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Non–Small Cell Lung Cancer, Version 1.2015

Clinical Practice Guidelines in Oncology

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Overview

This selection from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non–Small Cell Lung Cancer (NSCLC) focuses on the *Principles of Radiation Therapy* (see NSCL-C, pages 1740–1746). The complete version of the NCCN Guidelines, available at NCCN.org, addresses all as-

Abstract

This selection from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non–Small Cell Lung Cancer (NSCLC) focuses on the principles of radiation therapy (RT), which include the following: (1) general principles for early-stage, locally advanced, and advanced/metastatic NSCLC; (2) target volumes, prescription doses, and normal tissue dose constraints for early-stage, locally advanced, and advanced/palliative RT; and (3) RT simulation, planning, and delivery. Treatment recommendations should be made by a multidisciplinary team, including board-certified radiation oncologists who perform lung cancer RT as a prominent part of their practice. (J Natl Compr Canc Netw 2014;12:1738–1761)

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.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Non–Small Cell Lung Cancer are not printed in this issue of JNCCN but can be accessed online at NCCN.org.**

Disclosures for the Non–Small Cell Lung Cancer Oncology Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Non–Small Cell Lung Cancer Panel members can be found on page 1761. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

pects of management for NSCLC including screening, diagnosis, evaluation, staging, treatment, surveillance, and therapy for recurrence and metastasis.

This portion of the guidelines provides a brief overview of risk factors, prevention, screening, classification, and prognostic factors for lung cancer. A recent review discusses the progress that has been made in NSCLC.[1] By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the panel members while developing these NCCN Guidelines.

Lung cancer is the leading cause of cancer death in the United States. In 2014, an estimated 224,210 new cases (116,000 in men and 108,210 in women) of lung and bronchial cancer will be diagnosed, and 159,260 deaths (86,930 men and 72,330 women) will occur because of the disease.[2] Only 16.8% of all patients with lung cancer are alive 5 years or more after diagnosis.[3,4] However, much progress in lung cancer has been made recently, such as screening, minimally invasive techniques for diagnosis and treatment, and advances in RT, including stereotactic ablative radiotherapy (SABR), also known as stereotactic body RT (SBRT).[1,5,6] Common symptoms of lung cancer include cough, dyspnea, weight loss, and chest pain; patients with symptoms are more likely to have chronic obstructive pulmonary disease.[7]

Risk Factors

The primary risk factor for lung cancer is smoking tobacco, which accounts for most lung cancer-related

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PRINCIPLES OF RADIATION THERAPY

General Principles (see Table 1. Commonly Used Abbreviations in Radiation Therapy, on NSCL-C 5 of 9)

- Determination of the appropriateness of RT should be made by board-certified radiation oncologists who perform lung cancer RT as a prominent part of their practice.
- RT has a potential role in all stages of NSCLC, as either definitive or palliative therapy. Radiation oncology input as part of a multidisciplinary evaluation or discussion should be provided for all patients with NSCLC.
- The critical goals of modern RT are to maximize tumor control and minimize treatment toxicity. A minimum technologic standard is CT-planned 3D-CRT.[1]
- More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, IMRT/VMAT, IGRT, motion management, and proton therapy (https://www.astro.org/Practice-Management/Reimbursement/Model-Policies.aspx). Nonrandomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival.[2-4]
- Centers using advanced technologies should implement and document modality-specific quality assurance measures. The ideal is external credentialing of both treatment planning and delivery such as required for participation in RTOG clinical trials using advanced technologies. Useful references include the ACR-ASTRO Practice Guidelines for Radiation Oncology (http://www.acr.org/~/media/ACR/Documents/PGTS/toc.pdf).

Early-Stage NSCLC (Stage I)

- SABR (also known as SBRT) is recommended for patients who are medically inoperable or refuse to have surgery after thoracic surgery evaluation. SABR has achieved primary tumor control rates and overall survival comparable to lobectomy and higher than 3D-CRT in nonrandomized and population-based comparisons in medically inoperable or older patients.[5-10]
- SABR is also an appropriate option for patients with high surgical risk (able to tolerate sublobar resection but not lobectomy [eg, age ≥75 y], poor lung function). SABR and sublobar resection achieve comparable cancer-specific survival and primary tumor control.[10-12]
- For institutions without an established SABR program, more modestly hypofractionated or dose-intensified conventionally fractionated 3D-CRT regimens are alternatives.[13,14]
- In patients treated with surgery, PORT is not recommended unless they have positive margins or are upstaged to N2 (see *Locally Advanced NSCLC* below).

Locally Advanced NSCLC (Stage II-III)

- The standard of care for patients with inoperable stage II and stage III NSCLC is concurrent chemoRT.[15-17] (http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/NonsurgicalTreatmentForNSCLCGoodPerformanceStatusDefinitiveIntent.pdf) RT interruptions and dose reductions for manageable acute toxicities should be avoided through using supportive care.
- Sequential chemoRT or RT alone is appropriate for frail patients unable to tolerate concurrent therapy.[18,19] (http://www.acr.org/~/media/ACR/Documents/AppCriteria/OncologyNonsurgicalTreatmentForNSCLCPoorPerformanceStatusOrPalliativeIntent.pdf)
- Accelerated RT regimens may be beneficial, particularly if not concurrent with chemotherapy (ie, in a sequential or RT-only approach).[20,21]
- RT has a role before or after surgery. (http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/InductionAndAdjuvantTherapyForN2NSCLC.pdf)
  - Preoperative concurrent chemoRT is an option for patients with resectable stage IIIA (minimal N2 and treatable with lobectomy)[22] and is recommended for resectable superior sulcus tumors.[23-24]
  - Preoperative chemotherapy and postoperative RT is an alternative for patients with resectable stage IIIA.[25,26]
  - The determination of resectability in trimodality therapy should be made before initiation of all treatment.
  - In patients with clinical stage I/II upstaged surgically to N2+, PORT seems to improve survival significantly as an adjunct to postoperative chemotherapy in nonrandomized analyses.[27,28] Although the optimal sequence is not established, PORT is generally administered after postoperative chemotherapy. PORT with concurrent chemotherapy can be administered safely in medically fit patients[29-31] and is recommended for positive resection margins.
  - PORT is not recommended for patients with pathologic stage N0-1 disease, because it has been associated with increased mortality, at least when using older RT techniques.[32]

Advanced/Metastatic NSCLC (Stage IV)

- RT is recommended for local palliation or prevention of symptoms (eg, pain, bleeding, obstruction).
- Definitive local therapy to isolated or limited metastatic sites (oligometastases) (including but not limited to brain, lung, and adrenal gland) achieves prolonged survival in a small proportion of well-selected patients with good performance status who have also received radical therapy to the intrathoracic disease. Definitive RT to oligometastases, particularly SABR, is an appropriate option in such cases if it can be delivered safely to the involved sites.[33,34]
- See the NCCN Clnical Practice Guidelines in Oncology (NCCN Guidelines) for Central Nervous System Cancers regarding RT for brain metastases (to view the most recent version, visit NCCN.org).

Target Volumes, Prescription Doses, and Normal Tissue Dose Constraints (See Tables 2–5 on NSCL-C 6 of 9 and NSCL-C 7 of 9)

- ICRU Reports 62 and 83 detail the current definitions of target volumes for 3D-RT and IMRT. GTV comprises the known extent of disease (primary and nodal) on imaging and pathologic assessment, CTV includes regions of presumed microscopic extent or dissemination, and PTV comprises the ITV (which includes margin for target motion) plus a setup margin for positioning and mechanical variability. (http://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx)
- PTV margin can be decreased using immobilization, motion management, and IGRT techniques.
- Consistent delineation of normal structures is critical for evaluating plans for safety. The RTOG consensus lung-contouring atlas is a useful resource. (http://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx)
- Commonly used prescription doses and normal tissue dose constraints are summarized in Tables 2 through 5. These are based on published experience, ongoing trials, historical data, modeling, and empirical judgment.[35,36] Useful references include the recent reviews of normal organ dose responses from the QUANTEC project.[37-41]

Node-Negative Early-Stage SABR

- The high-dose intensity and conformity of SABR require minimizing the PTV.
- For SABR, intensive regimens of BED ≥100 Gy are associated with significantly better local control and survival than less intensive regimens.[42] In the United States, only regimens of ≤5 fractions meet the arbitrary billing code definition of SBRT, but slightly more protracted regimens are also appropriate.[42,43] For centrally located tumors (defined as within 2 cm of the proximal bronchial tree), 4- to 10-fraction risk-adapted SABR regimens seem to be effective and safe,[43,44] whereas 54 to 60 Gy in 3 fractions is unsafe and should be avoided.[45] The dose for 5-fraction regimens is being studied prospectively in RTOG 0813.
- SABR is most commonly used for tumors up to 5 cm in size, although selected larger isolated tumors can be treated safely if normal tissue constraints are respected.[46]
- Prescription doses incompletely describe the actual delivered doses, which also strongly depend on how the dose is prescribed (to the isocenter vs an isodose volume covering a proportion of the PTV), the degree of dose heterogeneity, whether tissue density heterogeneity corrections are used, and the type of dose calculation algorithm.[47,48] All of these must be considered when interpreting or emulating regimens from prior studies.

Locally Advanced Stage/Conventionally Fractionated RT

- IFI omitting ENI allows tumor dose escalation and is associated with a low risk of isolated nodal relapse, particularly in PET/CT–staged patients.[49-53] One randomized trial found improved survival for IFI versus ENI, possibly because it enabled dose escalation.[54] IFI is reasonable in order to optimize definitive dosing to the tumor.
- The most commonly prescribed doses for definitive RT are 60 to 70 Gy in 2-Gy fractions. Doses of at least 60 Gy should be given.[55] Dose escalation in RT alone,[56] sequential chemoRT,[57] or concurrent chemoRT[58] is associated with better survival in nonrandomized comparisons. Although doses of up to 74 Gy with concurrent chemotherapy can be delivered safely when normal tissue dose constraints are respected,[59-62] preliminary results from RTOG 0617, comparing 60 versus 74 Gy with concurrent chemotherapy, found that 74 Gy does not improve overall survival, and therefore is not currently a standard dose.[63] A meta-analysis demonstrated improved survival with accelerated fractionation RT regimens,[64] and individualized accelerated RT dose intensification is now being evaluated in a randomized trial (RTOG 1106).
- Doses of 45 to 50 Gy in 1.8- to 2.0-Gy fractions are standard preoperative doses. Definitive RT doses delivered as preoperative chemoRT can safely be administered and achieve promising nodal clearance and survival rates,[65-68] but require experience in thoracic surgical techniques to minimize the risk of surgical complications after high-dose RT.
- In PORT, the CTV includes the bronchial stump and high-risk draining lymph node stations.[69] Standard doses after complete resection are 50 to 54 Gy in 1.8- to 2.0-Gy fractions, but a boost may be administered to high-risk regions, including areas of nodal extracapsular extension or microscopic positive margins.[29,30] Lung dose constraints should be more conservative, because tolerance seems to be reduced after surgery. The ongoing European LungART trial provides useful guidelines for PORT technique.[70]

Advanced Stage/Palliative RT

- The dose and fractionation of palliative RT should be individualized based on goals of care, symptoms, performance status, and logistical considerations. Shorter courses of RT provide similar pain relief as longer courses, but with a higher potential need for retreatment,[71-74] and are preferred for patients with poor performance status and/or shorter life expectancy. For palliation of thoracic symptoms, higher dose/longer-course thoracic RT (eg, ≥30 Gy in 10 fractions) is associated with modestly improved survival and symptoms, particularly in patients with good performance status.[75] When higher doses (>30 Gy) are warranted, 3D-CRT should be used to reduce normal tissue irradiation.

Radiation Therapy Simulation, Planning, and Delivery

- Simulation should be performed using CT scans obtained in the RT treatment position with appropriate immobilization devices. Intravenous contrast with or without oral contrast is recommended for better target/organ delineation whenever possible in patients with central tumors or nodal disease. Because intravenous contrast can affect tissue heterogeneity correction calculations, density masking or use of a precontrast scan may be needed when intense enhancement is present.
- PET/CT significantly improves targeting accuracy,[76] especially for patients with significant atelectasis and when intravenous CT contrast is contraindicated. A randomized trial of PET/CT versus CT-only RT planning demonstrated improved preemption of futile radical RT, decreased recurrences, and a trend toward improved overall survival with PET/CT RT planning.[77] Given the potential for rapid progression of NSCLC,[78,79] PET/CT should be obtained preferably within 4 weeks before treatment. It is ideal to obtain PET/CT in the treatment position.
- Tumor and organ motion, especially owing to breathing, should be assessed or accounted for at simulation. Options include fluoroscopy, inhale/exhale or slow scan CT, or, ideally, 4D-CT.
- Photon beam energy should be individualized based on the anatomic location of the tumors and beam paths. In general, photon energies between 4 and 10 MV are recommended for beams passing through low-density lung tissue before entering the tumor. When there is no air gap before the beam enters the tumor (such as for some large mediastinal tumors or tumors attached to chest wall), higher energies may improve the dose distribution, especially when using a smaller number of fixed beam angles.
- Tissue heterogeneity correction and accurate dose calculation algorithms that account for buildup and lateral electron scatter effects in heterogeneous density tissues are recommended. Heterogeneity correction with simple pencil beam algorithms is not recommended.[48]
- Respiratory motion should be managed when motion is excessive. Methods include (but are not limited to) forced shallow breathing with abdominal compression, accelerator beam gating with the respiratory cycle, dynamic tumor tracking, ABC, and coaching/biofeedback techniques. If motion is minimal or the ITV is small, motion-encompassing targeting is appropriate. A useful resource for implementation of respiratory motion management is the report of AAPM Task Group 76.[80]
- IGRT, including (but not limited to) orthogonal pair planar imaging and volumetric imaging (such as CBCT or CT on rails), is recommended when using SABR and 3D-CRT/IMRT with steep dose gradients around the target, when OARs are close to high-dose regions, and when using complex motion management techniques.

Table 1. Commonly Used Abbreviations in Radiation Therapy

RT	Radiation therapy or radiotherapy
2D-RT	2-Dimensional RT
3D-CRT	3-Dimensional conformal RT
4D-CT	4-Dimensional computed tomography
AAPM	American Association of Physicists in Medicine
ABC	Active breathing control
ACR	American College of Radiology
ASTRO	American Society for Radiation Oncology
BED	Biologically effective dose
CBCT	Cone-beam CT
CTV*	Clinical target volume
ENI	Elective nodal irradiation
GTV*	Gross tumor volume
ICRU	International Commission on Radiation Units and Measurements
IFI	Involved field irradiation
IGRT	Image-guided RT
IMRT	Intensity-modulated RT
ITV*	Internal target volume
OAR	Organ at risk
OBI	On-board imaging
PORT	Postoperative RT
PTV*	Planning target volume
QUANTEC	Quantitative analysis of normal tissue effects in the clinic
RTOG	Radiation Therapy Oncology Group
SABR	Stereotactic ablative RT, also known as stereotactic body RT (SBRT)
VMAT	Volumetric modulated arc therapy

*Refer to ICRU Report 83 for detailed definitions.

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Table 2. Commonly Used Doses for SABR

Total Dose	No. of Fractions	Example Indications
25–34 Gy	1	Peripheral, small (<2 cm) tumors, especially >1 cm from chest wall
45–60 Gy	3	Peripheral tumors and >1 cm from chest wall
48–50 Gy	4	Central or peripheral tumors <4–5 cm, especially <1 cm from chest wall
50–55 Gy	5	Central or peripheral tumors, especially <1 cm from chest wall
60–70 Gy	8–10	Central tumors

Table 3. Maximum Dose Constraints for SABR*

OAR/Regimen	1 Fraction	3 Fractions	4 Fractions	5 Fractions
Spinal cord	14.0 Gy	18 Gy (6 Gy/fx)	26.0 Gy (6.5 Gy/fx)	30.0 Gy (6.0 Gy/fx)
Esophagus	15.4 Gy	27 Gy (9 Gy/fx)	30.0 Gy (7.5 Gy/fx)	105% of PTV prescription^
Brachial plexus	17.5 Gy	24 Gy (8 Gy/fx)	27.2 Gy (6.8 Gy/fx)	32.0 Gy (6.4 Gy/fx)
Heart/ Pericardium	22.0 Gy	30 Gy (10 Gy/fx)	34.0 Gy (8.5 Gy/fx)	105% of PTV prescription^
Great vessels	37.0 Gy	NS	49.0 Gy (12.25 Gy/fx)	105% of PTV prescription^
Trachea & proximal bronchi	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	105% of PTV prescription^
Rib	30.0 Gy	30 Gy (10 Gy/fx)	40.0 Gy (10.0 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Skin	26.0 Gy	24 Gy (8 Gy/fx)	36.0 Gy (9.0 Gy/fx)	32.0 Gy (6.4 Gy/fx)
Stomach	12.4 Gy	NS	27.2 Gy (6.8 Gy/fx)	NS

*Based on constraints used in recent RTOG SABR trials (RTOG 0618, 0813, & 0915).

^for central tumor location.

NS = not specified.

Table 4. Commonly Used Doses for Conventionally Fractionated and Palliative RT

Treatment Type	Total Dose	Fraction Size	Treatment Duration
Definitive RT with or without chemotherapy	60–70 Gy	2 Gy	6–7 wk
Preoperative RT	45–50 Gy	1.8–2.0 Gy	5 wk
Postoperative RT			
• Negative margins	50–54 Gy	1.8–2.0 Gy	5–6 wk
• Extracapsular nodal extension or microscopic positive margins	54–60 Gy	1.8–2.0 Gy	6 wk
• Gross residual tumor	60–70 Gy	2.0 Gy	6–7 wk
Palliative RT			
• Obstructive disease (SVC syndrome or obstructive pneumonia)	30–45 Gy	3.0 Gy	2–3 wk
• Bone metastases with soft tissue mass	20–30 Gy	4.0–3.0 Gy	1–2 wk
• Bone metastases without soft tissue mass	8–30 Gy	8.0–3.0 Gy	1 day–2 wk
• Brain metastases	CNS GLs*	CNS GLs*	CNS GLs*
• Symptomatic chest disease in patients with poor PS	17 Gy	8.5 Gy	1–2 wk
• Any metastasis in patients with poor PS	8–20 Gy	8.0–4.0 Gy	1 d–1 wk

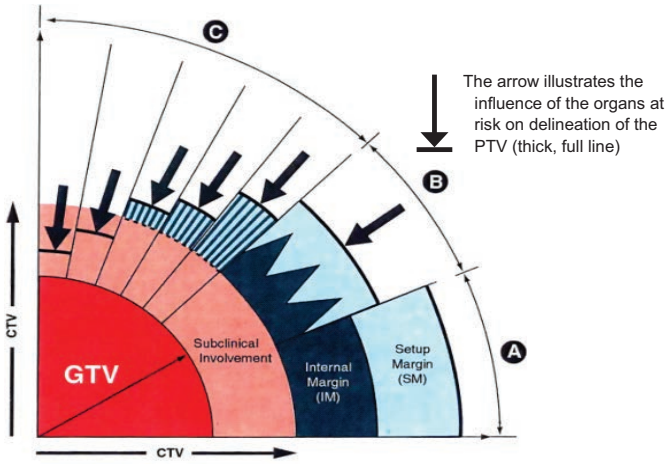
*NCCN Guidelines for Central Nervous System Cancers; to view the most recent version, visit NCCN.org.

Table 5. Normal Tissue Dose-Volume Constraints for Conventionally Fractionated RT

OAR	Constraints in 30–35 Fractions
Spinal cord	Max ≤50 Gy
Lung	V20 ≤35%; V5 ≤65%; MLD ≤20 Gy
Heart	V40 ≤80%; V45 ≤60%; V60 ≤30%; Mean ≤35 Gy
Esophagus	Mean ≤34 Gy; Max ≤105% of prescription dose
Brachial plexus	Max ≤66 Gy

Vxx = % of the whole OAR receiving ≥xx Gy.

Figure 1. ICRU Report 62 Schema of Target Volume Definitions



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Text cont. from page 1739.

deaths.[8–13] Cigarette smoke contains many carcinogenic chemicals (eg, nitrosamines, benzo[a]pyrene diol epoxide).[12,14] The risk for lung cancer increases with the number of packs of cigarettes smoked per day and the number of years spent smoking (ie, pack-years of smoking history). Exposed nonsmokers also have an increased relative risk (RR) of developing lung cancer from secondhand smoke (RR, 1.24); other studies have reported a modest risk (hazard ratio [HR], 1.05).[10,14–17] Radon gas, a radioactive gas that is produced by the decay of radium 226, also seems to cause lung cancer.[8,18–21] The U.S. Environmental Protection Agency estimates that radon is the main cause of lung cancer in nonsmokers; however, secondhand smoke may also be a factor. A review conducted by the International Agency for Research on Cancer of the WHO concluded that outdoor air pollution is a leading environmental cause of lung cancer deaths.[22]

Asbestos, a mineral compound that breaks into small airborne shards, is a known carcinogen that increases the risk for lung cancer in people exposed to airborne fibers, especially in individuals who smoke. It is estimated that 3% to 4% of lung cancers are caused by asbestos exposure.[23] In addition, other possible risk factors for lung cancer include recurring lung inflammation, lung scarring secondary to tuberculosis, family history, and exposure to other carcinogens (eg, bis[chloromethyl]ether, polycyclic aromatic hydrocarbons, chromium, nickel, organic arsenic compounds).[24,25] The International Agency for Research on Cancer lists several agents known to cause lung cancer, including arsenic, chromium, asbestos, nickel, cadmium, beryllium, silica, and diesel fumes.[26,27] Asbestos also causes malignant pleural mesothelioma (see the NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Malignant Pleural Mesothelioma; to view the most recent version of these guidelines, visit NCCN.org).

Smoking Cessation

Approximately 85% to 90% of cases of lung cancer are caused by cigarette smoking.[11] Active smoking and secondhand smoke both cause lung cancer (see Reports of the Surgeon General; www.surgeongeneral.gov). A causal relationship exists between active smoking and lung cancer and also between other cancers (eg, esophageal, oral cavity, laryngeal, pharyngeal, bladder, pancreatic, gastric, kidney, ovarian cancer, colorectal, and cervical cancers) and other diseases and conditions. Smoking harms nearly every organ in the body, and smokers have increased mortality compared with nonsmokers.[28] People who live with someone who smokes also have an increased risk for lung cancer. Further complicating this problem, cigarettes also contain nicotine, which is a highly addictive substance.

Oncologists should encourage smoking cessation, especially in patients with cancer.[29–31] The 5 A's framework is a useful tool: Ask, Advise, Assess, Assist, Arrange. It is in the best interest of patients to quit smoking. Persistent smoking is associated with second primary cancers, treatment complications, and decreased survival.[32] Some surgeons will not operate on a current smoker. Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA) can be very useful.

Agents that can be used to promote smoking cessation include nicotine replacement (eg, gum, inhaler, lozenge, nasal spray, patch), bupropion sustained release, and varenicline. Studies have shown that varenicline is better than bupropion or nicotine patch for smoking cessation.[33–35] However, almost 30% of patients had nausea while using varenicline.[36] The effectiveness of varenicline for preventing relapse has not been clearly established.[37] The FDA has issued an alert for varenicline regarding neuropsychiatric symptoms. Varenicline has also been associated with other disorders (eg, visual disturbances, movement disorders, unconsciousness, cardiovascular disorders) and, therefore, is banned in truck and bus drivers, pilots, and air traffic controllers.[38] Bupropion may be also associated with similar serious neuropsychiatric symptoms. Nicotine replacement has fewer adverse effects than varenicline or bupropion.[39] However, despite the potential adverse effects, it is probably more beneficial for motivated patients to use agents to promote smoking cessation.[39]

Lung Cancer Screening

Lung cancer is still the leading cause of cancer death worldwide, and late diagnosis is a major obstacle to improving lung cancer outcomes.[40,41] Because localized cancer can be managed curatively and because the mortality rate in other solid tumors (eg, cervix, colon) seems to be decreased by screening and early detection, lung cancer was an appropriate candidate for a population-based screening approach.

The National Lung Screening Trial (NLST; ACRIN Protocol A6654) was a randomized controlled study involving more than 53,000 current or former heavy smokers; this trial assessed the risks and benefits of low-dose helical CT scans compared with chest radiographs for detecting lung cancer.[42] Data from the NLST showed that screening individuals with high-risk factors using low-dose helical CT decreased the mortality rate from lung cancer by 20% compared with screening with chest radiograph.[43] Individuals with high-risk factors were current or former smokers with a 30 or more pack-year smoking history (former smokers had quit up to 15 years before enrollment), were 55 to 74 years of age, and had no evidence of lung cancer.[42,44] NCCN, the American Cancer Society, the U.S. Preventive Services Task Force, and other organizations recommend lung cancer screening using low-dose helical CT for select high-risk current and former smokers (see the NCCN Guidelines for Lung Cancer Screening; available at NCCN.org).[45,46]

Classification and Prognostic Factors

The WHO divides lung cancer into 2 major classes based on its biology, therapy, and prognosis: NSCLC and small cell lung cancer (see the NCCN Guidelines for Small Cell Lung Cancer, available at NCCN.org). NSCLC accounts for more than 85% of all lung cancer cases, and includes 2 major types: nonsquamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other cell types); and squamous cell (epidermoid) carcinoma. Adenocarcinoma is the most common type of lung cancer seen in the United States and is also the most frequently occurring histology in nonsmokers. In 2011, an international panel revised the classification of lung adenocarcinoma (see "Pathologic Evaluation of Lung Cancer" in the complete version of these guidelines at NCCN.org).[47] Certain prognostic factors are predictive of survival in patients with NSCLC. Good prognostic factors include early-stage disease at diagnosis, good performance status (PS; ECOG 0, 1, or 2), no significant weight loss (not more than 5%), and female sex.[48]

Treatment Approaches

Surgery, radiation therapy (RT), and chemotherapy are the 3 modalities most commonly used to treat patients with NSCLC. They can be used either alone or in combination depending on the disease status. This Discussion focuses on the use of RT for treatment of NSCLC.

Radiation Therapy

The "Principles of Radiation Therapy" include the following: (1) general principles for early-stage, locally advanced, and advanced NSCLC; (2) target volumes, prescription doses, and normal tissue dose constraints for early-stage, locally advanced, and advanced NSCLC; and (3) RT simulation, planning, and delivery (see NSCL-C, pages 1740–1746).[49–54] These RT principles are summarized in this section. Whole-brain RT (WBRT) and stereotactic radiosurgery (SRS) for brain metastases are also discussed in this section. The abbreviations for RT are defined in the algorithm (see Table 1, page1742).

General Principles: Treatment recommendations should be made by a multidisciplinary team. Because RT has a potential role in all stages of NSCLC, as either definitive or palliative therapy, input from board-certified radiation oncologists who perform lung cancer RT as a prominent part of their practice should be included in a multidisciplinary evaluation or discussion for all patients with NSCLC. Uses of RT for NSCLC include (1) definitive therapy for locally advanced NSCLC, generally combined with chemotherapy; (2) definitive therapy for early-stage NSCLC in patients with contraindications for surgery; (3) preoperative or postoperative therapy for selected patients treated with surgery; (4) salvage therapy for limited recurrences and metastases; and/or (5) palliative therapy for patients with incurable NSCLC.[55–62] The goals of RT are to maximize tumor control and minimize treatment toxicity. Advanced technologies such as 4D-conformal RT simulation, intensity-modulated radiotherapy/volumetric modulated arc therapy (IMRT/VMAT), image-guided RT, motion management strategies, and proton therapy have been shown to reduce toxicity and increase survival in nonrandomized trials.[63–67] CT-planned 3D-conformal RT is now considered to be the minimum standard.

Definitive RT, particularly SABR, is recommended for patients with early-stage NSCLC (ie, stage I–II, N0) who are medically inoperable or refuse surgery (see "Stereotactic Ablative Radiotherapy," page 1750).[61,62,68,69] Interventional radiology ablation is an option for selected patients.[70–72] Through extrapolation from surgical data, adjuvant

chemotherapy (category 2B) may be considered after definitive RT/SABR in patients with high-risk factors (eg, large tumors >4 cm). SABR is also an option for patients at high surgical risk who cannot tolerate a lobectomy (eg, age ≥75 years, poor lung function). However, resection is recommended for patients with early-stage NSCLC who are medically fit (see "Principles of Surgical Therapy" online, in these guidelines, at NCCN.org [NSCL-B]).[73] Definitive chemoradiation is recommended for patients with locally advanced (ie, stage II–III) disease who are not appropriate surgical candidates.[74] For patients with advanced lung cancer (ie, stage IV) with extensive metastases, systemic therapy is recommended; palliative RT can be used for symptom relief and potentially for prophylaxis at primary or distant sites.[61,75–77] Shorter courses of palliative RT are preferred for patients with poor PS and/or shorter life expectancy (eg, 17 Gy in 8.5-Gy fractions for symptomatic chest disease; see Table 4, page 1744). For patients with good PS, higher-dose and longer-course thoracic RT (eg, ≥30 Gy in 10 fractions) are associated with modestly improved survival and symptoms.[75] The RT recommendations for stages I to IV NSCLC are described in the algorithm (available online, in the compete version of these guidelines, at NCCN.org).

The indications for using preoperative or postoperative chemoradiation or RT alone are described in the algorithm (see NSCL-C, pages 1740–1746). In patients with clinical stage I or II NSCLC who are upstaged to N2+ after surgery, postoperative chemotherapy can be administered followed by postoperative RT depending on the margin status (see "Adjuvant Treatment" online, in these guidelines, at NCCN.org).[51,78] For clinical stage III NSCLC, definitive concurrent chemoradiation is category 1. However, the optimal management of potentially operable stage IIIA NSCLC is controversial (and is discussed in detail in "Principles of Surgical Therapy" online, in these guidelines, at NCCN.org [NSCL-B]).[79–82] For patients undergoing preoperative therapy before surgical resection of stage IIIA NSCLC, some prefer chemotherapy alone rather than chemoradiotherapy for preoperative treatment.[83] RT should generally be given postoperatively if not given preoperatively. NCCN Member Institutions are evenly split in their use of neoadjuvant chemotherapy versus neoadjuvant chemoradiation in patients with stage IIIA N2 NSCLC.[79] Similarly, some consider the need for pneumonectomy to be a contraindication to a combined modality surgical approach given the excess mortality observed in clinical trials,[81] but NCCN Member Institutions are also split on this practice.

Surgery is associated with potentially greater risk of complications in a field that has had high-dose RT (eg, 60 Gy), particularly stump breakdown and bronchopleural fistula. Thus, surgeons are often wary of performing resection in areas that have previously received RT doses of more than 45 Gy, especially in patients who have received definitive doses of concurrent chemoradiation (ie, ≥60 Gy) preoperatively. Soft tissue flap coverage and reduced intraoperative fluid administration and ventilator pressures can reduce the risk of these complications.[84–86] When giving preoperative RT to less than definitive doses (eg, 45 Gy), one should be prepared up front to continue to a full definitive dose of RT without interruption should the patient not proceed to surgery for some reason. For these reasons, when considering trimodality therapy, the treatment plan, including assessment for resectability and the type of resection, should be decided before initiation of any therapy.

Target Volumes, Prescription Doses, and Normal Tissue Dose Constraints: The dose recommendations for preoperative, postoperative, definitive, and palliative RT are described in the algorithm (see Table 4, page 1744).[50,52,58,84–87] After surgery, lung tolerance to RT is much less than for patients with intact lungs. Although the dose-volume constraints for conventionally fractionated RT for normal lungs are a useful guide (see Table 5, page 1744), more conservative constraints should be used for postoperative RT. For definitive RT, the commonly prescribed dose is 60 to 70 Gy in 2-Gy fractions.[88] The use of higher RT doses is discussed in the algorithm (see NSCL-C 3 of 9, page 1741).[89–94] Preliminary results from a phase III randomized trial (RTOG 0617) suggest that high-dose radiation using 74 Gy with concurrent chemotherapy does not improve survival when compared with a standard dose of 60 Gy.[60,94–97]

Reports 50, 62, and 83 from the International Commission on Radiation Units and Measurements provide a formalism for defining RT target volumes based on grossly visible disease, potential microscopic extension, and margins for target motion and daily

positioning uncertainty (see Figure 1, page 1744).[98,99] The American College of Radiology/American Society for Radiation Oncology (ACR/ASTRO) guidelines are also helpful references.[63,100,101] It is essential to evaluate the dose-volume histogram (DVH) of critical structures and to limit the doses to the organs at risk, such as spinal cord, lungs, heart, esophagus, and brachial plexus, to minimize normal tissue toxicity (see Table 5, page 1744).[102] These constraints are mainly empiric and have for the most part not been validated rigorously.[103–110] However, the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) review provides the most comprehensive estimates from clinical data of dose-response relationships for normal tissue complications.[111–115] For patients receiving postoperative RT, more strict DVH parameters should be considered for the lungs.

Radiation Simulation, Planning, and Delivery: Treatment planning should be based on CT scans obtained in the treatment position. Intravenous contrast CT scans are recommended for better target delineation whenever possible, especially in patients with central tumors or with nodal involvement. PET/CT can significantly improve target delineation accuracy, especially in the presence of atelectasis or contraindications to intravenous CT contrast.[116] In the algorithm, recommendations are provided for patients receiving chemoradiation (including those with compromised lung or cardiac function), photon beams, or IMRT (see NSCL-C 4 of 9, page 1742).[66,117–121] Respiratory motion should be managed. The report of AAPM Task Group 76 is a useful reference for implementing a broad range of motion management strategies, as described in the algorithm (see NSCL-C 4 of 9, page 1742).[122]

Stereotactic Ablative Radiotherapy: SABR (also known as SBRT) uses short courses of very conformal and dose-intensive RT precisely delivered to limited-size targets.[123–125] Clinical literature, including prospective multi-institutional trials, has demonstrated the efficacy of SABR in patients with inoperable stage I NSCLC or in those who refuse surgery.[62,126–129] With conventionally fractionated RT (CFRT), 3-year survival is only approximately 20% to 35% in these patients, with local failure rates of approximately 40% to 60%.[69] In prospective clinical trials, local control and overall survival seem to be considerably increased with SABR, generally more than 85% and approximately 60% at 3 years (median survival, 4 years), respectively, in patients who are medically inoperable.[69,71–73,121,128,130–135]

Substantially higher survival has been observed in potentially operable patients treated with SABR, comparable in population-based comparisons to surgical outcomes.[73,127,136–140] Thus, SABR is recommended in these guidelines for patients with stage I and II (T1–3N0M0) NSCLC who are medically inoperable, and is a reasonable alternative to surgery for patients who are high risk or elderly, or those who refuse surgery after appropriate consultation (see NSCL-C, pages 1740–1746).[71,129,131,141] After SABR, assessing recurrences through imaging can be challenging because of benign inflammatory/fibrotic changes that can remain FDG-avid for 2 or more years after treatment, emphasizing the importance of follow-up by a team with experience interpreting these posttreatment effects.[142,143] This is particularly relevant because selected patients with localized recurrences after SABR may benefit from salvage surgery or SABR.[144–148]

SABR can also be used for patients with limited lung metastases or limited metastases to other body sites.[5,123,129,149–154] SABR fractionation regimens and normal tissue constraints are provided in the algorithm (see Tables 2 and 3, page 1743).[126,128,135,155–162] Although none of these dose constraints have been validated as maximally tolerated doses, outcomes of clinical trials to date suggest that they are safe constraints. Aggressive local therapy of oligometastatic disease located in sites other than the brain remains controversial and thus is a category 2B recommendation; however, SRS or SABR may be useful in these settings (see "Stage IV, M1b: Limited Sites/Initial Treatment" online, in these guidelines, at NCCN.org [NSCL-13]).[129,163] Decisions about whether to recommend SABR should be based on multidisciplinary discussion. Hypofractionated or dose-intensified conventional 3D-conformal RT is an option if an established SABR program is not available.[164] Current nonrandomized clinical data indicate that local tumor control with SABR is higher than with interventional radiology ablation techniques. However, interventional radiology ablation may be appropriate for selected patients for whom local control is not necessarily the highest priority.[62,71,72]

Whole-Brain RT and Stereotactic Radiosurgery: Many patients with NSCLC have brain metastases (30%–50%), which substantially affect their quality

of life.[7,165] Options for treatment of single brain metastases include surgery followed by WBRT (category 1) for selected patients (eg, symptomatic metastases or need to obtain tumor tissue), surgery followed by SRS, SRS followed by WBRT (category 1), or SRS alone (see the NCCN Guidelines for Central Nervous System Cancers and the complete version of these guidelines at NCCN.org).[151,165–172] Decisions about whether to recommend surgery, WBRT, SRS, or combined modality therapy for brain metastases should be based on multidisciplinary discussion, weighing the potential benefit against the risk for each individual patient.[166,173–175] Treatment should be individualized for patients with recurrent or progressive brain lesions.[176]

For multiple metastases (eg, >3), WBRT is a standard option. WBRT has been found to be associated with measurable declines in neurocognitive function in clinical trials, particularly with increasing dose and advanced age of the patient.[177–179] On the other hand, control of brain metastases confers improved neurocognitive function.[180,181] For limited metastases, randomized trials have found that the addition of WBRT to SRS decreases intracranial recurrence but does not improve survival, and may increase the risk of cognitive decline.[181,182] Thus, an approach of SRS alone may strike an appropriate balance in patients with limited-volume metastases. Similarly, some investigators have suggested that following resection with SRS to the cavity (instead of resection with WBRT) will decrease the risk of neurocognitive problems.[183,184]

Combined Modality Therapy

Concurrent chemoradiation is superior to sequential chemoradiation for patients with unresectable stage III disease,[185–188] with several trials supporting the recommendations for chemoradiation.

Chemoradiation: Trial Data

The major controversies in NSCLC relate to the management of patients with stage IIIA disease (see "Role of Surgery in Patients with Stage IIIA (N2) NSCLC" in "Principles of Surgical Therapy" online, in these guidelines, at NCCN.org [NSCL-B]). All 3 treatment modalities—surgical resection, chemotherapy, and radiation—may be used in treating stage III disease.[79] The ongoing debate centers on which modalities to use and in what sequence.[189–193] For patients with unresectable stage IIIA or IIIB disease, combined modality therapy (chemoradiation) is superior to radiation alone.[189,190,192,193] Concurrent chemoradiation is superior to sequential chemoradiation.[185–188] However, concurrent chemoradiation has a higher rate of grade 3 or 4 esophagitis than sequential chemoradiation. Selection of patients should be based not only on the response to therapy but also on how well the patient tolerates therapy.

Concurrent chemoradiation regimens that may be used for all histologies for initial treatment include cisplatin/etoposide, cisplatin/vinblastine, and carboplatin/paclitaxel (see "Chemotherapy Regimens Used with Radiation Therapy" online, in these guidelines, at NCCN.org [NSCL-E]).[185,187,194,195] For non-squamous NSCLC, other concurrent chemoradiation regimens include carboplatin/pemetrexed and cisplatin/pemetrexed.[196,197]

Initial Therapy

Commonly used doses for conventionally fractionated RT are described in the algorithm (see Table 4, page 1744). In addition, the NCCN Guidelines also recommend regimens for chemoradiation (see "Chemotherapy Regimens Used with Radiation Therapy" online, in these guidelines, at NCCN.org [NSCL-E]). Details about surgery and chemotherapy for locally advanced disease and systemic therapy for metastatic disease are not provided in this discussion, because the focus is on RT (see "Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy" and "Systemic Therapy for Advanced or Metastatic Disease" online, in these guidelines, at NCCN.org [NSCL-D and NSCL-F, respectively]).

Stage I, Stage II, and Stage IIIA Disease

Depending on the extent and type of comorbidity present, patients with stage I or a subset of stage II (T1–2, N1) tumors are generally candidates for surgical resection and mediastinal lymph node dissection. However, definitive RT, particularly SABR, is recommended for patients with early-stage stage NSCLC who are high risk, medically inoperable, or refuse surgery (see "Stereotactic Ablative Radiotherapy," page 1750, and recommendations for initial treatment of stage I and II NSCLC online, in these guidelines, at NCCN.org).[61,62,68,69,71,198]

For patients with clinical stage IIB (T3, N0) and IIIA tumors who have different treatment options (surgery, RT, or chemotherapy), a multidisciplinary

evaluation is recommended. For the subsets of stage IIB (T3, N0) and IIIA (T4, N0–1) tumors, treatment options are organized according to the location of the tumor, such as the superior sulcus, chest wall, proximal airway, or mediastinum.[163] For each location, a thoracic surgeon needs to determine whether the tumor is resectable (see "Principles of Surgical Therapy" online, in these guidelines, at NCCN.org [NSCL-B]).

For patients with resectable tumors (T3 invasion, N0–1) in the superior sulcus, the NCCN NSCLC Panel recommends preoperative concurrent chemoradiation therapy followed by surgical resection and chemotherapy (see initial treatment for superior sulcus tumor in the complete version of these guidelines at NCCN.org [NSCL-5]). Preoperative concurrent chemoradiation followed by surgical resection of a superior sulcus tumor has shown 2-year survival in the 50% to 70% range.[85,87,163,199–202] The overall 5-year survival rate is approximately 40%.[87] Patients with possibly resectable superior sulcus tumors should undergo preoperative concurrent chemoradiation before surgical reevaluation. For patients with unresectable tumors (T4 extension, N0–1) in the superior sulcus, definitive concurrent chemoradiation is recommended, followed by 2 cycles of full-dose chemotherapy if full-dose chemotherapy was not initially given concurrently with RT.[195,203]

Surgical resection is the preferred treatment option for patients with tumors of the chest wall, proximal airway, or mediastinum (T3–4, N0–1). Other treatment options include chemotherapy or concurrent chemoradiation before surgical resection. For unresectable T4, N0–1 tumors without pleural effusion, definitive concurrent chemoradiation (category 1) is recommended.[81,185] If full-dose chemotherapy was not given initially as concurrent treatment, then an additional 2 cycles of full-dose chemotherapy can be administered (see "Adjuvant Treatment" online in these guidelines, at NCCN.org).[81,185,195]

Multimodality therapy is recommended for most patients with stage III NSCLC.[204] For patients with stage IIIA disease and positive mediastinal nodes (T1–3, N2), treatment is based on the findings of pathologic mediastinal lymph node evaluation (see "Adjuvant Treatment" online in these guidelines, at NCCN.org). Patients with negative mediastinal biopsy findings are candidates for surgery. For patients with resectable lesions, mediastinal lymph node dissection or lymph node sampling should be performed during the operation. Individuals who are medically inoperable should be treated according to clinical stage (see the complete version of these guidelines at NCCN.org). For patients with (T1–2 or T3) N2 node-positive disease, a brain MRI and PET/CT scan (if not performed previously) are recommended to detect distant metastases. When distant metastases are not present, the NCCN NSCLC Panel recommends that the patient be treated with definitive concurrent chemoradiation therapy.[60,186] Recommended therapy for metastatic disease depends on whether disease is in a solitary site or is widespread.

Patients with separate pulmonary nodules in the same lobe or ipsilateral nonprimary lobe without other systemic metastases are potentially curable with surgery; 5-year survival rates are approximately 30%.[205] Intrapulmonary metastases have been downstaged in the TNM staging (ie, AJCC 7th edition).[205–207] In patients with N2 nodes after surgery, concurrent chemoradiation is recommended for those with positive margins and an R2 resection; either sequential or concurrent chemoradiation is recommended after an R1 resection. Most NCCN Member Institutions favor concurrent therapy for positive margins, but sequential is reasonable in frailer patients. For those with N2 nodes and negative margins, sequential chemotherapy (category 1) with RT is recommended. In patients with synchronous solitary nodules (contralateral lung), the NCCN Guidelines recommend treating them as 2 primary lung tumors if both are curable, even if the histology of the 2 tumors is similar (see the complete version of these guidelines at NCCN.org).

Multiple Lung Cancers

Multiple lung cancers may be suspected or detected in various ways. Patients with a history of lung cancer or those with biopsy-proven synchronous lesions may be suspected of having multiple lung cancers.

Treatment of multiple lung cancers depends on status of the lymph nodes (eg, N0–1) and on whether the lung cancers are asymptomatic, symptomatic, or at high risk of becoming symptomatic (see initial treatment recommendations online, in these guidelines, at NCCN.org).[208–211] In patients eligible for definitive local therapy, parenchymal-sparing resection is preferred (see "Principles of Surgical Therapy" online, in these guidelines, at NCCN.org [NSCL-B]).[208,212] Video-assisted thoracoscopic surgery and

SABR are reasonable options depending on the number and distribution of the tumors requiring local treatment.[213]

Stage IIIB Disease

Stage IIIB tumors comprise 2 groups, including T1–3, N3 tumors, and T4 extension and N2–3 tumors, which are unresectable and include contralateral mediastinal nodes (T4, N3). Surgical resection is not recommended in patients with T1–3, N3 disease. However, in patients with suspected N3 disease, these guidelines recommend pathologic confirmation of nodal status (see pretreatment evaluation recommendations online, in these guidelines, at NCCN.org).[214,215] In addition, PET/CT scans (if not previously performed) and brain MRI should also be included in the pretreatment evaluation. If these tests are negative, then treatment options for the appropriate nodal status should be followed. If N3 disease is confirmed, definitive concurrent chemoradiation (category 1) is recommended, followed by 2 cycles of full-dose chemotherapy if full-dose chemotherapy was not initially given concurrently with RT.[81,185,195,216,217]

For patients with T4 extension N2–3 disease (stage IIIB), surgical resection is not generally recommended. The initial workup includes biopsies of the N3 and N2 nodes. If these biopsies are negative, the same treatment options may be used as for stage IIIA (T4, N0–1) disease. If either the contralateral or ipsilateral mediastinal node is positive, definitive concurrent chemoradiation therapy is recommended (category 1) followed by 2 cycles of full-dose chemotherapy if full-dose chemotherapy was not given concurrently with RT as initial treatment.[81,185,195,216–218]

Stage IV Disease

In general, systemic therapy is recommended for patients with metastatic disease. Because RT is the focus of this Discussion, systemic therapy will not be discussed.

Patients with limited oligometastatic disease (eg, single brain or adrenal metastasis) and otherwise limited disease in the chest may benefit from aggressive local therapy to both the primary chest and metastatic sites. Aggressive local therapy may constitute surgery or definitive RT including SABR to each site, and may be preceded or followed by chemotherapy. Metastases to the adrenal gland from lung cancer are a common occurrence, with approximately 33% of patients having such disease at autopsy. In patients with otherwise resectable primary tumors, however, many solitary adrenal masses are not malignant. Any adrenal mass found on a preoperative CT scan in a patient with lung cancer should be biopsied to rule out benign adenoma. Local therapy (category 2B) of the adrenal lesion has produced some long-term survivors when an adrenal metastasis has been found and the lung lesion has been curable.[219–222] Some NCCN NSCLC Panel members feel that local therapy for adrenal metastases is only advisable if the synchronous lung disease is stage I or possibly stage II (ie, resectable). Systemic therapy is another treatment option for adrenal metastasis.

Adjuvant Treatment

Chemotherapy or Chemoradiation

Postsurgical treatment options for patients with stage IA tumors (T1ab, N0) and with positive surgical margins (R1, R2) include re-resection (preferred) or RT (category 2B). Some of the settings in which adjuvant chemotherapy is recommended are not provided in this discussion, because the focus is on RT. If the surgical margins are positive in patients with T2ab, N0 tumors, options include re-resection (preferred) with (or without) chemotherapy, or RT with (or without) chemotherapy (chemotherapy is recommended for stage IIA).[51,223]

For patients with positive surgical margins and stage II disease, such as (1) T1ab–2a, N1; (2) T2b, N1; or (3) T3, N0 disease, options after an R1 resection include re-resection and chemotherapy, or chemoradiation (either sequential or concurrent). Most NCCN Member Institutions favor concurrent chemoradiation for positive margins, but sequential chemoradiation is reasonable in frailer patients. Options after an R2 resection include re-resection and chemotherapy, or concurrent chemoradiation. Patients with T1–3, N2 or T3, N1 disease (discovered only at surgical exploration and mediastinal lymph node dissection) and positive margins may be treated with chemoradiation; either sequential or concurrent chemoradiation is recommended for an R1 resection, whereas concurrent radiation is recommended for an R2 resection (see "Adjuvant Treatment" online in these guidelines, at NCCN.org). Patients with negative margins may be treated with either chemotherapy (category 1), or sequential chemotherapy plus RT (for N2 only).[224]

For superior sulcus tumors (T4 extension, N0–1) that convert to a resectable status (ie, become resectable) after preoperative concurrent chemoradiation, resection followed by chemotherapy is recommended. If the lesion remains unresectable after preoperative concurrent chemoradiation, the full course of definitive chemo/RT should be completed, followed by chemotherapy as an adjuvant treatment if full doses were not given with concurrent therapy. Among patients with chest wall lesions with T3 invasion–T4 extension, N0–1 disease, those who are initially treated with surgery (preferred) with positive surgical margins may receive either sequential or concurrent chemoradiation, depending on whether the resection is R1 or R2, or re-resection with chemotherapy. Concurrent chemoradiation is often used for positive margins, but sequential is reasonable in frailer patients. A similar treatment plan is recommended for resectable tumors of the proximal airway or mediastinum (T3–4, N0–1).

For patients with stage IIIA disease and positive mediastinal nodes (T1–3, N2) with no apparent disease progression after initial treatment, recommended treatment includes surgery with (or without) RT (if not given preoperatively) and/or with (or without) chemotherapy (category 2B for chemotherapy) (see "Adjuvant Treatment" online, in these guidelines, at NCCN.org). Alternatively, if the disease progresses, patients may be treated with either local therapy using RT (if not given previously) with (or without) chemotherapy, or systemic treatment. In patients with separate pulmonary nodules in the same lobe or ipsilateral nonprimary lobe, surgery is recommended. In patients with N2 disease, if the margins are negative, sequential chemotherapy (category 1) with radiation is recommended. If the resection margins are positive in patients with N2 disease, concurrent chemoradiation is recommended for an R2 resection, whereas either concurrent chemoradiation or sequential is recommended for an R1 resection. Concurrent chemoradiation is often used for positive margins, but sequential is reasonable in frailer patients.

Because patients with stage III disease have both local and distant failures, theoretically, the use of chemotherapy may eradicate micrometastatic disease that is obviously present but undetectable at diagnosis. The timing of this chemotherapy varies. Such chemotherapy may be given alone, sequentially, or concurrently with RT. In addition, chemotherapy could be given preoperatively or postoperatively in appropriate patients. Several phase II studies have evaluated neoadjuvant chemotherapy for stage III NSCLC, with (or without) RT, followed by surgery. Details about neoadjuvant and adjuvant chemotherapy, including specific regimens, are not provided in this discussion (see the complete version of these guidelines at NCCN.org).

Radiation Therapy

After complete resection of clinical early-stage NSCLC, postoperative RT has been found to be detrimental in the context of pathologic N0 or N1 stage in a meta-analysis of small randomized trials using older techniques and dosing regimens and a population based analysis of data from SEER. [PORT meta-analysis].[78] However there was an apparent survival benefit of PORT in patients with N2 nodal stage diagnosed surgically.[78] Similarly, an exploratory secondary analysis of the ANITA trial also found that PORT increased survival in patients with N2 disease who received adjuvant chemotherapy.[51] Postoperative adjuvant sequential chemotherapy with RT is recommended for patients with T1–3, N2 disease and negative margins (see "Adjuvant Treatment" online in these guidelines, at NCCN.org).

A meta-analysis assessed postoperative chemotherapy with (or without) postoperative RT in patients mainly with stage III disease.[225] In this meta-analysis, 70% of the eligible trials used adjuvant chemotherapy before RT, and 30% used concurrent chemoradiation. Regimens included cisplatin/vinorelbine followed by RT or concurrent cisplatin/etoposide. The ACR Appropriateness Criteria provide specific recommendations for postoperative adjuvant therapy.[226,227] Either concurrent or sequential chemoradiation may be used for postoperative adjuvant therapy, depending on the type of resection and the setting (eg, N2 disease) (see "Adjuvant Treatment" online in these guidelines, at NCCN.org). Concurrent chemoradiation is recommended for R2 resections, whereas either sequential or concurrent chemoradiation is recommended for R1 resections. Cisplatin/etoposide and carboplatin/paclitaxel are concurrent neoadjuvant chemoradiation regimens recommended by the NCCN NSCLC Panel.[194] Pemetrexed with either cisplatin or carboplatin may be used for concurrent chemoradiation in patients with nonsquamous cell histology. Chemoradiation

regimens cited in these guidelines may also be used for stage II to III disease.[52,53,185,186,195–197]

Treatment of Recurrences and Distant Metastases

Recurrences are subdivided into locoregional recurrences and distant metastases. Management of locoregional recurrences (eg, endobronchial obstruction, mediastinal lymph node recurrence, superior vena cava obstructions, severe hemoptysis) is described in the NCCN Guidelines (see "Therapy for Recurrence and Metastasis" online, in these guidelines, at NCCN.org [NSCL-15]). For patients with endobronchial obstruction, relieving airway obstruction may increase survival, especially in patients who are severely compromised, and may improve the quality of life.[228] After treatment for the locoregional recurrence, observation or systemic therapy (category 2B for therapy) is recommended if disseminated disease is not evident. However, for observed disseminated disease, systemic therapy is recommended. The type of systemic therapy depends on the histologic type, whether any genetic alterations are present, and PS (see "Systemic Therapy for Advanced or Metastatic Disease" online, in these guidelines, at NCCN.org [NSCL-F]).

Management of distant metastases (eg, localized symptoms; bone, solitary, diffuse brain, or disseminated metastases) is described in the complete version of these guidelines (see "Therapy for Recurrence and Metastasis" online, in these guidelines, at NCCN.org [NSCL-15]).[229] Palliation of symptoms can be achieved with external-beam RT for distant metastases with localized symptoms, diffuse brain metastases, or bony metastasis.[58,230,231] Recent data suggest that SABR can be used as a local treatment option for patients with oligometastatic disease.[230]

Notably, recurrent and metastatic disease have historically been regarded as incurable. However, selected limited locoregional recurrences may be treated with curative intent salvage therapy (surgery or RT with or without chemotherapy). Similarly, patients with limited-site oligometastatic disease may benefit from aggressive local therapies to the metastatic and primary sites, with clinical data suggesting the possibility of long-term survival.[5,149,152,229,232–236] In addition, emerging clinical data suggest the feasibility of definitive reirradiation of local recurrences within prior RT fields using highly conformal techniques, although this should be limited to highly selected cases in specialty centers with appropriate expertise because of the potential for severe toxicity with high cumulative radiation doses to critical structures.[55,146–148,237–240]

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The NCCN guidelines staff have no conflicts to disclose.