支气管冲洗液找到癌细胞但影像学或支气管镜没有可见的肿瘤。

T0 没有原发肿瘤的证据。

Tis 原位癌。

T1 肿瘤最大径≤3 cm， 周围被肺或脏层胸膜所包绕， 支气管镜下肿瘤侵犯没有超出叶支气管近端 （即没有累及主支气管）[a]。

T1a 肿瘤最大径≤2 cm

T1b 肿瘤最大径>2 cm但≤3 cm

T2 肿瘤>3 cm但≤7 cm或者肿瘤具有以下任一特征[b]：

- 累及主支气管， 但距隆突≥2 cm
- 侵犯脏层胸膜
- 伴有扩展到肺门的肺不张或阻塞性肺炎， 但未累及全肺

T2a 肿瘤最大径>3 cm但≤5 cm

T2b 肿瘤最大径>5 cm但≤7 cm

T3 肿瘤>7 cm或肿瘤已直接侵犯了下述结构之一者： 胸壁 （包括肺上沟瘤） 、 膈肌、 膈神经、 纵隔胸膜、 心包壁层； 或肿瘤位于距隆突2 cm以内的主支气管[a]， 但尚未累及隆突； 或伴有累及全肺的肺不张或阻塞性肺炎或原发肿瘤同一叶内出现分散的单个或多个瘤结节。

T4 任何大小的肿瘤已直接侵犯了下述结构之一者： 纵隔、 心脏、 大血管、 气管、 喉返神经、 食管、 椎体、 隆突； 同侧非原发肿瘤所在叶的其他肺叶出现分散的单个或多个瘤结节

N　区域淋巴结

Nx 区域淋巴结不能评估。

N0 无区域淋巴结转移。

N1 转移至同侧支气管旁淋巴结和/或同侧肺门淋巴结， 和肺内淋巴结，包括直接侵犯。

N2 转移至同侧纵隔和/或隆突下淋巴结。

N3 转移至对侧纵隔淋巴结、 对侧肺门淋巴结、 同侧或对侧斜角肌或锁骨上淋巴结。

M　远处转移

Mx 远处转移不能评估。

M0 无远处转移。

M1 有远处转移。

M1a 对侧肺叶出现分散的单个或多个瘤结节； 胸膜结节或恶性胸腔 （或心包） 积液c

M1b 远处转移

[a]任何大小的非常见的表浅播散的肿瘤， 只要其浸润成分局限于支气管壁， 即使临近主支气管， 也定义为T1。

[b]肿瘤大小≤5 cm或者大小无法确定的T2肿瘤定义为T2a， 肿瘤>5 cm但≤7 cm的T2肿瘤定义为T2b。

[c]大多数肺癌患者的胸腔积液 （以及心包积液） 由肿瘤引起。 但是有极少数患者的胸腔积液 （心包积液） 多次细胞学病理检查肿瘤细胞均呈阴性， 且积液为非血性液， 亦非渗出液。 如综合考虑这些因素并结合临床确定积液与肿瘤无关时， 积液将不作为分期依据， 患者仍按T1、T2, T3, 或 T4分期。

*经许可使用. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumors. J Thorac Oncol 2007;2:706-714.

表 2. 解剖分期和预后组

隐匿癌	TX	N0	M0
0期	Tis	N0	M0
IA期	T1a	N0	M0
	T1b	N0	M0
IB期	T2a	N0	M0
IIA期	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
IIB期	T2b	N1	M0
	T3	N0	M0
IIIA期	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
IIIB期	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
IV期	Any T	Any N	M1a
	Any T	Any N	M1b

经the American Joint Committee on Cancer (AJCC) 许可使用, Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

表3. 描述符, T 和M 分类, 和分期分组*

第6版 T/M 描述符	第7版 T/M	N0	N1	N2	N3
T1 (2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (<2-3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (5 cm)	T2a	IB	**IIA**	IIIA	IIIB
T2 (<5-7 cm)	T2b	**IIA**	IIB	IIIA	IIIB
T2 (>7 cm)	T3	**IIB**	**IIIA**	IIIA	IIIB
T3侵犯胸壁等		IIB	IIIA	IIIA	IIIB
T4 (同一肺叶结节)		**IIB**	**IIIA**	**IIIA**	IIIB
T4 侵犯心脏等	T4	**IIIA**	**IIIA**	IIIB	IIIB
M1 (同侧肺)		**IIIA**	**IIIA**	**IIIB**	**IIIB**
T4 (胸腔积液)	M1a	**IV**	**IV**	**IV**	**IV**
M1 (对侧肺)		IV	IV	IV	IV
M1 (远转)	M1b	IV	IV	IV	IV

方格中粗体字代表同第6版相比该期别所包含的TNM类别有改动

*经许可使用。 Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumors. J Thorac Oncol 2007;2:706-714.

Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

目录

概述

在美国， 肺癌是癌症死亡的主要原因。 2014年美国肺癌和支气管癌的新发病例估计有224,210例 （男性116,000例， 女性108,210例） ， 死亡159,260例 （男性86,930例，女性72,330例）。[1]只有16.6%的患者在确诊肺癌后能生存5年或以上。(http://seer.cancer.gov/statfacts/html/lungb.html).[2]
然而, 近10年来肺癌方面的很多进展 (例如, 筛查,诊断和治疗微创技术，靶向)。[3,4]肺癌的常见症状包括咳嗽、呼吸困难、体重下降和胸痛，有症状的病人常有慢性阻塞性肺病。[5]
指南更新的摘要叙述了流程的最新版本, 也加入到这个更新的讨论文本中(见 NCCN 指南的 NSCLC)。根据定义，NCCN 指南不能编入所有可能的临床变化而且并不试图代替好的临床判断或个体化治疗。除了在制订这些指南的过程中 NCCN 指南专家组已经讨论过的规则。

危险因素

吸烟是肺癌的主要危险因素, 它与多数肺癌相关死亡有关 (http://www.surgeongeneral.gov/library/smokingconsequences/)[6-11]。
烟草的烟中包含多种致癌化学物质(如, 亚硝胺类, 二羟环氧苯并(a)芘). [10,12]随着每天吸烟支数以及吸烟年数(如,包一年吸烟史)的增多，患肺癌的危险增加。非吸烟者因“二手烟”而发展成肺癌的危险相对升高 (RR=1.24);也有其他研究报导了中度危险 (危险比 [HR]=1.05) [8,12-15] 。氡气是226镭的衰变产物， 有放射性， 也是导致肺癌的原因[6,16-19]。据美国环保总署的估计， 不吸烟者中肺癌主要病因是氡气， 而被动吸烟也是重要因素 (http://www.epa.gov/radon/healthrisks.html)。
石棉是一种已知的能致癌的无机化合物， 它可以分裂为空气传播的碎片，曝露于空气中的石棉纤维会增加人们尤其是吸烟人群罹患肺癌的危险。据估计约有 3%~4%的肺癌发病是由于曝露于石棉 [20]。除此之外， 其他可能的危险因素包括反复发作的肺部感染，肺结核继发疤痕形成，家族史以及曝露于双（氯甲基） 乙醚、 多环芳香烃、 铬、镍、 有机砷化合物等其他致癌物 [21,22]。
国际癌症研究所（The International Agency for Research on Cancer）列出了多个已知的致癌因子, 包括砷、铬、石棉、镍、镉、铍、二氧化硅和汽车尾汽. [23,24]石棉也可导致恶性胸膜间皮瘤 (见 NCCN 恶性胸膜间皮瘤指南)。
尚不清楚激素替代治疗(HRT)是否影女性肺癌危险。这方面已经发表了超过20个研究，但结果仍有争议 。在一个大样本的随机对照研究中,[25] 绝经后妇女用雌激素联合孕激素替代治疗，并未增加肺癌发生率;但是非小细胞肺癌(NSCLC)的死亡率却是增加的.[25]

预防和筛查

约85%~90%以上的肺癌由吸烟所致[9]。 根据美国医事总署 （Surgeon General）的报告（下方两个链接） ， 主动吸烟和被动吸烟都可以导致肺癌。主动吸烟与肺癌的这种因果关系也存在于其他肿瘤中， 比如食管癌、 口腔癌、 喉癌、 咽癌、 膀胱癌、 胰腺癌、 胃癌、 肾癌和宫颈癌以及其他疾病状态

(http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/executivesummary.pdf). 。 吸烟几乎可以危害全身的每一个器官。嗜烟者比无嗜烟者的死亡率更高[26]。 和吸烟者生活在一起的人群罹患肺癌的风险上升20%~30% (http://www.surgeongeneral.gov/library/secondhandsmoke/report/executivesummary.pdf). 烟草中还含有高度成瘾性物质尼古丁， 这使问题进一步复杂化。 肿瘤医生应该鼓励患者戒烟， 尤其是癌症患者 (http://www.smokefree.gov/). 5 A's 结构是一个有用的工具(指的是, 问Ask, 建议Advise, 评估Assess, 帮助Assist, 安排Arrange) (http://www.ahrq.gov/clinic/tobacco/5steps.htm). 最有益的是患者戒烟。持续吸烟与第二原发癌、治疗并发症和生存下降有关。某些外科医生对当前嗜烟者不进行手术。

通过改变行为联合促进戒烟药物[美国食品药物管理局 （FDA） 已批准的药物]的计划对戒烟很有用[见Treating Tobacco Use and Dependence: 2008 Update， 由卫生保健研究和质量机构 （AHRQ） 发布] （(http://www.ahrq.gov/professionals/clinicians-providers/resources/tobacco/treating-tobacco-use.html). 美国癌症协会有一个戒烟指南 (http://www.cancer.org/healthy/stayawayfromtobacco/guidetoquittingsmoking/index). E-Quit 研究应用电子邮件帮助嗜烟者戒烟 (http://www.cancer.org/healthy/stayawayfromtobacco/acs-gwu-e-quit-study).

戒烟品包括尼古丁替代品 （如， 口香糖、 吸入剂、片剂、 鼻腔喷雾、贴片） 、 安非他酮缓释剂和varenicline. 。 研究表明varenicline的戒烟效果优于安非他酮或尼古丁贴剂.[31-33]
然而, 近30%的患者在使用varenicline期间会出现恶心。[34]
Varenicline预防烟瘾复发的效用如何仍不十分确定。[35] 使用varenicline还会出现神经精神症状， FDA就此已发布警告 (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106540.htm). Varenicline还和其他异常有关系(如,视觉障碍、运动障碍、神志不清、心血管疾病) 因而在货车和汽车驾驶员、警察和飞机交通调度员中禁用。[36]
安非他酮还和严重神经精神病学症状有关 (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020711s036lbl.pdf)。
尼古丁代替品比varenicline或安非他酮的副作用小。[37]
尽量存在潜在的副作用，鼓励患者应用药物促进戒烟可能有更多获益。[37]

肺癌仍然是世界范围内肿瘤死亡的首要原因， 而肺癌疗效得不到提高的主要障碍是诊断时病期已晚。[38,39] 由于认识到局限期的肿瘤有可能被治愈，筛查和早期检测似乎对其他实体瘤 (如,宫颈、结肠) 的生存有利，因此肺癌适合于普查。据报道用低剂量螺旋 CT 进行肺癌筛查是有应用前景的 [40-42]。

美国国家肺部筛查试验 （NLST， ACRIN方案A6654） 是一项随机对照研究， 有超过53,000名正在吸烟或既往吸烟的重度吸烟者参加， 目的是比较低剂量螺旋CT和胸片进行肺癌筛查的风险和获益。[43]

NLST 的数据表明， 与 X 线胸片相比， 对高危患者用低剂量螺旋 CT 筛查能使肺癌死亡率降低 20%。[44] 高危患者定义为包括每年吸烟 30 包的正在吸烟或既往吸烟的烟民 （既往吸烟的戒烟 15 年） 、 年龄 55~74 岁且无肺癌证据。[43,45] NLST 的其他信息见以下链接 http://www.cancer.gov/nlst. NCCN 、美国癌症协会、美国预防医学工作组和其他组织推荐对特定高危的当前嗜烟或既往嗜烟者采用低剂量螺旋 CT 进行肺癌筛查(见 NCCN 肺癌筛查指南)。

国际早期肺癌行动计划 （I-ELCAP） 已经在评估每年进行低剂量螺旋CT筛查是否能增加有肺癌危险因素的患者早期肺癌的检出率。 I-ELCAP的数据表明每年进行低剂量CT筛查可以检出I期肺癌。 I期肺癌患者如果立即进行手术切除肿瘤， 其10年生存率达92%， 然而所有未治疗的I期患者将在5年内死亡[48] 其他有关I-ELCAP的信息见 http://www.ielcap.org/index.htm.筛查能够增加早期肺癌的诊断率。NLST的数据显示肺癌CT筛查可降低死亡率。[44]

分类和预后因子

基于肺癌的生物学特性、 治疗和预后， 世界卫生组织 （WHO）将其分为两大类： 非小细胞肺癌 （NSCLC， 本指南所讨论的） 和小细胞肺癌（SCLC，见NCCN小细胞肺癌指南）。 NSCLC占所有肺癌病例的85%以上， 它主要包括2种类型： （1） 非鳞状细胞癌 （包括腺癌、 大细胞癌、 其他细胞类型） ； （2） 鳞状细胞 （表皮样）癌。腺癌是美国最常见的肺癌类型， 也是非吸烟患者中发生率最高的类型。一个国际专家组最近修改了肺腺癌的分类 (见本讨论中的肺癌的病理评价)。[49] 特定预后因子预测非小细胞肺癌患者的生存。好的预后因子包括疾病诊断时处于早期状态，好的行为能力状态(PS) (ECOG 0, 1, 或2), 无明显的体重下降 (下超过 5%), 和女性[50]

肺部结节的诊断评价

非小细胞肺癌NCCN指南的更新增加了一个部份评价可疑肺部结节(见诊断评价原理和相应流程页面)。[51] 这个诊断部份描述了如何评价在低剂量螺旋CT扫描中见到的可疑肺部结节。如前文所述，低剂量CT能降低肺癌所致死亡率，是检测肺癌有价值的工具。NLST的数据显示低剂量CT可以用于检测早期肺癌（可能是可治愈的）。[44] NCCN 肺癌筛选指南推荐低剂量CT用于当前和既往嗜烟的高危选择性无症状肺癌患者(如, 那些有≥30 包年嗜烟史者)。非小细胞肺癌（NSCLC）NCCN指南诊断流程加入了肺癌筛查NCCN指南的信息。危险评估应用于决定哪些个体是肺癌高危患者和适用低剂量CT。

在确定肺癌诊断和开始治疗前，所有表现和患者因素需经多学科诊断组认真评估。NCCN指南推荐对于在低剂量CT扫描上高度可疑的结节采取活检或手术切除，对于根据结节类型和根据患者的其他因素经多学科评价认为是低度可疑癌的，可以进一步随诊。(见NCCN指南的NSCLC危险评估).

然而，应该注意到低剂量CT常见假阳性结果(如, 良性的肺内淋巴结，非钙化肉芽肿) (见 NCCN 指南的肺癌筛查)。[44]在肺叶切除术前应该确定肺癌的组织学诊断。 一个开放性程序允许在肺叶切除、包括楔形切除或空蕊针穿刺活检等 更多的诊断步验以确认是癌。

NCCN指南推荐对于每例患者的诊断应该个体化，个体化依据是肿瘤大小和部位、纵隔和远处病灶是否存在、患者特征（如并发症）以及地方经验。诊断策略应经多学科组决定。 是否活检（包括什么类型的活检）或手术才合适的决定是根据NCCN指南流程列出的多个因素决定的 (见诊断评估原则)。例如,当术中诊断很困难或很危险时，术前活检可能是合适的。NCCN流程中所描述的哪种活检技术是合适的，决定于病灶的位置 (见诊断评估原则)。例如,对于可疑的外周结节，推荐采用径向支气管内超声(EBUS),导航支气管镜或经胸壁针吸(TTNA) [52]

如果活检或手术病理结果确定诊断是 NSCLC, 接着需进一步的评估和分期，以便于患者的健康护理团队可以决定最合适和有效的治疗计划 (见本讨论中的肺癌的病理评估和分期以及 NCCN 的 NSCLC 流程)。诊断、分期和计划性切除（如肺叶切除）是早期患者是理想手术程序。(见诊断评估原则)

肺癌的病理评估

组织学评估以进行肺癌的组织学类型分类、决定外侵程度、决定是原发肺癌或转移癌、确定手术切缘的受侵状态(如, 阳性或阴性切缘), 并进行分子诊断研究以确定是否存在特定的基因变异(如, 表皮生长因子受体突变[EGFR]) (见 NCCN指南 NSCLC流程的病理学评估原则) [53]。数据表明在特定基因变异或重排的患者中靶向治疗可能是非常有效的 (见本讨论中的EGFR突变和ALK基因重排部份) [3,54-59]

术前评估包括以下检查：支气管刷检, 支气管冲洗, 细针穿刺 (FNA)[42-46]活检, 中心穿刺活检, 支气管内活检, 和经支气管活检。[52,60]微创技术可以用于获取晚期不可手术NSCLC患者的标本。[61,62] 然而，应用小活检或细胞学的诊断可能更困难。[63]另外，对纵隔淋巴结进行系统取样以评估分期和治疗选项。同时需要排除(如肺结核、肉瘤样病) [64,65]。

如果活检或手术病理结果确定诊断是NSCLC, 接着需进一步的评估和分期，以便于患者的健康护理团队可以决定最合适和有效的治疗计划 (见后续的两个关于病理和分期的部份，也可见NCCN的NSCLC流程)。诊断、分期和计划性切除（如肺叶切除）是早期患者是理想手术程序。(见诊断评估原则)

术中评估肺叶切除或肺切除标本以确定手术切缘状态、诊断手术时发现的偶发结节以及评价区域淋巴结。术后评价提供了肿瘤类型分类的病理特征、分期和预后因素。手术病理报告应该包括WHO出版的肺癌组织学分类。[66]最近国际专家组修改了肺腺癌的分类（见腺癌）[49]

49

这个分类要求行免疫组织化学、组织化学和分子研究 (见 NCCN指南 NSCLC流程的病理评估原则) [67]。

另外，修改后的分类建议尽量少用笼统的分类（如，非小细胞肺癌），这是因为当明确组织学类型后，可以选择更有效的治疗。

腺癌

在修改后的腺癌分类中，不再应用支气管肺泡腺癌(BAC)和混合亚型的腺癌。[49]如果需要,可以使用“以前的BAC”这个名称。 腺癌的分类包括: 1) 原位腺癌 (AIS) (以前的BAC), 这是一个侵袭前病灶; 2) 微浸润腺癌(MIA); 3) 侵袭性腺癌 (包括以前的非粘液上皮BAC); 和 4) 变异型侵袭性腺癌(包括以前的粘液 BAC)。如果手术切除后，AIS和MIA的预后良好 。国际专家组和NCCN推荐所有腺癌患者检测EGFR敏感突变；而NCCN专家同时推荐这些患者检测间变淋巴瘤酶（ALK）基因重排。因为细胞学标本的异义，*AIS*, *MIA*和大细胞癌这三个名称不能小标本中应用。[49]

免疫组织化学染色

免疫荧光染色通常用于区分肺原发腺癌和肺转移性腺癌(如,来源于乳腺,前列腺,结直肠), 区分腺癌与恶性间皮瘤，确定肿瘤的神经内分泌状态。NCCN NSCLC流程中描述了免疫组织化学染色(见病理学评价原则)。然而，对于小标本推荐限制免疫组织化疗的应用，以保留足够的肿瘤组织用于分子研究，特别是晚期患者中更是如此。[62,68]

虽然细胞学可以区分腺癌与鳞癌,免疫组织化学对于小活检标本和/或细胞学标本中低分化NSCLC也是有用的。[49,69]

鳞状细胞癌经常是TTF-1 阴性而p63 阳性, 而腺癌通常TTF-1 阳性[40]这两个标志对于区分腺癌和鳞癌是足够的.[40,51] 其他标志(如, p40)对于区分鳞癌和腺癌可能也是有用的 。[70,71]

免疫组织化学最大的价值在于区分恶性间皮瘤与肺腺癌。[72，73]在腺癌中染色呈阳性的包括CEA (癌胚抗原), B72.3, Ber-EP4, MOC-31, 和TTF-1; 间皮瘤中这些都呈阴性。[74]间皮瘤中染色具有敏感性和特异性的包括WT-1, calretinin（钙网膜蛋白）, D2-40 (podoplanin抗体), [75] 和细胞角蛋白5/6.[72,73] 4种标志的组合可以用于区分间皮瘤和腺癌—2种间皮瘤阳性另外2种腺癌阳性而间皮瘤阴性— 包括钙膜蛋白 calretinin, 细胞角蛋白 cytokeratin 5/6 (或 WT-1), 癌胚抗原CEA, 和MOC-31 (或 B72.3, Ber-EP4, 或BG-8). [72,73,76]

因为绝大多数原发肺腺癌中TTF-1 阳性，所以TTF-1在区分肺原发腺癌与肺转移性腺癌中起重要作用。典型的鳞状细胞癌中TTF-1阴性[69]。然而，甲状腺癌来源的肿瘤TTF-1也可以阳性。[77]

另外，甲状腺球蛋白在来自甲状腺癌的病灶中阳性，而在肺癌中呈阴性。肺腺癌中CK7+和CK20- ，然而来自结直肠腺癌的转移灶中通常CK7- 和CK20+.

CDX-2是转移性胃肠道肿瘤的一个标记物， 可用于鉴别原发性肺癌和胃肠道肿瘤肺转移。 所有的典型和不典型类癌均为嗜铬素和突触素染色阳性， 而小细胞肺癌中25%染色为阴性。

虽然细胞学诊断NSCLC一般是可信的，而诊断SCLC较为困难[52,69,78]。但是很多SCLC患者有其CT和临床表现特征 (如, 大块淋巴结转移, 纵隔受侵)。多数SCLC患者对TTF-1E 免疫反应; 典型 的SCLC CK34βE12和p63阴性[79,80]。许多SCLCs的神经内分泌分化标记物， 如嗜铬素A、神经特异性烯醇酶、 神经细胞粘附分子（NCAM） 以及突触素， 染色阳性。然而， 仅凭这些标记物无法区分SCLC和NSCLC， 因为约10%的NSCLCs对至少一种上述的神经内分泌标记物有免疫反应[81]，数据揭示，检测微小RNA （miRNA） 表达可用于鉴别SCLC与NSCLC。[82]

分期

NCCN指南应用AJCC (第7版) 肺癌分期系统[83]。表 2列举了这个分期分组 (见NCCN NSCLC流程中的分期)。TNM分类法的描述列在表3，分期表（见NCCN NSCLC流程中的分期）。肺癌分期系统由国际肺癌研究协会（IASLC）修订[84,85] 并被AJCC采纳[86,87] 。最近的TNM分期修订版 (AJCC第7彼)从2010年1月1日开始对新诊断病例生效。[66] 根据AJCC分期系统，局部晚期为III期； 晚期为IV期。

病理学分期既包括临床分期中无创性检查内容 （如病史、 体检、 影像学检查）， 也包括那些有创性的分期手段 （即开胸术、 纵隔镜检查切除淋巴结）[88]。

2003~2009年，美国人肺癌的总体5年相对生存率为16.6%。在肺癌和支气管癌病例中， 15%确诊时肿瘤仍局限于原发部位 （局限期）； 22%确诊时肿瘤已扩展至区域淋巴结或直接侵犯周围组织；57%确诊时肿瘤已发生转移（远处转移）； 其余6%分期信息不明。 相对应的5年相对生存率为： 局限期54%，区域转移者26%， 远处转移者3.9%， 分期不明者7.8% (http://seer.cancer.gov/statfacts/html/lungb.html) 。但是， 这些数据包含了小细胞肺癌， 而后者的预后更差。

病理分期为I期的NSCLC行肺叶切除术后， 其5年生存率达45%~65%， 这取决于患者是处于IA期还是IB期， 以及肿瘤的生长部位[89]。 另一项在I期患者中开展的研究 （n=19,702） 发现： 82%的患者接受了手术切除， 其5年总生存率为54%； 而未治的I期NSCLC患者的5年生存率仅6%[90]。 拒绝手术 （尽管并不推荐） 的I期患者中， 78%在5年内死于肺癌。

预后和预测生物标记

多种生物标记物可以作为NSCLC的预后判断和疗效预测标记物。预测生物标记物是预示疗效的生物分子； 即，生物分子与患者的治疗结果之间存在交互作用。预测生物标志是一种不依赖于所接受的治疗而能预测患者生存的生物分子；也就是说生物分子是肿瘤固有侵袭性的预测因子 (见本节的最后)。

预测性生物标志包括： 表皮生长因子受体 （EGFR） 和ALK融合癌基因[其他基因融合（如棘皮动物微管相关蛋白样4 （EML4））与间变淋巴瘤激酶（ALK） 的融合]。其他生物标志，如HER2 (也称为ERBB2) 和 BRAF 突变, ROS1 和 RET 基因重排, 和MET 扩增(见NCCN指南NSCLC中基因修饰患者的靶向药物)。EGFR外显子19缺失或外显子21 L858R突变可以预测接受EGFR-TKI治疗的受益情况；因而这个突变称为敏感 EGFR突变(见本讨论的EGFR突变)[91,92]。出然而, 现EGFR外显子19缺失 （LREA缺失） 或外显子21 L858R突变似乎不能判断NSCLC患者的生存预后 （与治疗无关）[93]。ALK融合基因（即ALK基因重排）在一小部份NSCLC患者中证实是一个新的预测生物标志(见本讨论和NCCN指南NSCLC流程 中的病理学评价原则ALK基因重排部份)。最近证实的（如ROS1）其他基因重排（如基因融合）是靶向治疗敏感的[94-97]。

NSCLC 的 NCCN 指南推荐(1 类)对选择性患者（如腺癌患者）进行 EGFR 突变和 ALK 基因重排的检测，使有这些基因异常的患者能接受有效的治疗 (如，厄罗替尼、阿法替尼、克唑替尼) (见本讨论的靶向治疗)[98]。虽然很罕见，EGFR 突变或 ALK 基因重排患者可以杂有鳞状细胞癌 [99,100] 。因为，对无嗜烟史、检测的是小活检标本或报告混合组织学类型时，检测 EGFR 突变或 ALK 重排是合理的。

NSCLC 患者可能有其他基因改变(见非小细胞肺癌 NCCN 指南基因改变患者靶向药物)。[54,101,102] 多标志检测的变异筛查实验 (如， Sequenom's MassARRAY system, SNaPshot Multiplex System) 的发展已经能够检测超过 50 个变异位点（包括 EGFR 在内）(http://www.mycancergenome.org/content/disease/lung-cancer) [103]。但是因为基因重排没有点突变，这些系统无法检测。ALK重排的检测应用 荧光原位杂交技术(FISH) (见本讨论中的ALK基因重排部份)。新一代的测序(NGS)能检测多套突变和基因重排[104-106]。其他驱动突变和基因融合（即，驱动事件）也得到证实，包括HER2（也称为ERBB2）和BRAF突变，ROS1和RET基因重排和MET扩增[95,97,107-113]。这些基因改变患者所需的靶向药物都可获得，虽然FDA批准用于其他适应症(见非小细胞肺癌NCCN指南的基因改变患者的靶向药物) [104,114]。因而，NCCN指南推荐应用多通道/新一代基因修饰检测以保证患者接受最合适的治疗；患者可能入选某种这类靶向药物的临床试验。已有多个在线资源描述了NSCLC驱动事件，如DIRECT(DNA-mutation Inventory to Refine and Enhance Cancer Treatment，改进和增强癌症治疗的DNA突变清单) [115]和*My Cancer Genome* (http://www.mycancergenome.org/content/disease/lung-cancer)。[116]

预测生物标志包括 K-ras 癌基因、核苷酸剪切修复复合体 （ERCC1） 的 5' 核酸内切酶。与无 K-ras 突变相比， 携带 K-ras 突变预示 NSCLC 患者的生存结果较差 （与治疗无关）(见本讨论的 *KRAS* 突变)[117]。K-ras 突变还预示铂类/长春瑞滨化疗或 EGFR TKI 治疗无效 [91,118,119]。与 ERCC1 低水平相比， ERCC1 高水平预示 NSCLC 患者的生存结果更佳 （与治疗无关）[120,121]。

EGFR 突变

NSCLC患者最常见的EGFR突变为外显子19缺失(E19del [LREA序列的保守缺失]见于45%的患者)和外显子21突变 (L858R见于40%的患者). ，二者都会导致酪氨酸激酶结构域活化， 且都与肿瘤对小分子TKIs（厄洛替尼、 吉非替尼和阿法替尼）的敏感度相关(见本讨论中的靶向药物)[122]。因而，这些突变称为敏感EGFR突变。因为吉非替尼的应用受限制，在美国厄罗替尼通常用于EGFR敏感突变的选择性病人。但是如果能获得吉非替尼也可以用。阿法替尼是一种口服的TKI，能抑制包括EGFR 和HER2在内的整个 ErbB/HER家族[123,124] 。The FDA 最近批准阿法替尼用于有敏感EGFR突变的转移性NSCLC非鳞癌患者一线治疗[125,126]。这些EGFR敏感性突变见于近10%的高加索人NSCLC患者及高达50%的亚洲患者[127] 。其他的药物敏感性突变类型包括外显子21 （L861Q）和外显子18（G719X） 点突变[128] 。TKI原发耐药与KRAS突变和ALK基因重排相关。T790M突变可导致TKI类药物耐药，有关报告显示该突变类型见于约50%的肿瘤初始对厄罗替尼有效后进展的患者。[129-132]然而，研究显示T790M 突变也出现在既往未接受TKI治疗的患者中[133]。获得性耐药也与从NSCLC到SCLC组织学转化和上皮间质化有关(见NCCN NSCLC流程的病理学评估原则) [134,135]。

DNA突变分析是一种检测EGFR状态的首选方法。[136-138] 多种DNA突变检测分析可以用于检测肿瘤细胞的EGFR突变状态。外显子18~21（或仅外显子19和21） 的直接DNA测序是一种合理的选择；但此外还有更多敏感的检测方法可供使用[127,137,139-141] 。多重PCR突变筛选检测(如, Sequenom's MassARRAY system, SNaPshot Multiplex System) 可以检测包括EGFR在内的超过50个位点的突变[103]。

药物敏感性EGFR突变—Exon19del(LREA缺失)和L858R—的预测作用已经证实。这些突变的患者应用厄罗替尼、吉非替尼或阿法替尼有明显较好的疗效。[122]回顾性研究表明细支气管肺泡腺癌和EGFR突变患者单药治疗的客观有效率约80%、中位进展时间13个月[91]。 前瞻性研究表明北美NSCLC非鳞癌和EGFR突变(53% Exon19del [LREA 缺失], 26% L858R, 21% 其他突变) 患者，客观有效率55%、中位PFS9.2个月[92]。在纯鳞状细胞癌患者中EGFR突变检测通常不推荐检测，除非在从不吸烟或混合组织学类型，如果是小活检（即非手术切除标本）只能用于组织学评价[99]。 数据表明EGFR突变可以出现在腺鳞癌患者中，这种类型在小活检标本中很能与鳞状细胞癌鉴别[99]。

最近的数据表明厄罗替尼或阿法替尼(代替标准一线化疗)应该用于一线治疗前确定是EGFR突变的患者一线系统治疗中[126,142-147] 。数据表明与标准的化疗比较，EGFR突变患者应用EGFRTKI改善PFS，虽然OS没有统计学差异[126,142]。与那些接受化疗者相比，接受厄罗替尼者治疗相关的严重副反应较少[142,148]。最近一个III 期随机研究中，与顺铂/培美曲塞化疗患者比较，应用阿法替尼者的咳嗽、呼吸困难改善，而且健康相关生活质量提高。[148] 但是，阿法替尼出现4例潜在的治疗相关死亡，而化疗组中未出现。[126]

ALK 基因重排

美国估计约2%~7%的NSCLC患者为ALK基因重排，绝对数量约在10,000例[59]。 这些患者对EGFR-TKIs耐药， 但在其它临床特征和EGFR突变患者相似 （即为腺癌、 不吸烟或轻度吸烟患者），

但它们更常见于男性和可能更年轻。[102]这部分人群中， 大约30%的患者可能发生ALK重排[102,149]。ALK重排通常不出现在鳞状细胞癌中。虽然罕见，但是ALK重排患者中可以混杂有鳞状细胞组织类型[100]。小活检标本中准确判断组织学类型是一个挑战；因而患者可能不是纯鳞状细胞癌，而是混合型的鳞状细胞癌（或鳞状细胞成分）。NCCN 专家组推荐当小活检标本用于评价组织学类型、混合组织学类型或患者从未吸烟时要检测ALK重排。FISH法检测已被FDA批准用于ALK重排的检测，这是克唑替尼治疗前的先决条件。研究表明免疫组织化学可以用于ALK重排的筛查，如果免疫组织化学阳性，行FISH分析以确认。[98，150-153] NGS新一代测序也能用于评价是否有ALK重排[154.155]。

克唑替尼是 ALK、ROS1和 MET酪氨酸激酶抑制剂，FDA批准用于ALK基因重排(即ALK阳性)的局部晚期或转移性NSCLC患者。(http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202570s003lbl.pdf).[156-158]当应用于ALK重排的晚期NSCLC患者，克唑替尼显示有很高的有效率（＞60%）[59,159,160]。克唑替尼的副反应相对较少(如, 眼睛不适、水肿、短暂的肾功能改变) [159,161]。但是，少数病人出现危及生命的肺炎；对于这部份病人应该中止应用克唑替尼[156]。患者使用克唑替尼后快速起效而改善症状 (如，咳嗽、气促和疼痛), 然而克唑替尼的中位进展时间小于1年[162,163]。新的ALK 抑制剂正在研制中[164-169]。随机III期临床试验（PROFILE-1007）以及标准一线化疗(PROFILE 1014)[3,170] 正在比较克唑替尼与标准二线化疗。与单药化疗比较(多西紫杉醇或培美曲塞).，二线克唑替尼改善PFS和有效率[171]。

EGFR 突变和 ALK 重排通常是相互排斥的 [172,173] 。因而, 厄罗替尼（或吉非替尼）或阿法替尼不推荐用于 ALK 重排患者克唑替尼治疗复发后的二线治疗(见 NCCN 指南非小细胞肺癌的二线治疗) [101,102]。增加了一个克唑替尼进展后的患者二线治疗新的流程(见 NCCN 指南非小细胞肺癌) [159,174,175]。

KRAS 突变

数据表明接近 25%的北美腺癌人群有KRAS突变; KRAS是最常见的 突变. [57,91,104,114,119]KRAS 突变普遍与嗜烟有关. [176]形式上 , KRAS属于组成性活化, 能转化永生化细胞, 而且能启动增殖并存活.

KRAS 突变状态是生存的预后因素. KRAS突变患者较KRAS野生型者生存期明显较短. [117,119,177] KRAS 突变状态同时予预示EGFR-TKIs 疗效较差; 然而, KRAS 突变状态并不影响化疗疗效. [57,91,118] EGFR 和 KRAS突变明显是相互排斥的.[178]MEK抑制已经在进行临床试验,但是目前仍没有KRAS变异患者的靶向治疗. [114,179]

治疗方式

治疗NSCLC的3种常用手段是手术治疗、 放射治疗和化学治疗。 根据疾病状态， 这些手段可以单独或联合应用。 在后面部分将描述确立标准治疗方案的相关临床试验。

手术

一般情况下， I期或II期患者最有可能通过手术治愈[180]。 但是， 每一位考虑行根治性局部治疗的患者在接受评估时， 都应咨询胸部肿瘤外科医生的意见。 在任一非急诊手术治疗前， 应完成全面治疗计划的制订和必要的影像学检查。决定患者是否可以耐受手术或是否有不可手术的医学原因;某些病人认为是不能手术的，却可能可以耐受微创手术[180,181]医学原因不能手术的患者可能是立体定向消融放射治疗的适应症(SABR), 也称为立体定向体部放疗（SBRT）。如果对高危患者考虑立体定向体部放疗 （SBRT） 时， 建议进行多学科评估 （包括肿瘤放疗医生在内）[182] 。

手术治疗原则详见流程图， 在此进行总结（见NCCN指南NSCLC）。 应当由通过专科认证的胸外科医生来判断手术切除的可能性、 进行外科分期和实施肺切除术。 这些胸外科医生应积极参加针对肺癌患者的多学科综合治疗门诊和/或肿瘤委员会。罕见类型肺癌的特定患者的手术可能是合适的 (如，肺上沟、胸壁受累) (见NCCN指南NSCLC)[183]。病理分期为II期或以上的患者应当在肿瘤内科进行评估。术后的 IIIA期患者可考虑转诊至肿瘤放疗科。避免因各专科医生协作不良而导致治疗延误。

手术方式需根据病变范围和患者的心肺功能贮备进行选择。 如解剖位置合适且能够做到切缘阴性， 保留肺组织的解剖性切除术 （袖状切除术）优于全肺切除术； 否则， 只要身体条件允许， 应该行肺叶切除或全肺切除术[180,184,185]。亚肺叶切除术——肺段切除 （首选） 或楔形切除——适用于部分特定患者；肺实质切缘定义见 “NCCN指南NSCLC流程图” （见 “外科治疗原则” ）[186,187]。 与肿瘤消融术相比， 手术切除 （包括楔形切除术） 更优[180,185]。楔形切除可能改善疗效[188]。 然而， 对于那些肺功能严重不足本来不能手术的患者， 进行保留肺组织的切除术 ，如肺段切除术和楔形切除术是否对他们有用仍存在争议[180,185,189，190]。 这些患者可能更适合接受SBRT(见讨论中的立体定向放射部份) [191] 。

淋巴结清扫

一项随机研究（ACOSOGZ0030） ，在N0（无区域淋巴结转移）或N1 （有同侧支气管旁淋巴结和/或肺门淋巴结转移， 包括直接侵犯）的NSCLC患者中比较了在肺切除术中纵隔淋巴结取样与完全淋巴结清扫术。在经过系统淋巴结清扫淋巴结阴性的早期患者中，完全纵隔淋巴结清扫并不改善生存[192-194] 。 因而肺部手术中应进行系统性淋巴结取样是合适的；所有纵隔区应取样一个或多个淋巴结。

对于右侧肺癌，行纵隔淋巴结充分清扫时应包括2R、 4R、 7、 8、 9站淋巴结。左侧肺癌则应包括4L、 5、 6、 7、 9站淋巴结[192]。患者应行N1和N2淋巴结切除并定位 （美国胸科协会定位）， 最少对3个N2站的淋巴结进行取样或行完全淋巴结清扫术。 注意， IASCL（国际肺癌研究协会）的淋巴结图谱可能是有用的[195]。。 IIIA期 （N2） 患者在接受切除术时应行正规同侧纵隔淋巴结清扫术。 对于接受亚肺叶切除的患者，应当对适当的N1和N2淋巴结站进行取样活检， 除非因手术风险显著增加而在技术上不可行。

亚肺叶切除术—肺段切除（首选）或楔形切除—适用于部分特定患者（见 NCCN指南NSCLC流程的外科治疗原则 ）： 1） 不适合接受肺叶切除术； 2） 周围型结节≤2 cm且存在低危因素 （2B类） 。肺段切除（首选） 或楔形切除应当达到肺实质切缘1） ≥2 cm， 或2） ≥结节的大小。

IIIA期N2肺癌

手术在病理确诊为IIIA期 （N2） 患者中的地位， 已在NCCN指南 NSCLC流程中进行了讨论 （见 外科治疗原则）， 在此进行概述。在治疗前， 有必要通过放射学和有创性分期手段 （即支气管内镜超声引导下检查、 纵隔镜检查、 胸腔镜检查） 仔细评估是否为N2病变， 并应由多学科团队 （包含专科认证的胸外科医师） 来评估是否适合手术[196,197]。 多项随机对照试验显示， 手术不能改善这类患者的生存[198,199]。 但其中的一项研究（EORTC）只纳入了不可切除的患者[199]。

大多数临床医师同意， 对于术前评估没有纵隔受累且开胸见仅有一个淋巴结阳性 （<3 cm）的患者， 适合手术切除治疗[200]。对部分患者推荐新辅助治疗。在N2病变患者新辅助治疗中， 主张化放疗和化疗的NCCN机构各占一半[201]。但是，没有证据表明对IIIA (N2)患者在诱导治疗方案中加入放疗与单纯化疗比较能改善疗效[202]。也有临床医师认为， 对于病理学证实有多发淋巴结受累>3 cm的患者不适合手术； 推荐对这些患者使用根治性化放疗。

NCCN专家组认为， 手术可能适用于部分N2病变患者， 尤其是那些对诱导化疗有效的患者 （见NCCN指南 NSCLC流程中的手术治疗原则 ）[196,203] 。 然而， 新辅助化疗后行全肺切除是否合理仍存有争议[198,203-209]。 可切除的N2病变患者不应拒绝手术， 因为其中部分患者手术后有可能长期生存或治愈[203-210]。

胸腔镜肺叶切除术

电视辅助胸腔镜外科手术 （VATS）， 又称为胸腔镜肺叶切除术， 是一种微创外科治疗技术， 目前在肺癌的各个领域中都进行了相关研究[211,212] (见NCCN指南 NSCLC流程中的手术治疗原则)。已发表的数项研究显示胸腔镜肺叶切除术比标准胸廓切开术 （或胸膜切开术）有一些优势[213-217]。比如， 胸腔镜肺叶切除术引起的急性和慢性胸痛很少， 因而可以缩短住院时间[218,219] 胸腔镜肺叶切除术的术后并发症和死亡率低， 术中出血或局部区域复发的风险也小[220-224]。胸腔镜肺叶切除术同开胸肺叶切除术相比并发症更少，功能恢复更快[225-228]。

与常规开胸手术相比， I期NSCLC患者行胸腔镜肺叶切除术加淋巴结切除后的5年生存率、 远期生存及局部复发情况相似[229-232]。 胸腔镜肺叶切除术能改善老年患者及高危患者出院后的自理能力[233,234]。 数据显示胸腔镜肺叶切除术可改善患者完成术后化疗的承受力[235,236]。基于胸腔镜肺叶切除术在患者术后恢复容易和并发症较少方面的优势，只要不违反胸部手术切除标准原则，它作为一种可手术（且无解剖学和手术方面的禁忌证）患者的可接受术式，已被NCCN指南NSCLC流程推荐（见“外科治疗原则” ）[237-240]。 机器人 VATS 似乎比常规VATS更贵且手术时间更长。[241]

放射治疗

一般原则

放疗可以用作： 1） 无手术禁忌证的病灶可切除的NSCLC患者的辅助治疗手段； 2） 原发灶局部治疗（即因医学原因不可手术或不可切除的NSCLC患者的根治性放疗或SABR）； 和/或3） 无法治愈的NSCLC患者的姑息治疗方式[182,242]。 应由多学科小组决定NSCLC患者的治疗。放射治疗的目的是最大程度的肿瘤控制和最小的治疗毒性。非随机研究表明，4D适形放疗模拟、调强放疗/容积调强放疗（IMRT/VMAT）、图像引导放疗、运动管理策略和质子治疗等先进的技术可以减少毒性和改善生存[243-247]。目前CT模拟的3D适形放疗是最低标准。

NCCN 指南 NSCLC 流程中包含放射治疗原则部分， 该部分包括下述内容：1） 早期、局部晚期和晚期 NSCLC 的一般原则； 2）早期、局部晚期和晚期 NSCLC 的靶区、处方剂量和正常组织剂量限制，和 3） 放疗模拟、 计划和实施[248-253]。放疗原则在本节进行概述。 全脑放疗和立体定向放射外科治疗脑转移也在本部分进行讨论。 放疗专用术语和缩写列于 NCCN 指南 NSCLC 流程中（见放射治疗原则的表 1） 。美国大学放射学适合标准可能是有用的(http://www.acr.org/Quality-Safety/Appropriateness-Criteria/Oncology/L ung)。

根治性放疗或SABR推荐用于医学原因不可手术或拒绝手术的NSCLC早期（即I-II期, N0）患者 (见本讨论的*SABR*)[182,242,254,255]。辅助化疗(2B类)是高危因素患者（如，低分化肿瘤）根治性放疗或SABR后的选项。SABR也是不能耐受肺叶切除的手术高危患者(如，年龄大于等于75岁，肺功能差)的选择 。但是对于早期NSCLC，医学上适合手术的患者还是推荐手术切除(见NCCN指南NSCLC流程中的外科治疗原则)[256]。局部晚期 (即, II–III期)医学上不可切除患者推荐根治性化放疗[257]。对于有远处转移的晚期肺癌患者 (即 IV期)，对原发灶和转移灶姑息放疗是有用的[242,258-260]。 NCCN指南的NSCLC流程的放射治疗原则部份描述了放射治疗用于I 到IV期患者的建议。

NCCN指南的NSCLC流程描述了术前或术后化放疗或单纯放疗的适应症。(见放射治疗原则)。例如，临床I 或II期NSCLC患者术后升期N2阳性，根据切缘状态，术后化疗后可予术后放疗(见NCCN指南NSCLC流程中的辅助治疗)。[250,261]

然而，在IIIA期 NSCLC患者中某些术前单纯化疗的建议是足够的;[202] 这也是NCCN指南中 NSCLC流程的一个选项，虽然根治性同步化放疗是1类推荐。NCCN成员机构在IIIA期 N2 NSCLC选择新辅助化疗或新辅助化放疗时平分秋色。[196]

为了避免术后肺毒性,某些医师认为，如果需要行肺切除术时应该避免术前化放疗; 但这是一个有争议的问题(见NCCN指南NSCLC流程中的外科治疗原则)[196,198,208,262,263]。在照射60Gy的照射野中手术难以进行，这是因为高剂量照射后界限消失。因而，在先前受到大于45Gy的区域切除时，外科医师通常显得很谨慎，而在受到放射治疗剂量超过60Gy时更是如此(即, 接受根治性同步化放疗患者)。因而，如果患者适合手术时应该认真考虑放射剂量。 这些患者可以考虑软组织皮瓣覆盖[264,265]。如果患者不适合手术，放射治疗不间断地做到根治剂量。

靶区, 处方剂量,和正常组织剂量限制

术前放疗、术后放疗、根治性放疗和姑息放疗的推荐剂量在NCCN指南的NSCLC流程的放射治疗原则中有描述 (见表4)[249,251,266-270]。经历了手术，肺对放疗的耐受能力明显低于肺未受损者。 因而，应该尽各种努力使术后放疗剂量降到最低。

虽然正常肺剂量体积限量是有用的指南(见NCCN指南NSCLC流程放射治疗原则的表5),但是术后放疗应该选用较严格的参数。 根治性放疗患者，通常处方剂量是60-- 70 Gy，2 Gy /次[271]。 NCCN指南NSCLC流程的放射治疗原则部份讨论了更高放射治疗剂量的应用[272-277]。III期随机研究(RTOG 0617) 的结果显示高剂量放疗(74 Gy)同步化疗与标准剂量放疗(60 Gy)相比未改善生存[277-280]。

关于3D适形放疗的治疗体积，计划靶区应当按照ICRU-50国际辐射单位与测量委员会50号报告）和ICRU-62（国际辐射单位与测量委员会62号报告），根据大体肿瘤靶区 （GTV） 、 加上微小病灶的临床靶区（CTV）边界、 靶区运动的内靶区 （ITV）边界、以及每日靶区摆位误差边界来制定计划靶区 （PTV）（见图1）[281,282]。ICRU83号报告是用于IMRT的。 ACR-ASTRO 指南可也有用的(http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/IMRT.pdf).[43,283,284]。关于其他放疗体积的描述，见NCCN指南的NSCLC流程图(见放射治疗原则)。

有必要评估重要组织器官的剂量体积直方图 （DVH） ， 以限制脊髓、肺、心脏、食管和臂丛神经的受照射剂量从而尽可能减轻正常组织的毒性反应（见NCCN指南NSCLC流程放射治疗原则的表5）[285]。 这些限制大多是根据经验制定的[286-293]。 对于接受术后放疗的患者， 应考虑采用更严格的肺DVH参数。

放疗模拟、 计划和实施

放疗计划应基于与放疗体位相同的CT图像。 只要可能， 就建议使用静脉造影剂以更好地勾画靶区， 尤其对于存在中央型肿瘤或者淋巴结转移的患者。对部分患者 （即伴有明显肺不张或静脉造影剂禁用的患者） 建议行PET-CT检查。 PET-CT能够明显改善靶区制定的准确性[294]。

在NCCN指南NSCLC流程中的放射治疗原则部分， 阐述了对患者接受化放疗 （包括那些有心肺功能受损的患者） 、 光子射线、 或调强放疗 （IMRT） 的相关建议 （见 “放疗模拟、 计划和实施” ）[246,295-299]。

尽可能地进行呼吸运动管理。AAPM工作组76指南关于解决肿瘤运动的可行方法的描述在NCCN指南 NSCLC流程放射治疗原则部分 （见 “放疗模拟、 计划和实施” ）[300]。

立体定向消融放射治疗

SABR (也称为SBRT) 采用短期高剂量对目标病灶予精准照射[302-303] 研究表明， 对于拒绝手术的I期非小细胞肺癌患者SABR很有效[182,304-306] 这些病人常规放疗的3年生存率仅约20%~35%[255] 常规放疗患者的局部失败率高。 而SBRT治疗后可提高局部控制率。[180，307，308] SABR后疾病复发是罕见的[309]。SBRT同三维适型放疗相比显著提高了I期非小细胞肺癌患者的5年生存率[256,299,310] 接受SABR的I期患者中位生存时间是32个月， 3年总生存率约43%； T1期肿瘤患者较 T2期肿瘤患者存活得更久 （39月 vs 25月）[311]. 因而, NCCN指南推荐医学原因不可手术的I 和 II期无淋巴结转移 NSCLC患者行SABR [180,306]。

SBRT也适用于肺内局限性转移患者以及姑息治疗[312,313]也有研究表明SABR能用于骨、肝和脑转移.[301,306] 最近一项研究报导了 SABR 改善老年(75 岁或以上) I期 NSCLC患者的生存，这些病人除接受这个治疗外无法接受治疗[314]。

NCCN NSCLC流程的放射治疗原则中讨论了SBRT; 同时给出了分次方案和正常组织限量(见表 2和 3)[305,311,315-321]。 应该按多学科讨论意见决定是否推荐SABR。如果无法进行确定的SABR方案，超分割或加大剂量常规3维适形放疗也是一种选择。[322] RFA虽然有些建议认为SABR比RFA更有效,但是它们没有在随机研究中比较过[180,182,310]。

射频消融

数据表明 射频消融 （RFA） 可以作为拒绝手术或因为体力状态差、 明显心血管风险、 肺功能差和/或合并症而不能耐受手术的淋巴结阴性患者的治疗选择[182]。最适合进行RFA的患者为外周孤立病灶小于3 cm； RFA可用于既往照射过的组织以及用于姑息治疗[180,310,323] 。RFA 不推荐用于治疗靠近肺部大血管的肿瘤[180,310]。一项研究发现， 接受RFA的33例NSCLC患者1年和2年的总生存率分别达到70%(95% CI, 51%–83%) 和 48% (95% CI, 30%–65%)。I期NSCLC患者 （n=13） 接受RFA的2年总生存率为75% （45%~92%）。[324] 射频消融相关的30天死亡率被报告为2.6%[325]。 因医学原因不可手术患者SABR和 RFA比常规放疗更有效[310]。Although虽然有更多的数据支持应用SABR，因为只有一个治疗涉及RFA，RFA对选择性病人也可以是合理的选择[180]。

全脑放疗和立体定向放射外科

许多NSCLC患者伴有脑转移许多NSCLC患者伴有脑转移(30%–50%)，这大大影响了患者的生活质量[326] 对于部分伴单发脑转移瘤的患者（体力状态良好），建议手术后进行全脑放疗（1类证据）（见“NSCLC和中枢神经系统流程图NCCN指南”[327-330] 。立体定向放射外科（SRS）是另一种术后治疗选择，但仅获得少量回顾性病例系列的支持[327] 存在单发脑转移灶的患者如不能耐受手术或拒绝手术， 可以使用SRS联合/或不联合全脑放疗。[326,331-333] 有数据表明， 厄洛替尼用于对脑转移治疗可能有效。[334-336] 伴脑转移的患者是否推荐行手术、 全脑放疗、 SRS或综合治疗， 应当经过多学科讨论后决定， 并应针对每例患者的潜在获益和风险进行权衡[327,337-339]

对于脑转移复发或恶化的患者应进行个体化治疗。[340]

曾有研究者担心全脑放疗对患者的神经认知功能会有不利影响[341]。 然而，一项针对208例脑转移患者进行的研究发现， 对全脑放疗有反应（肿瘤缩小）的患者其神经认知功能亦得到改善， 肿瘤进展对于神经认知功能的影响更甚于全脑放疗。[342] 另一项研究对132例存在1~4个脑转移灶的患者进行SRS联合或不联合全脑放疗，结果显示两组的生存情况相似。[332] 在这些接受SRS联合或不联合全脑放疗的患者中，对其中92例患者的亚组分析显示，采用联合治疗控制脑肿瘤对于稳定神经认知功能具有更为重要的意义。[343] 然而，另一项包含58例患者的研究显示，接受SRS联合全脑放疗的患者同单纯使用SRS的患者相比，其中枢神经系统复发事件减少，但是神经认知功能下降更为明显。[344] 有人建议使用手术切除联合SRS（替代手术切除联合WBRT）可减少神经认知障碍。[345, 346]

综合治疗

如前所述，手术能为身体状况良好可耐受手术的I期或II期患者提供最大的治愈机会。然而，无淋巴结转移的不能手术或拒绝手术I期患者可以考虑SABR(见本讨论中的立体定向消融放射治疗部份)。作为在肿瘤完全切除的NSCLC患者中，辅助化疗已被证实能够改善早期肺癌患者的生存。[347-349] 研究表明新辅助化疗(手术前给予化疗)与辅助化疗疗效相当且耐受性更好(见本讨论中的新辅助化疗后手术试验数据) [196,350-357] 。但是，一个最近的随机研究发现术前与术后化疗的生存无差别[358]。

新辅助化疗也称为诱导化疗或术前化疗。对于肿瘤不能切除的III期患者，同步化放疗优于序贯化放疗[359-362]。

对于体力状态良好的IV期患者， 采用含铂的化疗将受益。[363-368] 数据显示，与单纯接受标准治疗相比， 早期姑息治疗联合标准治疗即便是在强度较低时也能够改善转移性肺癌患者的生活质量、 情绪和生存时间[369]患者应该接受减轻症状的治疗[5,370,371] 。最近的研究也显示，社会支持，如结婚，与化疗一样有效[372] 。IV期患者几乎不用手术。 但对于部分IV期患者， 单发脑转移手术切除可能可改善患者生存， 该推荐已收录在NSCLC的NCCN指南流程图中(也可见于中枢神经系统NCCN指南).[373] 除了脑转移外的其他部位孤立转移灶局部治疗仍有争议，是2B类推荐; 对于这类病人，SRS或SABR可能是有用的(见NSCLC的NCCN指南流程的 *IV期, M1b: 孤立部位/初始治疗*) [183,306]。 本文讨论支持推荐综合治疗的试验。

手术序贯化疗： 试验数据

在本指南中， IA期患者不推荐术后辅助化疗是基于以下临床试验。辅助化疗只推荐用于IB期切缘阴性高危患者(见NCCN NSCLC流程)。 推荐的新辅助和辅助化疗方案见NCCN NCSLC流程图。

国际辅助肺癌试验 （IALT）报道，在I期、 II期、 III期NSCLC患者完全切除术后给予含顺铂方案辅助化疗，可以明显改善其生存期， 差异有统计学意义。[347]共有1,867例接受手术切除的肺癌患者参加了此研究，他们随机接受含顺铂方案的辅助化疗或观察，中位随访时间56个月。 与观察组相比， 辅助化疗组的生存率（5年生存率分别为44.5%和40.4%； 死亡风险比， 0.86； 95% CI，0.76~0.98； P<0.03）及无病生存率 （5年无病生存率分别为39.4%和34.3%； 风险比， 0.83； 95% CI，0.74~0.94； P<0.003）均有明显提高。IALT的结果显示含顺铂方案的辅助化疗改善了根治术后NSCLC患者的5年总生存率。但随访7.5年后， 化疗组的死亡率更高， 化疗的优势随时间延长而削弱。[374]数据显示辅助化疗可预防复发。NCIC CTG JBR.10试验和ANITA 试验比较了早期NSCLC患者给予长春瑞滨联合顺铂辅助化疗与观察的疗效。 在JBR.10试验中，482例IB期 （T2N0） 或II期 （T1N1或T2N1） 根治术后的NSCLC患者（ECOG PS评分0或1） 随机接受长春瑞滨联合顺铂化疗（242例）或观察 （240例）[348]与观察组相比，辅助化疗显著延长了总生存期 （分别为94个月和73个月；死亡风险比， 0.69； P =0.04）和无复发生存期 （分别为尚未达到中位无复发生存期和46.7个月； 复发风险比， 0.60；P<0.001） 。5年生存率分别为69%和54%（P=0.03）。然而，来自JBR.10试验随访9年的最新数据显示， 同单纯观察相比， 辅助化疗能使II期患者获益，但IB期患者无获益[345] II 期患者接受辅助化疗与仅观察者中位生存时间分别是6.8 与 3.6年。接受化疗的患者死亡率不增加。

在ANITA研究中， 840 例IB (T2, N0), II,或 IIIA期非小细胞肺癌患者随机分成辅助长春瑞滨联合顺铂组或观察组。[349] 3/4级毒性反应在化疗组是可控的; 但是报导了7例毒性相关死亡。中位随位76个月后，化疗组中位生存66个月，观察组中位生存时间44个月。[349]
II 和 IIIA期患者完全切除后辅助化疗可显著改善(8.6%) 5年总生存，而在I期患者中没有观察到这种获益。一些临床学家结合研究数量和应用数量，认为长春瑞滨/顺铂是早期完全切除的早期非小细胞肺癌首选方案。[376]

一项对4,584例患者所做的荟萃分析 （肺癌顺铂辅助化疗评估） 发现，术后含顺铂化疗提高了5年生存率 （绝对获益5.4%） ； 不同的化疗方案（长春瑞滨、 依托泊苷、 其他） 之间疗效无差别。[376]项亚组分析也发现顺铂/长春瑞滨提高生存[377] 。 II期、 III期和体力状态较好的患者获益较大。术后辅助化疗甚至年龄高达80岁的老年患者都有获益。[378]

CALGB 9633试验评估了紫杉醇联合卡铂方案治疗IB期 （T2N0M0）患者的疗效[379]。 该研究的更新结果已报道[380,381]。 在该研究中，344例患者在手术切除后4~8周内被随机分为化疗组 （紫杉醇联合卡铂） 和观察组， 中位随访时间74个月。进行辅助化疗的患者耐受良好， 无化疗相关死亡发生。 6年总生存率无显著差异，尽管3年生存率差异显著（分别为80%和73%， P=0.02）。[380，381]

CALGB的原先结果显示紫杉醇联合卡铂方案可以改善I期患者的生存，但更新结果并未显示能够改善生存 （尽管CALGB亚组分析显示肿瘤大于4 cm的患者受益）。 因此， 卡铂/紫杉醇方案仅仅在患者无法耐受顺铂时才被推荐用于早期患者 （见NCCN指南NSCLC流程之新 辅助和辅助治疗的化疗方案）[382] 因而，必需明确的是CALGB研究在1B期患者亚组中说服力是不足的[383]

新辅助化疗后手术：试验数据

来自切除后NSCLC患者的辅助临床研究数据显示化疗是一个重要的问题。在术后治疗系列中，因为手术后明显的并发症和不完全恢复通常使患者无法耐受治疗。这个问题在NATCH III期 研究 (该研究比较了单纯手术与术前或术后联合紫杉醇/卡铂化疗)中得到证实,因为90%的术前化疗组完成了3周期的化疗，而只有61% 的术后化疗组完成化疗；而3组的生存是一致的[355]。一个最近的随机研究发现早期NSCLC术前和术后化疗比较3年总生存无差别 (67.4% vs. 67.7%); 两组有效率和生活质量相似[358]。术后化疗是早期疾病是标准治疗[180]。

多个研究提示新辅助治疗使N2患者获益[196,202,354]。也有其他研究显示新辅助治疗使更早期患者获益。[351,352,357]

一个随访的随机团体协作研究 (SWOG 9900) 比较了在354例IB 到IIIA期 (但没有N2) 患者中新辅助紫杉醇/卡铂与单纯手术 。 这个研究因为实践的改变而没有合适的作用所以提早结束。但是，SWOG确实提示新辅助化疗PFS (33 vs. 20 个月) 和总生存 (62 vs. 41 个月) 改善的趋势,而两组间的切除率没有差别。[357]

Scagliotti等进行的III期研究， 270例IB 到IIIA期患者术前顺铂联合吉西他滨与单纯手术比较 。虽然研究提早关闭，但是接受化疗的IIB 和 IIIA患者有显著的生存获益 (HR, 0.63)。[351] Song 等进行的Meta分析，对象是所有可获得的评价可切除NSCLC患者术前化疗的随机临床研究。这个Meta分析评价了13个随机研究，结果显示新辅助化疗与单纯手术患者总生存的改善(HR, 0.84; 95% CI, 0.77–0.92; *P* = .0001)。[350]这些结果与最近报导的另一个meta分析相似 (HR, 0.89;95% CI, 0.81–0.98; *P* = .02)[351]。新辅助化疗的获益与术后化疗相似[351,358,377]。

化放疗： 试验数据

目前关于NSCLC的主要争议在于IIIA期患者的治疗 （见 NCCN指南NSCLC流程外科治疗原则之手术在IIIA期(N2)NSCLC患者中的作用）。3种治疗手段即手术切除、 化学治疗和放射治疗都可用于III期患者。目前争论的焦点在于应该采用哪些手段以及各手段的应用顺序如何[384-388]。 不可切除的IIIA期或IIIB期患者， 综合治疗 （化放疗） 优于单纯放疗[384,385,387,388]。同步化放疗优于序贯化放疗[359-362]。但是，同步化放疗3或4级食管炎的发生率高于序贯化放疗。 病例的正确选择不仅影响到治疗的效果， 而且影响到患者对治疗的耐受性。

用于所有组织学类型初始治疗的同步化放疗方案包括顺铂/依托泊苷（首选） 、 顺铂/长春花碱 （首选）（见 NCCN指南NSCLC流程图的化放疗方案） [359,361,389,390]。 对于非鳞癌，其他同步化放疗方案包括卡铂/培美曲塞和顺铂/培美曲塞[391,392]。 一个随机对照研究，入组了203例不可切除的IIIA 或 IIIB 期NSCLC患者，比较化疗后接受单纯放疗与联合紫杉醇的化放疗 ；中位生存时间分别为14.1 与18.7 个月 (*P* =0 .091) [393]。

化疗： 试验数据

PS评分较好的IV期患者可从化疗中获益 ，通常采用含铂方案。[365,367,394] IV 期NSCLC中多种药物都是有用的。这些药物包括铂类（顺铂、 卡铂）、紫杉类 （紫杉醇、白蛋白结合紫杉醇、 多西他赛）、长春瑞滨、 长春碱、依托泊苷、 培美曲塞和吉西他滨 （见NCCN指南NSCLC流程的晚期转移性疾病系统治疗 ） 。

联合应用这些药物， 1年生存率为30%~40%， 优于单药治疗。 方案包括卡铂/紫杉醇、顺铂/紫杉醇、顺铂/长春瑞滨、 吉西他滨/顺铂、顺铂/培美曲塞和多西他赛/ 顺铂[382,395-398]。 在美国，经常用于非鳞癌NSCLC的一线方案包括1) 顺铂 (或卡铂)/培美曲塞; 或2) 卡铂/紫杉醇 (加或不加贝伐单抗) [399,400]。吉西他滨/顺铂 应用于鳞状细胞癌患者[398-401]。这个方案的应用通常是根据III期随机研究的(即， 顺铂/培美曲塞, 卡铂/紫杉醇 [加或不加贝伐单抗], 吉西他滨/顺铂) [398,402]。

最近很多肿瘤学家在腺癌中应用以培美曲塞为基础的方案(如果患者无靶向治疗适应症),这是因为以紫杉类药物为基础的方案与更多的毒性有关 (如神经毒性)。[398,403,404] POINTBREAK 研究表明卡铂/培美曲塞/贝伐单抗是一个合理的选择，而且确定了紫杉为基础的方案比培美曲塞为基础的方案毒性更多[404,405]。然而POINTBREAK研究显示两个方案的总生存相似，因而肿瘤学家可能换回紫杉为基础的方案，这个方案很成熟[404]。一个回顾性队列研究提示在老年晚期非鳞癌NSCLC患者中加入贝伐单抗(到卡铂/紫杉醇) 并不改善生存[406]。

PS 2 分(即PS评分差)的晚期NSCLC患者, NCCN指南中推荐单药化疗或含铂联合化疗[407]。单药化疗包括长春瑞滨, 吉西他滨, 培美曲塞, 或紫杉类; 联合化疗方案包括卡铂/紫杉醇或卡铂/培美曲塞[408-410]。 但是,PS2分的患者因为毒性的缘故，通常只是采用单药化疗[411]。最近的研究结果报告对于PS2分的患者卡铂/培美曲塞与培美曲塞单药比较中位总生存提高 (9.3 vs. 5.3个月, $P = .001$); 但有卡铂/培美曲塞治疗组有4例治疗相关死亡[408,412]。

III期随机研究表明多个含铂两药联合方案的客观缓解率和生存相似[413,414]。含铂两药方案在毒性、方便程度和费用上有轻微差别，临床医师可以针对患者个体化治疗[401,415,416]。其他以卡铂为基础的方案包括吉西他滨/卡铂, 多西紫杉醇/卡铂, 和培美曲塞/卡铂; [395,417-419]非铂类为基础的方案如吉西他滨/长春瑞滨和吉西他滨/多西紫杉醇也是选项之一[420-423]。尽管发展出了新的化疗方案,晚期 不可手术肺癌的预后仍然很差。

注意， 对于以下患者， 白蛋白结合型紫杉醇可以替代紫杉醇或多西他赛：1） 尽管给以预处理， 接受紫杉醇或多西他赛后仍发生过敏反应者； 2） 使用标准预处理药 （即， 地塞米松、 H2阻滞剂、 H1阻滞剂） 预防过敏有禁忌者[424,425]。最近的 III随机研究报告，晚期NSCLC患者中与标准紫杉醇/卡铂比较，白蛋白结合紫杉醇/卡铂方案有更少的神经毒性并提高有效率。[426]

FDA 批准白蛋白结合紫杉醇/卡铂 用于局部晚期或转移性NSCLC（无根治性手术或放疗适应症者）(http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021660s03_8lbl.pdf)。根据最近的研究和FDA的批准，NCCN 专家推荐一个白蛋白结合紫杉醇/卡铂方案用于晚期PS评分好的(0–1)晚期NSCLC患者的一线治疗。

靶向治疗

已有一些特异性的靶向治疗用于治疗晚期NSCLC (见NCCN指南NSCLC，有基因改变患者的靶向药物)[427,428]。 贝伐珠单抗是一种重组单克隆抗体， 它能阻断血管内皮生长因子 （VEGF） 。 厄洛替尼、吉非替尼和阿法替尼是表皮生长因子受体 （EGFR） 的小分子抑制剂。克唑替尼是以ALK、ROS1和MET为靶点的小分子抑制剂。厄罗替尼、克唑替尼、吉非替尼和阿法替尼都是口服的TKIs。西妥昔单抗是以EGFR为靶点的单克隆抗体。

贝伐珠单抗

2006年， 美国食品药物管理局 （FDA） 批准贝伐珠单抗用于不能手术切除的、 局部晚期、 复发或转移的非鳞状细胞NSCLC患者。 基于II~III期临床试验（ECOG 4599） 的结果[402]， 东部肿瘤协作组 （ECOG） 推荐贝伐珠单抗联合紫杉醇加卡铂用于治疗经选择的晚期NSCLC （非鳞癌） 患者。 接受贝伐珠单抗联合化疗的患者必须满足以下标准： 非鳞状细胞NSCLC， 无咯血史。 任何具有导致血小板减少并有可能造成出血危险的方案与贝伐珠单抗联合使用时都需谨慎。 对于EGFR突变和ALK基因融合均阴性且PS评分0~1的非鳞状细胞癌患者， 贝伐珠单抗联合化疗是本指南推荐的方案之一 （见NCCN指南 NSCLC流程的腺癌、大细胞、NSCLC非特指型：EGFR突变和ALK阴性的一线治疗 ） 。

厄洛替尼

FDA于2004年批准厄洛替尼用于至少一次化疗失败后的局部晚期或转移性NSCLC的治疗。对于明确有敏感EGFR活化突变的晚期、 复发或转移的非鳞状细胞癌患者， 无论其体力状态如何， 也可推荐厄洛替尼作为一线治疗（见NCCN指南 NSCLC的腺癌、大细胞、NSCLC非特指型：EGFR突变和ALK阴性的一线治疗 ）[57,429-431]。 该推荐是基于一个III期随机临床试验（IPASS）。 在这个试验的EGFR突变患者中， 吉非替尼同化疗 （卡铂/紫杉醇） 相比， 提高了无病生存率 （24.9% vs 6.7%）、缓解率 （71.2% vs. 47.3%）和生活质量， 而且副作用 （如白细胞减少） 更少见[430]。

来自IPASS研究的更新结果表明不管EGFR突变状态如何接受吉非替尼者与化疗患者的总生存相似[432]

然而,这个结果可能是因为被分入一线化疗的患者，如果是EGFR突变，可以在序贯治疗中接受TKIs。 因为与化疗相比TKIs可以提高生存质量，所以TKIs推荐有于EGFR突变的患者。吉非替尼在美国不容易获得，因而厄罗替尼经常使用。厄罗替尼是一种口服有活性的TKI且多数患者耐受性良好。

一项包含5个临床试验的分析中主要纳入了西方的晚期 （IIIB或IV期） 非小细胞肺癌患者 （n=233） ， 分析结果发现， 接受酪氨酸激酶抑制剂的EGFR突变患者中， 缓解率67%， 总生存时间约24个月[433]。 最近的TORCH试验提示， 晚期非鳞型非小细胞肺癌患者应进行EGFR突变检测[434]。 在EGFR野生型患者，接受一线化疗与接受厄洛替尼一线治疗后采用二线化疗相比， 生存期得到延长 （11.6 vs. 8.7个月） 。

OPTIMAL研究发现EGFR突变患者接受厄罗替尼治疗PFS延长[145,146]。

ASCO建议患者应该检测EGFR突变[435]。 但是,NCCN和 ESMO指南指定只有非鳞癌NSCLC 患者(如，腺癌) 需要评估敏感EGFR突变[407]。纯鳞状细胞癌患者不大可能有EGFR突变; 但是，那个腺鳞癌者可能有突变。[99]

最近,一个研究(CALGB 30406)更新比较了晚期NSCLC患者（主要是高加索人种）单纯厄罗替尼与厄罗替尼/卡铂/紫杉醇[436,437] 。数据表明EGFR突变患者中单纯厄罗替尼与厄罗替尼/化疗比较副反应较少。因而，在化疗期间发现EGFR突变的患者转换成厄罗替尼治疗是合适的 (见 NCCN 指南非小细胞肺癌，EGFR突变阳性/一线治疗) 。根据这个研究，NCCN专家组考虑厄罗替尼联合化疗做为2B类推荐。

阿法替尼

最近的随机 III 期研究表明有敏感突变转移性腺癌患者阿法替尼与顺铂/培美曲塞比较，阿法替尼改善 PFS (11.1 vs. 6.9 个月, *P* = .001)[126] 。 FDA 最近批准了阿法替尼用于有 EGFR 敏感突变的转移性 NSCLC 患者一线治疗 [125,438]。根据这个 III 期随机研究和 FDA 的批准，NCCN 专家组推荐阿法替尼用于有 EGFR 敏感突变转移性非鳞癌 NSCLC 患者的一线治疗(1 类) (见 NCCN 指南 NSCLC) [123,126,175]。根据一线化疗后进展患者的有效性数据，阿法替尼也推荐用于二线治疗 (见本讨论中的二线和三线系统治疗) [122]。

克唑替尼

FDA 批准克唑替尼用于 ALK 重排阳性的局部晚期或转移性 NSCLC 患者。 之所以批准这个适应症是根据 II 期研究表现出在先前进展患者中戏剧性的有效率(>80%) [156,157] 。接受克唑替尼的患者疼痛、呼吸困难和咳嗽等临床表现明显改善。 最近，在 ALK 重排患者中，二线治疗中克唑替尼与化疗比较显示出有效性 [171]。

西妥昔单抗

一项大型III期随机试验 （FLEX） 对顺铂/长春瑞滨加（或不加）西妥昔单抗用于晚期NSCLC （大部分患者疾病分期为IV期） 进行了评估[439]。 西妥昔单抗的加入略微延长了总生存期 （11.3个月 vs 10.1个月， P=0.04） 。 西妥昔单抗/顺铂/长春瑞滨方案是无EGFR突变或ALK重排的各种组织类型晚期非小细胞肺癌患者的一种治疗选择（见NCCN指南NSCLC流程中的腺癌或鳞癌一线治疗 ）。 然而， 由于西妥昔单抗/顺铂/长春瑞滨方案带来的获益很小，方案执行困难，与其他方案比较患者的耐受性更差(如，差不多40% 的患者出现4度中性粒细胞减少)，本指南中对该方案作为2B类推荐。患者可能同时有禁忌使用顺铂的合并症 (如，肾功能差)。某些临床学家认为，虽然FLEX研究结果有统计学意义，但没有临床意义。

维持治疗

维持治疗指的是可能给予晚期NSCLC患者4-6周期一线化疗后的系统治疗[440]然而，患者进行维持治疗的唯一适应症是，假如他们在先前的治疗中有效(即肿瘤有反应)或疾病稳定且肿瘤没有进展。继续维持治疗是指使用至少一种在一线治疗中使用过的药物。换药维持治疗是指开始使用另一种不包含在一线方案中的药物进行治疗。选择合适的维持治疗取决于多个因素 (如, 组织学类型,突变状态和基因重排和 PS)。维持治疗是NCCN指南给特定病人（肿瘤有效或疾病稳定）的一个选择，而不是所有病人的标准治疗 (如，不推荐用于PS3-4分和进展的病人);密切观察也是可行的治疗选择 (见 NCCN指南 NSCLC流程)。[441]

继续维持治疗

关于继续维持治疗，按促使该方案得到批准的临床试验设计，选择药物(最初在常规化疗中与其他药物联用的)应该持续应用至出现疾病进展的证据或无法耐受的毒性

单药贝伐单抗 (1类) 可以在EGFR突变或ALK重排阴性的非鳞癌NSCLC患者经4-6周期初始治疗（即含铂两药联合贝伐单抗）后维持[402,442,443] 。单药培美曲塞 (1类) 也可以在非鳞癌NSCLC患者(EGFR突变或ALK重排融合阴性)中做继续维持[442,444] 。最近一项III期随机研究(PARAMOUNT) 发现，与安慰剂比较，培美曲塞继续维持轻微延长PFS (4.1vs. 2.8 个月) [444,445]。结果提示培美曲塞继续维持也能延长总生存 (13.9 vs. 11.0 个月) [446,447]。

根据最近的研分和FDA的批准，NCCN专家组推荐单药培美曲塞作为无EGFR突变或ALK融合的非鳞癌NSCLC患者的继续维持(1类)。单药西妥昔(1类)在非鳞癌（无EGFR突变或无ALK重排融合）或鳞癌NSCLC患者初始治疗4-6周期后继续 (即顺铂, 长春瑞滨, 和西妥昔治疗) [439] 。

应用贝伐单抗/培美曲塞继续维持治疗也是非鳞癌NSCLC患者(无EGFR突变，无ALK融合)的选择; 这是个2A 类推荐。最近的POINTBREAK研究数据显示与单纯的贝伐单抗比较贝伐单抗/培美曲塞维持有轻微的PFS改善 (6 vs. 5.6 个月) ；初始治疗方案是贝伐单抗/卡铂/培美曲塞或贝伐单抗/卡铂/紫杉醇[404，405]。重要的一点是与含紫杉醇组比较培美曲塞组的毒性较低 (如，较少的神经毒、较少的中性粒细胞减少、较少脱发) 。作为维持治疗，贝伐单抗/培美曲塞与单纯贝伐单抗相比，AVAPERL研究的数据显示PFS延长3.7个月(7.4vs.3.7个月); 初始方案是贝伐单抗/顺铂/培美曲塞[448，449]。

最近的一项III期随机临床试验对比了吉西他滨+顺铂一线化疗后以吉西他滨或厄洛替尼维持治疗的差异。结果显示， 与观察组 （1.9个月）相比，吉西他滨继续维持治疗PFS延长程度（3.8个月）大于厄洛替尼换药维持 （2.9个月）[450,451] 。另一个 III期随机研究比较了初始顺铂/吉西他滨后吉西他滨继续维持治疗与最佳支持治疗[452]。数据显示轻微的PFS差别但OS没有差别。NCCN指南推荐EGFR 突变或ALK重排融合阴性的患者，不管组织学类型都采用吉西他滨继续维持。

应用继续维持治疗是根据多个因素，如患者在治疗期间是否有最小毒性。对于某些病人药物休假可能是更合适的[403]。一些临床学家认为继续维持只适用于特定病人，因为它并没有改善总生存或生活质量，而只是延长PFS[403,453]。此外，维持治疗并不优于在疾病进展后才开始的二线治疗。
来自III 期随机研究的数据表明常规毒性的药物不能在4-6周期后继续应用；但是，很多分入更长持续时间治疗的患者没有接受计划周期数(见本讨论的维持治疗)[453,454]。

换药维持

换药维持的文献越来越多，包括试验设计、适度的生存获益、生活质量和毒性[403,455]。然而,换药维持治疗是NCCN指南中是2B类推荐。2个 III 期随机研究显示在无疾病进展的患者中，4-6周期一线化疗后开始培美曲塞或厄罗替尼，有PFS和OS获益[456,457]。

培美曲塞换药维持可以引入组织学类型除鳞癌外，EGFR突变或ALK重排融合阴性的患者[457]。FDA已经批准培美曲塞用于维持治疗(http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021462s045lbl.pdf)[458]。同样的，厄罗替尼换药维持可以引入到患者 1）无 EGFR 突变或基因重排，或 2）鳞状细胞癌的患者[451,456]。NCCN 指南 NSCLC 流程中厄罗替尼和培美曲塞用于换药维持都是 2B 类推荐，但是培美曲塞不推荐用于鳞状细胞癌。FDA 批准厄罗替尼用于维持治疗(http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021743s018lbl.pdf).[459]
一个 III期研究比较了化疗后立即给予或延迟到进展时才给予多西紫杉醇[460]。但是，多西紫杉醇换药维持治疗是NCCN指南针对鳞状细胞癌患者的2B类推荐，因为延迟化疗组的很多患者没有接受多西紫杉醇。

临床评估

如前所述，目前推荐低剂量CT用于特定无症状肺癌高危病人的筛查(见NCCN指南NSCLC和肺癌筛查)。低剂量CT筛查可能发现可疑为癌症的肺结节，针对这些肺结节的检查和评估在NCCN流程中有的描述(见本讨论的肺结节诊断评估和见NCCN指南NSCLC流程的诊断评估原则)。

根据病理诊断患者确诊为NSCLC后，需要做一个临床评估 (见NCCN指南NSCLC流程)。在有症状的患者中，对临床分期的确定需要从采集病史（即咳嗽、 呼吸困难、 胸痛、 体重减轻等）开始， 然后进行体格检查及完善一系列必要的检查 (见NCCN指南NSCLC流程的评估和临床分期)。
注意在某些病人中，诊断、分期和手术切除是在同一个手术过程中完成的。治疗前应该完成多学科评估。NCCN专家组推荐患者接受戒烟咨询和药物治疗(http://www.smokefree.gov/expert.aspx)。根据初始评估可以确定患者的临床分期， 这时患者可被归入根据分期、 分组和肿瘤部位所划分的治疗路线中的一条。

其他治疗前评估

纵隔镜

如上所述， 纵隔淋巴结的评估是进一步分期的关键步骤。 尽管胸部PET/CT可以用于肺门和纵隔淋巴结的初始评估 （即是否存在N1、 N2或N3， 这是确定II期和III期的关键因素），但已知CT扫描在评估肺癌累及淋巴结的范围上存在一定的局限性(见本讨论中的纵隔镜和其他影像研究)[461-464]。

纵隔镜检查被认为是评估纵隔淋巴结的金标准， 因此鼓励将纵隔镜检查作为初始评估的一部分， 特别是在影像学不能得出结论时， 或考虑纵隔受累可能性大（根据肿瘤大小、 位置）时。 因此， 即使胸部PET/CT未提示纵隔淋巴结受累， T2~T3病变患者也适宜纵隔镜检查。 同时， 可采用纵隔镜检查以证实PET/CT显示的阳性纵隔淋巴结。 与此相反的是， 由于周围型T1abN0患者淋巴结受累可能性低[465]，有些NCCN单位不常规对这部分病例进行纵隔镜检查（2B类）。 但是， 对PET/CT扫描纵隔淋巴结阴性的周围型T2a、 中央型T1ab或T2患者建议进行纵隔镜检查和/或内镜超声引导下FNA (EUS-FNA)和EBUS引导经气管针吸活检(EBUS-TBNA)， 因为这种情况下纵隔淋巴结受累的风险较高（见本讨论中的其他影像研究和NCCN指南NSCLC流程)。

Dillemans等在一项研究中探讨了选择性纵隔镜检查策略问题， 即对术前CT上无纵隔淋巴结增大的周围型T1直接行开胸手术而不做纵隔镜检查， 结果显示开胸手术时仅16%为N2阳性[466]。
胸部CT诊断N2病变的敏感度和特异度分别为69%和71%， 但是胸部CT加纵隔镜检查N2的准确度却明显高于单独的胸部CT （分别为89%和71%） 。 CT根据淋巴结的大小确定阳性与否， 因此会遗漏体积没有增大的转移性小淋巴结。 为明确这一问题， Arita等检查了90例肺癌患者中正常大小淋巴结的转移情况， 结果发现对大小正常的淋巴结（经组织学证实有隐匿性N2或N3转移）胸部CT假阴性率为16% (14/90)[467] 。

支气管镜用于中央型和外周型病变的诊断和局部分期， 推荐用于I期、II期和IIIA期肿瘤的治疗前评估。 但对于单发性肺结节， 高度怀疑为恶性肿瘤的患者， 不进行创伤性检查而直接行外科切除也是合理的。

其他影像检查

如前所述，CT扫描在评估肺癌累及淋巴结的范围上存在一定的局限性[462]。PET扫描已被用于评估肿瘤侵犯范围， 对肺癌进行更精确的分期。NCCN指南专家组回顾了CT与PET的诊断价值。NCCN 指南专家组认为PET扫描能在NSCLC的评估和更准确分期中起到一定的作用，例如，在确定I 期(周围和中央型 T1–2, N0), II期, III期,和IV 期疾病[461,468,469]。然而， PET/CT因为更为敏感而受到NCCN推荐[470-472]。

专家组成员评价了关于胸部CT对纵隔淋巴结进行分期的敏感性和特异性的研究[473]。据临床资料显示， CT对纵隔淋巴结分期的敏感度为40%~65%，特异度为45%~90%[474]。PET检测的是肿瘤的生理变化而非解剖学改变， 因此可能比CT扫描更敏感。此外， 如果出现阻塞性肺炎， 纵隔淋巴结的大小与肿瘤侵犯几乎无相关性[475] 。

Chin等发现PET用于评估纵隔淋巴结分期时， 敏感度为78%， 特异度为81%， 阴性预测值为89%[476]。 Kernstine等比较了PET与CT在鉴别NSCLC患者N2和N3病变中的作用[477，478]， 结果显示PET在判断纵隔淋巴结转移方面的敏感度较CT更高 （分别为70%和65%） 。 已经证实PET/CT对辅助治疗后的患者重新分期有用[479,480]。

采用PET/CT对早期患者进行准确分期， 可以避免不恰当的手术[470]。 但是， PET/CT扫描阳性结果的远处转移仍需病理学或其他放射学证据证实 （如，骨MRI）。如果纵隔的PET/CT扫描结果为阳性， 应该进行病理检查明确淋巴结情况[461，481]。

经食管内镜超声引导下的细针穿刺（EUS-FNA）和支气管内镜超声引导下的细针穿刺（EBUS-TBNA）被证实对患者分期或诊断纵隔病变有用，这些技术在部分患者可以替代创伤性分期方法[482-485]。 与CT和PET相比，EBUS-TBNA对肺癌患者纵隔和肺门淋巴结分期具有更高的敏感度和特异度[486]。 对于CT或PET显示淋巴结阳性的患者， 可通过EBUS-TBNA来证实结果[487，488]。 然而， 对于EBUS-TBNA显示阴性结果的患者， 可进行常规纵隔镜检查以证实结果[483,488-490]。注意EBUS也称为腔内超声。

不常规推荐应用骨扫描（用于排除骨转移）。如果考虑应用积极的综合治疗，II, III, 和IV期患者推荐行脑 MRI (以排除无症状的脑转移)以排除转移性疾病 [491]。

对于IB期 NSCLC患者, 脑部MRI只是2B类推荐，这是因为这一期病人较少出现脑转移。注意PET扫描不推荐用于评估是否有脑转移 (见 NCCN 中枢神经系统肿瘤指南).

初始治疗

治疗前，强烈推荐由以肺癌手术为主要专业并且通过专科认证的胸外科医生来判断手术切除的可能性 （见NCCN指南NSCLC流程的外科治疗原则） 。放射治疗原则推荐的放射治疗剂量(见 NCCN指南 NSCLC 流程)。另外， NCCN 指南NSCLC流程也推荐化疗和化放疗方案(见*新辅助和辅助化疗的化疗方案*, 放射治疗的同步*化疗方案*, 和晚期/转移性疾病的系统化疗)。

I期、 II期、IIIA期

根据病变的程度和并发疾病， 一般认为I期或部分II期 （T1~2N1） 的患者适合接受手术和对纵隔淋巴结清扫。 在某些情况下， 术中发现纵隔淋巴结阳性（N2） ， 这时应重新评估分期和肿瘤的可切除性，治疗计划需做相应修改（包括系统的纵隔淋巴结清扫）。 所以， 在本指南流程图中对T1~3N2(即 IIIA 期疾病)病变提供了两种不同的治疗路线，1) 在手术探查中意外发现T1–3, N2 ； 2) 开胸术前就确认是T1–3, N2。在第二种情况下，推荐开始就行头颅MRI和PET/CT 扫描(如果先前没有做过)以排除转移灶。

对于IIB期 （T3N0） 和IIIA期的患者， 通常考虑使用多种治疗手段 （手术、放疗、 化疗） 进行治疗， 并建议进行综合评估。 对某些IIB期 （T3N0） 和IIIA期（T4N0-1）的肿瘤患者，应根据肿瘤位置 （即肺上沟、 胸壁、近端气道或纵隔）选择治疗方式。对上述各部位的肿瘤， 胸外科医生需要确定其可切除性（见NCCN指南NSCLC流程的外科治疗原则） 。

对于可切除的肺上沟瘤 （T3外侵， N0~1） ， 专家组建议术前同步化放疗后手术切除和化疗 （见 NCCN指南NSCLC） 。 新辅助同步化放疗加手术治疗肺上沟瘤的2年生存率为50%~70%[183,267，269,492-495]， 5年总生存约40%[267]。可能切除的肺上沟瘤患者需在术前同步化放疗后进行手术再评估。 不可切除的肺上沟瘤 （T4外侵， N0~1） ， 推荐行根治性同步化放疗之后再序贯2周期足剂量的化疗 （如初始同步放疗时未使用足量剂量化疗）[325,427]。

胸壁、 近端气道或纵隔受侵犯的T3~4N0~1病变首选外科切除。 其他治疗包括术前化疗或同步化放疗加外科手术。

没有胸腔积液的不可切除T4, N0–1 肿瘤，推荐根治性同步化放疗(1类推荐)[198，359]。如果初始同步治疗时已给予足剂量的化疗，可以再给予4周期足剂量化疗(见NCCN指南NSCLC流程辅助治疗)[198,359,392]。

对于纵隔淋巴结阳性的IIIA期 （T1~3N2） 患者， 应根据纵隔淋巴结病理的检查结果决定治疗方案 （见 NCCN指南 NSCLC流程） 。纵隔淋巴结活检阴性的患者适合接受手术治疗， 在手术时再评估切除肿瘤的可行性。对于可切除病变， 术中应做纵隔淋巴结清扫或纵隔淋巴结取样。对于因医学原因不可切除病变， 应按照病理分期治疗 （见 NCCN指南 NSCLC流程） 。对于T1~2或T3且N2淋巴结阳性的患者， 推荐行脑MRI和PET/CT扫描 （如尚未检查）寻找远处转移。 如无远处转移， 专家组建议行根治性同步化放疗 （见 NCCN指南 NSCLC流程）[360]。 诱导化疗±放疗对于T1~3N2的患者也是一种选择[199]。 对有远处转移的患者， 推荐按病变是孤立或广泛播散来治疗详见 NCCN指南 NSCLC流程。

肺内转移常见于合并其他部位远处转移的患者， 该类患者预后较差， 大多已不能接受手术治疗，推荐系统治疗。 存在肺内转移但不伴其他部位转移的NSCLC患者少见， 其预后相对较好， 可以接受手术治疗(见本讨论的多发肺肿瘤)[497]。原发肿瘤同一叶内或同侧肺内存在分散的肺结节而不伴有其他部位远处转移的患者有可能通过手术治愈； 此类患者的5年生存率约为30%[498]。TNM分期（AJCC第7版） 标准对肺内转移的分期进行了下调[87,498,499]。

对于术后N2淋巴结阳性者，切缘阳性和R2切除者推荐同步化放疗;R1切除者推荐行序贯或同步化放疗。对于N2淋巴结阳性和切缘阴性者推荐行序贯化放疗(1类)。N0-1 者推荐单纯化疗 (见NCCN指南非小细胞肺癌辅助治疗)。对于同期存在的多个肺结节 （对侧肺） ， 指南建议如果二者均可治愈则将它们作为双原发肺肿瘤进行治疗， 即使二者的组织学类型相似 （见 NCCN指南 NSCLC流程）[500]。

多发肺癌

多发性肺癌患者可能是多种方法怀疑或检测到的。有肺癌病史或经活检证实有同时存在的病灶的患者，应该怀疑为多发性肺癌患者 (见 NCCN指南 NSCLC流程的临床表现) [501,502]。因为多数多发肺肿瘤是转移的[49,183,503,504],所以判定多发性肺癌是转移性的或肺原发的(同时性或异时性)很重要。因为，确定肺肿瘤的性质很重要(见 NCCN指南 NSCLC流程的病理评价原则)。同时需要排除感染和其他良性病 (如炎性肉芽肿) [505,506]。虽然已经制定了多发性肺癌的诊断标准，但是在治疗前最终方法还没确定[506-509] 。通常用于诊断多发性肺癌的Martini 和 Melamed标准如下: 1) 组织学类型不同; 2) 虽然组织学类型相同，但无淋巴结受侵且无胸外转移[509]。

多发性肺癌的治疗按以下因素决定：淋巴结状态（如N0-1）和肺癌患者是有症状还是没症状或是发展成有症状的危险性高的 (见 NCCN指南 NSCL的初始治疗) [503,510-512]。对于适合行根治性局部治疗的患者，首选保留肺实质的切除(见 NCCN指南 NSCLC流程的外科治疗原则) [502,503]。VATS或SABR对特定患者可能是有用的[513]。

多发性肺结节 (如实性、亚实性结节) 也可以用低剂量CT扫描检查; 某些结节可以影像学随访, 然而其他的病灶需要活检或切除 (见 NCCN指南的肺癌筛查) [514]。Fleischner协会有对实性结节患者的推荐，最近已经发展出针对亚实性结节的推荐[515,516]。
亚实性结节包括纯毛玻璃样结节和部份实性毛玻璃样结节[515]。毛玻璃样结节也称为非实性结节或毛玻璃影[517] 。实性结节比部份实性结节更可能是恶性的，而毛玻璃样结节很少是恶性的，这些内容反应在NCCN指南的肺癌筛查中[516,518]。

IIIB 期

IIIB期肿瘤包括2组： 1）T1~3N3 者； 2）T4外侵和N2-3者，这些是不可切除的且侵及对侧纵隔(T4, N3)。 不建议对T1~3N3病变 （即对侧淋巴结转移）的患者进行手术， 但对怀疑N3者， 本指南推荐应获得淋巴结病理学证据 （见 NCCN指南 NSCLC流程的治疗前评估 ）[519,520]。 另外， 治疗前评估应包括PET/CT扫描和脑MRI。 如果这些检查结果为阴性， 则根据相应的淋巴结状态选择治疗方案 （见 NCCN指南 NSCLC流程） 。 如果这些检查结果证实为N3病变， 推荐同步化放疗 （1类） 之后再序贯4个周期足剂量的化疗 （如初始未使用足量化疗） [164,297,325,452,453]。PET/CT扫描和脑MRI证实有远处转移患者的治疗详见NCCN指南 NSCLC流程。

对于T4外侵N2~3的IIIB期患者一般不推荐手术切除。初始检查应包括N3和N2淋巴结活检。如果活检结果阴性， 应考虑用与T4N0~1的 IIIA期患者相同的治疗 （见 NCCN指南 NSCLC流程）。如对侧或同侧纵隔淋巴结阳性， 推荐根治性同步化放疗 （1类） 之后再序贯2周期足剂量的化疗 （如初始同步放疗中未使用足量化疗） （见 NCCN指南 NSCLC流程） [198,359,390,521,522]。

IV期

胸腔或心包积液是诊断IV期M1a的一项标准。 注意， 在新版分期 （AJCC第7版） 中， 伴积液的T4划归为IV期M1a（见 NCCN指南 NSCLC流程的分期部份，表3）[87]。虽然90%~95%胸腔积液为恶性， 但它也可能由阻塞性肺炎、 肺不张、 淋巴管或静脉阻塞或肺栓塞引起。因此， 推荐行胸腔或心包穿刺检查获得病理学证实。在胸腔穿刺不能得出结论的病例， 可行胸腔镜检查。胸腔积液如为渗出性或血性， 且没有非肿瘤性病因 （如阻塞性肺炎） ， 则无论细胞学检查结果如何， 均认为是恶性的。 如考虑胸腔积液是阴性的， 则根据已证实的TN分期选择治疗方案 （见 NCCN指南 NSCLC流程 ）。但是， 在所有胸腔积液患者 （不论是否为恶性） 中有95%的病例是不能手术的[524]。恶性积液患者按照M1a期予局部治疗处理， 即携带式胸腔细管引流、 胸膜固定术和心包开窗术，其他同IV期的治疗 （见 NCCN指南 NSCLC流程）[525] 。

NCCN 指南 NSCLC 流程对有远处转移 (即, IV 期, M1b)患者的治疗策略取决于转移部位—脑或肾上腺的孤立病灶，可以通过纵隔镜检查、支气管镜检查、PET/CT 和脑 MRI 来帮助诊断。与其他影像诊断方法相比，PET/CT 敏感 性的提高能发现其他转移灶，从而使一些患者免于不必要的手术。但是 PET/CT 阳性结果需要病理或其他影像学检查证实。 如果 PET/CT 扫描纵隔阳性，则淋巴结状态需经病理证实。

孤立性脑转移患者可能从手术切除获益(见本讨论的全脑放疗和立体定向放射外科，和 NCCN 指南中枢神经系统肿瘤和非小细胞肺癌) [183,326,327]。这类方法治疗后的 5 年生存率在 10% 至 20%之间;[526] 中位生存期约 40 周[330] 。全脑放疗(1 类)或 SRS 后应该随访 [328,342,527]。另一种选择是单纯 SRS 或之后联合全脑照射 [331,332]。这种治疗方法对外科手术无法切除的脑转移和多发性脑转移患者可能有效 [528] 。脑转移灶经治疗后，T1–2, N0–1 或 T3, N0 患者进一步治疗选择包括：1)手术切除肺部病灶序贯化疗; 2) 肺部病灶 SABR;或 3) 增加化疗后再针对肺部病灶手术切除或 SABR。全身治疗是高分期 NSCLC 患者手术后的一种选择。

肺癌的肾上腺转移常见， 尸检时发现约 33%的患者有肾上腺转移。 但是在那些原发肿瘤可切除的病例中， 很多的肾上腺单发肿块并非恶性。 因此术前 CT 扫描发现肾上腺肿块的肺癌患者需行活检以排除良性腺瘤。如果发现肾上腺转移而肺部病变可切除， 行肾上腺转移灶切除后可使部分患者获得长期生存 （2B 类） （见 NCCN 指南 NSCLC 流程）[529-531]。 一些专家组成员认为， 只有同时存在的肺部病变为 I 期或可能为 II 期 （即可切除） ， 切除肾上腺才是有意义的。 肺癌肾上腺转移的另一个治疗选择为全身治疗。

辅助治疗

化疗或化放疗

IA 期（T1abN0） 且切缘阳性（R1、R2） 患者的手术后治疗选择包括：1）再次手术切除（首选） ；2）放疗（2B 类） 。 T1abN0 且切缘阴性（R0）的患者推荐接受观察。T2abN0 且切缘阴性的患者一般仅接受观察， 但是，有高危特征[低分化癌、脉管受侵、 楔形切除术、肿瘤靠近切缘、肿瘤>4 cm、脏层胸膜受累、不完全的淋巴结取样（Nx）]的患者推荐行辅助化疗目前是 2A 类推荐（见 NCCN 指南 NSCLC 流程）[381,532] ； T2abN0 的患者如果切缘为阳性，可选择的有 1）再切除术（首选）±化疗；或 2）放疗加 化疗(化疗推荐用于 IIA 患者)[250,381]。

对于手术切缘阴性的II期病变（包括T1ab~2aN1；T2bN1；和T3N0），专家组推荐化疗（1类）[377,533]。如果上述患者手术切缘为阳性，R1切除后的可选治疗方法包括：1）再次手术切除加化疗；或2）化放疗（序贯或同步）。R2切除后的可选治疗方法包括：1) 再次手术切除加化疗；或 2) 同步化放疗。T1~3N2 或T3N21（只在手术探查和纵隔淋巴结清扫时才发现）且切缘阳性的患者可予化放疗，R1切除者推荐序贯或同步化放疗化疗，而R2切除者推荐同步化放疗（见 NCCN指南 NSCLC流程）。切缘阴性的患者可予1) 化疗（1类）; 或2)序贯化疗加放疗(只用于N2)[377]。

根据E3590临床试验[249]的结果，专家组成员不推荐II期且切缘阴性的患者应用化放疗。在此试验中，II期和IIIA期患者接受手术切除术后辅助放疗（中位生存期39个月）或术后同步化放疗（中位生存期38个月），两治疗组的生存率无差异。

与IB期和II期术后NSCLC患者一样，辅助化疗可用于III期NSCLC手术后患者（见 NCCN指南 NSCLC）。对于可能切除的肺上沟瘤（T4外侵，N0~1），如果经同步化放疗后转为可切除，推荐行手术治疗加化疗（见 NCCN指南 NSCLC）；如病灶仍不可切除，应予全程根治性放疗继以化疗作为辅助治疗。对于胸壁受侵犯的患者（T3~4N0~1），先给予手术切除（首选），如切缘阴性则可以单接受化疗；如术后标本切缘阳性，则可选择1)根据手术是R1或R2行序贯或同步化放疗; 或 2)再切除加化疗。可切除的近端气道肿瘤或侵犯纵隔肿瘤（T3~4N0~1）处理方式与之相似。

IIIA 期纵隔淋巴结阳性（T1~3N2）的患者如在初始治疗后无疾病进展，推荐接受手术加（或不加）RT (如果术前没有做) 和/或加（或不加）化疗（化疗是 2B 类）（见 NCCN 指南 NSCLC）。此外，如术前未放疗，则术后需行放疗。如疾病进展，则患者可接受下述两种治疗之一：1）局部放疗（如尚未放疗过）加（或不加）化疗；2）全身治疗（见 NCCN 指南 NSCLC 流程）。对于原发肿瘤的同一肺叶或同侧非原发肺叶存在分散的肺结节的患者，推荐行手术治疗（见 NCCN 指南 NSCLC 流程）。如果 N2 疾病的切缘阴性，推荐序贯化放疗。如果 N2 疾病切缘阳性，R2 切除者（有时 R1 切除者）推荐同步化放疗。

由于 III 期患者可出现局部和远处失败，采用化疗理论上可清除诊断时显然已存在但无法发现的微小转移灶。目前对于化疗时机的选择各异(见 NCCN 指南的非小细胞肺癌)。化疗可单独给予，也可与放疗序贯或同期给予。此外，对于合适的患者，化疗可以在术前，也可以在术后进行。

基于近来 NSCLC 新辅助和辅助化疗临床研究结果[347-349]， NCCN 专家组将顺铂联合长春瑞滨、 长春花碱、或依托泊苷辅助化疗纳入指南；其他方案包括顺铂联合吉西他滨、 培美曲塞或多西紫杉醇（见 NCCN 指南 NSCLC 流程）[382,395,398]。对于伴有合并症或无法耐受顺铂的患者， 可使用卡铂加紫杉醇方案[382,534]。新近一项针对老年（70 ~89 岁）晚期非小细胞肺癌患者的临床 I I I 期随机试验报告显示， 紫杉醇每周联合卡铂每月的治疗方案与单药使用吉西他滨或长春瑞滨的治疗方案相比，具有改善患者生存的优势（10.3 个月 vs 6.2 个月）[535,536]。然而，关于贝伐单抗对老年人是否有益的数据仍有争议[406,537]。已有多项 II 期试验评估了 III 期 NSCLC 患者新辅助化疗联合或不联合放疗后手术的疗效[538-540]。

3 项 III 期临床试验比较了新辅助化疗后手术与单纯手术治疗 III 期 NSCLC 的疗效[354,541-543]。 SWOG （西南肿瘤协作组） 的 S9900 试验是最大的随机临床试验之一， 它研究了早期 NSCLC 行术前化疗的作用， 比较了单纯手术与紫杉醇联合卡铂化疗后再手术对 IB/IIA 期和 IIB/IIIA 期 NSCLC 患者（肺上沟瘤除外） 的疗效。 术前化疗组无进展生存期和总生存期延长[542,543]。 这 3 项研究均显示接受新辅助化疗的患者具有生存优势。2 项更早期的 III 期研究病例数较少， 而 SWOG 的研究因为 IALT 研究的阳性结果被提前终止。 然而， 现需要进行大规模的随机临床试验对诱导化疗+手术与诱导化疗+放疗两种治疗策略进行比较。

放射治疗

根据 1998 年发表的报道（PORT Meta-analysis Trialists Group, 1998）[544]， NCCN 专家组成员对于 T1abN0 切缘阳性的肺癌单独辅助放疗的意见不一致（2B 类） 。 该研究显示早期完全切除的 NSCLC 患者行术后放疗是有害的， 故对这些患者不应常规行术后放疗。 但本指南的专家组成员在该 Meta 分析中发现几个缺陷， 这些缺陷包括：

- 多数患者接受的是剂量分布不均匀的 60 钴放疗设备的治疗；
- Meta 分析包含了许多自 20 世纪 60 年代以来的研究， 而当时并没有明确的临床分期；
- 数据分析中缺乏术后放疗的具体时机的选择；
- 有淋巴结阴性的 NSCLC 患者 （这些患者常规不予术后放疗） ；
- Meta 分析中包括了未发表的资料。

在 7,465 例肿瘤已切除的 I I、 I I I 期 NSCLC 患者中对术后放疗的评价研究显示， 术后放疗可延长 N2 患者的生存期， 但对 N1 和 N0 患者无此作用[261]。因而，某些癌症组织的指南推荐术后放疗只用于 N2 期患者[545]。ANITA 试验也发现，在接受辅助化疗的患者中，术后放疗可延长 N2 患者的生存期[250]。术后辅助化疗（1 类）加放疗推荐用于 T1~3N2 且切缘阴性的患者（见 NCCN 指南 NSCLC 流程辅助治疗） 。

一个 Meta 分析评估了在 III 期 NSCLC 为主的患者中术后化疗加或不加术后放疗[533]。在这个 Meta 分析中，70%的合格研究在放疗前应用辅助化疗；30%应用同步化放疗。方案包括顺铂/长春瑞滨后放疗或同步顺铂/伊托泊甙。美国大学的放射学适用标准提供了术后辅助治疗的特别推荐[546,547]。

术后辅助同步或序贯化放疗可能是有用的，依手术方式和类别（如 N2 期）而异 (见 NCCN 指南 NSCLC 辅助治疗)。R2 切除推荐同步化/放疗，而 R1 切除推荐序贯化/放疗。NCCN 专家组推荐顺铂/伊托泊甙 作为首选同步新辅助化放疗方案 [389]。培美曲塞联合顺铂或卡铂可能可以用于非鳞癌患者的同步化放疗。

NCCN 指南里出现过的化放疗方案对于II 到 III期患者可能也是有用的[251,252,359,360,390-392]。

随访

无临床或放射影像证据患者的随诊指南如下 (见NCCN 指南非小细胞肺癌)。 手术后的2年内推荐每6~12月进行1次胸部增强或不增强CT， 而后推荐每年1次胸部非增强CT[40,548-551]。 告知患者戒烟（如戒烟劝告、 辅导和治疗） 将有助于肺癌的治疗以及提高患者的生活质量 (http://www.smokefree.gov/) 。最近的数据显示对特定的现在或既往嗜烟者，有肺癌高危（即嗜烟≥ 30-年）者行低剂量CT筛选可降低肺癌死亡率[44]。但NCCN专家组当前不推荐对以前因肺癌治疗过的患者应用低剂量CT随访。

NCCN指南NSCLC包含NSCLC幸存者的长期随访措施（见 NCCN指南NSCLC流程的“癌症幸存者照护” ）。 这些建议包括： 常规的癌症监测、 免疫接种、 健康监测、 促进健康的建议及癌症筛查。最近的分析提示肺癌幸存者在诊断后1年存在高症状负荷而且在治疗后仍需要处理[552]。

复发和远处转移的治疗

复发分为局部区域复发和远处转移。 NCCN指南NSCLC流程（见复发与转移的治疗）列出了许多针对局部区域复发 （如支气管内阻塞、 纵隔淋巴结复发、 上腔静脉阻塞、 严重咯血） 的局部治疗方法。 对于支气管腔内阻塞的患者， 特别是生命受到严重威胁的患者， 减轻气道阻塞可以延长生存， 改善生活质量[553]。 如果局部区域复发治疗后无进一步播散的证据， 建议予观察或全身化疗 （化疗为2B类推荐） 。 但是对于观察到有播散性转移的患者， 推荐全身治疗。而全身治疗的类型应根据组织类型、是否存在任何基因改变，以及体力状态进行选择 （见 NCCN指南NSCLC流程 ） 。

远处转移 （如伴有局部症状骨转移、单发或弥漫性脑转移、或多发转移）的治疗在NCCN指南NSCLC流程图部分进行了描述（见复发和转移的治疗）。远处转移伴有局部症状、 弥漫性脑转移或骨转移的患者应采用外照射放疗以减轻症状[266,554]。 有骨转移的患者可予双膦酸盐或地诺单抗治疗[555-557]。 数据显示，NSCLC骨转移患者应用地诺单抗与唑来膦酸比较可以提高中位总生存(9.5 vs. 8 个月)[483]。地诺单抗可导致严重的低钙血症； 甲状旁腺功能减退的患者或维生素D缺乏的患者发生低钙血症的风险升高。 FDA最近批准地诺单抗用于实体瘤骨转移的治疗[558]。

对于复发和转移的患者， NCCN 指南 NSCLC 推荐在开始治疗前， 应明确组织学类型， 以便于选择最佳治疗 （见 NCCN 指南 NSCLC 组织学亚类）[398]。 另外,因为靶向治疗对于有特定基因改显的患者已经显示出减少肿瘤负荷、减轻症状和戏剧性地改善生活质量，所以当前推荐对于选择性的 NSCLC 患者检测基因改变(即，驱动事件)。可获得的靶向治疗药物越来越多。流程中新增了一个部份用于有特定基因改变患者的治疗推荐 (见 NCCN 指南的非小细胞肺癌中有基因改变患者的靶向药物)。目前推荐用于有特定基因改变患者的靶向药物如下: 阿法替尼，卡博替尼（cabozantinib）, 克唑替尼, 达拉非尼（dabrafenib）, 厄罗替尼,吉非替尼, 曲妥珠单抗, 和维罗非尼（vemurafenib）[54,59,94,95,104,109,112,113,124,126,429,560-564]。

非鳞状细胞癌 （即腺癌、 大细胞癌）或 NSCLC 非特指型（NOS）患者推荐进行 EGFR 突变检测，因为厄洛替尼或阿法替尼 (两者都是 1 类) 被推荐用于有 EGFR 突变阳性患者的治疗 （见 NCCN 指南 NSCLC 流程 EGFR 突变阳性/一线治疗部份）[57,122,144,430,565]。组织学类型为非鳞癌的患者也推荐检测 ALK 重排(1 类)，因为克唑替尼推荐用于 ALK 重排阳性的患者 [98,566]。克唑替尼也推荐用于 ROS1 重排阳性和 MET 扩增的患者(见基因改变患者的靶向药物，NCCN 指南非小细胞肺癌) [95,112,567]。NCCN 专家组推荐 EGFR 突变检测应该作为多变异筛选评估或新一代测序的一部份 。ALK 基因重排可以用 FISH 法或 NGS 检测 [104-106]。

如前文提到的，国际专家组最近的推荐建议避免笼统的组织学分类（如 NSCLC），因为当明确组织学后可能选择更有效的治疗 [49]。纯鳞状细胞癌患者像是没有 EGFR 突变或 ALK 重排;因而这些患者不推荐常规检测 [99,568-570] 。然而，在从未吸烟和从小活检标志中判断的组织学类型或混合组织学类型标本，鳞状细胞癌可以考虑检测 EGFR 突变和 ALK 重排 [99]。然而， 纯鳞状细胞癌患者中很少有 EGFR 突变 （<4%）； 所以， 在这些患者中不推荐常规 EGFR 突变检测 [111,487,488]。

NCCN 指南 NSCLC 流程部分描述了 EGFR 突变或 ALK 重排阴性的非鳞状细胞肺癌患者的治疗推荐和治疗标准。 鳞状细胞肺癌患者的治疗推荐和治疗标准也在 NCCN 指南 NSCLC 流程部分进行了描述。 下文将概述这些相关推荐， 并给出相应的支持性数据 （见本讨论的 “试验数据” ）。

通常 2 药方案（即双药化疗）推荐优于单药（见 NCCN 指南 NSCLC 流程晚期或转移性疾病的系统治疗）；但是靶向治疗也可以加入 2 药方案（如贝伐单抗加入到卡铂/紫杉醇）。单药靶向治疗可能也推荐用于 EGFR 突变、ALK 重排或其它驱动突变的特定患者(见基因改变患者的靶向药物，NCCN 指南非小细胞肺癌) 。

EGFR 突变或 ALK 重排阴性的非鳞状细胞肺癌患者如符合治疗标准， 推荐双药化疗方案如顺铂联合培美曲塞 （1 类），这些方案也推荐用于没有检测变异或突变的患者 [398]。这类患者如符合治疗标准， 贝伐珠单抗联合化疗是另一种选择 [571]。既往， 存在脑转移的患者曾被排除了使用贝伐珠单抗治疗的机会， 原因是担心脑转移会增加中枢神经系统出血的可能性， 然而，数据提示贝伐珠单抗可以用于经治疗的中枢神经系统转移灶患者 [572]。 这类患者还推荐了其他化疗选择， 但某些化疗方案可能更适用于特定的患者，这取决于组织学类型、PS 评分和其它因素(见本讨论的试验数据，晚期或转移性疾病的系统治疗“NCCN 指南非小细胞肺癌”和 NCCN 药物和生物学纲要 [NCCN Compendium®])。 NCCN 专家组成员对西妥昔单抗与顺铂和长春瑞滨联合使用存在分歧 （2B 类） ， 因为数据显示， 治疗方案中西妥昔单抗的加入仅能略微延长患者的生存期 （11.3 个月 vs 10.1 个月，P=0.04），另一个原因是这个方案在美国因为担心顺铂的毒性所以通常不使用 [363,439]。

对于鳞状细胞癌患者， 顺铂联合吉西他滨（1 类）是一种选择 [398]。卡铂/紫杉醇, 顺铂/长春瑞滨(两者都是 1 类), 以及流程中列举的其他方案也可以用(见晚期或转移性疾病的系统治疗，NCCN 指南非小细胞肺癌和 NCCN 纲要)。这类患者的另一选择是西妥昔单抗联合顺铂和长春瑞滨， 但仅做 2B 类推荐 [439]。如前所述，包含培美曲塞或贝伐单抗的方案不推荐用于鳞状细胞癌的患者。 目前，与非鳞癌 NSCLC 相比，鳞状细胞癌患者的治疗选择较少。人们正在进行研究以发现更新的选择 。[3,54,106,573,574]

研究数据

在一个II/III期研究 (ECOG 4599), 878例患者随机分入两组1) 贝伐单抗联合紫杉醇和卡铂；或 2) 单纯紫杉醇和卡铂[402,575]。两个方案的特定毒性但都可耐受。与单纯紫杉醇和卡铂组患者比较贝伐单抗联合紫杉醇和卡铂组患者中位生存改善 (10.3vs. 12.3 个月, *P* = .003) [402]。联合贝伐单抗组与单纯紫杉醇和卡铂组的1年和2年总生存分别为51% vs. 44%和23% vs. 15%，联合贝伐单抗组有优势[402]。但是, 与单纯紫杉醇和卡铂组患者比较贝伐单抗联合紫杉醇和卡铂组有更显著的毒性(4 级中性粒细胞减少: 16.8% vs. 25.5%, 5级咯血: 0% vs. 1.2% 而3级 高血压: 0.5% vs. 6.8%)。
治疗相关死亡贝伐单抗联合紫杉醇和卡铂组（15例）比紫杉醇和卡铂组（2例）多(*P* =.001)。

最近的ECOG 4599研究发现，贝伐单抗联合紫杉醇和卡铂组与单纯化疗组比较 (14.2 vs. 10.3 个月)，组织学类型为腺癌与生存提高有关[571]。然而, 一个研究(AVAiL) 比较了顺铂/吉西他滨联合与不联合贝伐单抗，结果加入贝伐单抗后生存并没有改变[576,577]。

一个非劣效性研究比较了 1725例晚期NSCLC患者(IIIB期 或 IV期; 多数是IV期)人，两组分别为顺铂/吉西他滨与顺铂/培美曲塞[398] 。顺铂/培美曲塞组的腺癌或大细胞癌（即非鳞癌NSCLC）患者生存有改善(腺癌: 12.6 vs. 10.9个月)。顺铂/吉西他滨组鳞状细胞癌患者生存有改善 (10.8 vs. 9.4个月)。

与顺铂/吉西他滨方案相比， 顺铂/培美曲塞方案组发生率显著较低的不良事件有： 3/4级中性粒细胞减少、 贫血和血小板减少 （P≤0.001）； 发热性中性粒细胞减少 （P=0.002）； 脱发 （P<0.001） 。 两种方案的治疗相关死亡率相近[顺铂加培美曲塞， 9例 （1.0%）； 顺铂加吉西他滨， 6例 （0.7％）]。最近对3个3期研究分析证实培美曲塞在非鳞癌NSCLC的一线、二线和维持治疗都可改善生存[578]。

在 FLEX 研究中， 1,125 例晚期 NSCLC 患者（I I IB 期或 IV 期；多数为 IV 期） 被随机分配至以下两组： 1） 西妥昔单抗联合长春瑞滨和顺铂； 或 2） 仅长春瑞滨加顺铂 [439]。 西妥昔单抗的加入使缓解率得以提高 （36% vs 29%，P=0.01）； 但无进展生存期无差别。 接受西妥昔单抗的患者总生存期显著更长 （11.3 个月 vs 10.1 个月， P=0.04） 。 然而， 接受西妥昔单抗的患者比对照组的 4 级事件更多见 （62% vs 52%， P<0.01） ， 且该组患者出现了 2 级痤疮样皮疹。 治疗相关死亡率两组相近 （3% vs 2%） 。
研究数据显示， 对于不可治愈的晚期患者， 含顺铂的联合治疗方案优于最佳支持治疗。 已有研究证实顺铂或卡铂同下述任一药物联用有效： 多西他赛、 依托泊苷、 吉西他滨、 紫杉醇(和白蛋白结合紫杉醇)、 培美曲塞、 长春花碱、 长春瑞滨 [382,395-398,417,418,426]。数据显示非铂方案（如吉西他滨/多西他赛，吉西他滨/长春滨瑞）有活性且毒性比含铂方案小，是合理的替代方案[420-423,579]。

一线系统治疗的周期数

晚期患者一线系统治疗应该用CT扫描评价疗效。约25%的患者在化疗第 1 周期后出现疾病进展。这些患者推荐行二线治疗(见 NCCN 指南的 NSCLC 流程)。有效或稳定的患者可以连续接受总共 4-6 周期的系统治疗 [364,454,580]。当前 NCCN 指南不推荐 4-6 周期后继续化疗。

最近来自PARAMOUNT研究的数据建议4周期含铂方案治疗不是最佳的;[444]肿瘤在4-6周期化疗中可能缩小。然而患者可能无法耐受超过4周期化疗，大多数维持研究只有应用4周期化疗[403]。一个Meta分析显示继续维持初始治疗超过4-6周期可以延长PFS;然而，这些患者出现更多的副反应[581]。一个 III期随机研究提示超过4-6周期继续化疗并不受益；而很多分组到长疗程治疗组的病人没有接受计划的周期数[453,454]。在这个III期研究中，应用以紫杉类为基础的方案，应用更多周期化疗的病人神经毒性增多[454]。

现在很多患者接受培美曲塞为基础的方案，而不是紫杉类为基础的方案。培美曲塞为基础的方案比紫杉类为基础的方案的毒性较少。因而，一线化疗不超过6周期的建议可能只适用于紫杉类基础的方案[403]。研究报导60%的病人可以接受6周期培美曲塞为基础的化疗(而且毒性反应低), 然而，只有42%能接受超过5周期紫杉类为基础化疗，通常因为神经毒性中途退出。[442,454]

维持治疗

维持治疗是一线系统治疗后有效或稳定的晚期 NSCLC 患者的另一种选择, (见 NCCN 指南 NSCLC 流程)。非鳞癌的 EGFR 无突变或 ALK 重排阴性 NSCLC 患者，持续维持治疗方案包括贝伐单抗 (1 类), 西妥昔单抗(1 类), 培美曲塞(1 类),贝伐单抗 /培美曲塞, 或吉西他滨 (见 NCCN 指南 NSCLC 流程) [402,404,439,444,445,449-451]。这些病人的转换维持治疗方案包括培美曲塞或厄罗替尼 (都是 2B 类)[450,451,456,457]。一个 III 期随机研究 (n = 663)评价了接受含铂方案化疗后没有进展的晚期 NSCLC 患者最佳支持治疗用（或用）培美曲塞换药维持治疗 [457]。在非鳞癌的 NSCLC 患者中, 应用培美曲塞组与空白组对比总生存改善 (15.5 vs. 10.3 个月, *P* =.002)。密切观察是另一种选择。维持治疗在本章的前部份已经更详细讨论了。

对于鳞状细胞癌患者, 西妥昔单抗(1类)或吉西他滨(2B类)可以用于持续维持治疗(见NCCN指南 NSCLC流程) [451,456]。这些病人的转换维持包括厄罗替尼或多西他赛 (都是2B类)。密切观察是另一种选择。一个III期研究比较了化疗后立即予多西他赛转换维持或延迟到进展后才用[460]。但是,多西他赛转换维持是NCCN指南的2B类推荐，因为很多延迟化疗组的病人没有接受多西他赛[582]。

厄罗替尼、吉非替尼或阿法替尼进展后维持

因为吉非替尼的应用受限制，厄罗替尼通常在美国应用于EGFR突变的选择性病人。然而，在吉非替尼能获得的情况下可以应用。在疾病进展后，患者可能继续从厄罗替尼或吉非替尼中获益;
停用厄罗替尼或吉非替尼将导致更快的疾病进展(症状, 肿瘤大小, 和PET扫描中的FDG活性)[583]。这个策略在其他癌基因“成瘾”肿瘤中的经验也反应出来, 特别是HER-2扩增的乳腺癌。应用曲妥珠单抗进展的HER-2扩增的乳腺癌妇女，在曲妥珠单抗加入常规化疗后，能观察影像学反应、疾病进展时间和总生存改善[584]。数据支持*EGFR突变的肺腺癌患者在厄罗替尼获得性耐药进展后，继续应用厄罗替尼*。NCCN专家组推荐在无症状进展的患者中继续应用厄罗替尼或阿法替尼；但在有症状进展患者中治疗应该改变(见NCCN指南的非小细胞肺癌)[561,585,586]。多数病例中，厄罗替尼继续使用；但是应该加入额外的治疗 (如,全脑放疗，局部治疗、系统治疗)。

越来越多的数据说明癌症患者是如何对EGFR抑制剂抗拒的[587]。已知的最常见机制是EGFR-T790M二次突变的获得，这个突变使激酶对厄罗替尼和吉非替尼抗拒[588,589]。MET癌基因的扩增是另一个证实的耐药机制。为了克服耐药，EGFR仍然应该抑制。在MET扩增的病例中，应该在EGFR抑制剂基础上加入新抑制剂;

然而, EGFR抑制仍然要求用于诱导缓解。进而，Riely等的数据显示当癌症患者开始进展，这些病人一度对EGFR抑制剂敏感，中断EGFR-TKI将导致癌症加速进展[583,590]。因而,即使是EGFR TKIs耐药后，继续使用EGFR TKIs对很多患者仍是有益的。

二线和三线全身治疗

虽然对于肺癌已有多个有活性的新药, 在二线全身治疗中的应用中报导有效率通常低于 10%。对于所有组织学类型来说，如果之前没有用过多西他赛, 厄罗替尼或吉西他滨，可以推荐作为一线治疗期间或治疗后进展，PS0-2 分患者的二线系统治疗方案(见 NCCN 指南非小细胞肺癌) [591-600]。对于非鳞癌 NSCLC 没有敏感 EGFR 突变者, 培美曲塞推荐用于二线治疗。对于有敏感 EGFR 突变或 ALK 阳性的非鳞癌 NSCLC 患者，按患者是否有症状推荐二线治疗流程。已证实多西他赛优于最佳支持治疗, 长春瑞滨或异环磷酰胺能改善生存和生活质量[597,598]。培美曲赛与多西他赛比较中位生存相似但毒性降低[599,601]。培美曲赛推荐用于腺癌或大细胞癌患者 (如, 非鳞的 NSCLC) [457] 。已证实厄罗替尼优于最佳支持治疗，显著改善生存及延迟疾病出现恶化的时间[600]。在EGFR突变，PS评分 3到4分的患者中，厄罗替尼推荐用于疾病进展后的二线或三线治疗 (见NCCN 指南NSCLC流程)。非鳞癌NSCLC患者一线厄罗替尼、阿法替尼或克唑替尼治疗后出现有症状的全身多发病灶可选择含铂双药联合（或不联合）贝伐单抗和/或联合（或不联合）厄罗替尼[402] 。根据多个研究，阿法替尼推荐用于敏感EGFR突变患者一线治疗进展后的二线治疗[122,561,585,586]。

在一个随机、空白对照、双盲试验中(NCIC CTG trial),731例患者（IIIB 或 IV 期, PS 0–3）在一线或二线化疗失败后随机分组 (2:1) 接受厄罗替尼或安慰剂[600]。

厄罗替尼组总生存6.7个月而安慰剂组4.7 个月 (危险比, 0.70; *P* < .001). 厄罗替尼组PFS2.2个月而安慰剂组1.8个月 (危险比, 0.61; *P* < .001)。然而5%的患者因为毒副反应中断厄罗替尼。这个研究证实了一线或二线系统治疗失败后的病人应用厄罗替尼能延长生存。一个入组829例病人的随机III期研究发现口服拓扑替康不优于多西他赛[602]。

培美曲塞 (只用于非鳞癌), 多西他赛, 吉西他滨或厄罗替尼推荐用于晚期NSCLC患者的二线或三线治疗，如果这些药物之前的治疗没用过[592,603,604]。如果三线化疗进展后，患者PS0-2分，应该选择最佳支持治疗或入组临床研究(见NCCN指南的姑息治疗)[5,370,371]。三线治疗的疗效有限，虽然它在姑息治疗中有用[605]。

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