WHITE PAPER - SBRT for Non Small Cell Lung Cancer

I. Introduction

This white paper will focus on non-small cell lung carcinoma with sections one though six comprising a general review of lung cancer from the National Cancer Institute, more information can be found at **cancer.gov**. Section seven will provide a literature review on stereotactic body radiotherapy (SBRT) for non-small cell lung cancer and section eight (for society members only) will provide clinical indications and treatment guidelines on SBRT for the lung.

II. Definition and Incidence

Non-small cell lung carcinoma (NSCLC) is any type of lung cancer other than small cell carcinoma (SCLC). As a class, NSCLCs are relatively insensitive to chemotherapy, compared to small cell carcinoma. There are 3 sub-types of NSCLC. The cells in these sub-types differ in size, shape, and chemical make-up. Squamous cell carcinoma make up about 25% to 30% of all lung cancers of this kind, are linked to smoking and tend to be found in the middle of the lungs, near a bronchus. Adenocarcinoma accounts for about 40% of lung cancers and are usually found in the outer part of the lung. Large-cell (undifferentiated) carcinoma accounts for about 10% to 15% of lung cancers, can start in any part of the lung, tend to grow and spread quickly, which makes them more difficult to treat. Although the most common types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma, there are many other types that occur less frequently. Carcinoid is also included in this category. About 8 to 9 out of 10 cases of all lung cancers are the non-small cell type.

There are an estimated 228,190 new cases and 159,480 deaths from all lung cancer (non-small cell and small cell combined) in the United States in 2013. [1] Lung cancer is the leading cause of cancer-related mortality in the United States. The incidence rate has been declining in men over the past twenty years, but just recently started to decline in women. The gender differences in lung cancer incidence and mortality are a reflection of the uptake and reduction of smoking over the past 50 years. The 5-year relative survival rate for all stages of lung cancer is 16%. The 5-year relative survival rate varies markedly depending on the stage at diagnosis, from 49% to 16% to 2% for patients with local, regional, and distant stage disease, respectively. [2] Only 15% of lung cancers are diagnosed at a localized stage. The 5-year survival rate for small cell lung cancer is 6% and lower than that for NSCLC (18%).[1]

III. Prognostic Factors

Squamous cell carcinoma and adenocarcinoma have defined premalignant precursor lesions. Before becoming invasive, lung epithelium may undergo morphological changes that include hyperplasia, metaplasia, dysplasia, and carcinoma *in situ*. Dysplasia and carcinoma *in situ* are considered the principal premalignant lesions because they are more

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likely to progress to invasive cancer and less likely to spontaneously regress. In addition, after resection of a lung cancer, there is a 1% to 2% risk for a second lung cancer per patient per year. [3] Screening for early detection of lung cancer and chemoprevention strategies are currently under evaluation for this patient population.

Multiple studies have attempted to identify prognostic determinants after surgery and have yielded conflicting evidence as to the prognostic importance of a variety of clinicopathologic factors.[4-7] Factors that have correlated with adverse prognosis include the following:

- Presence of pulmonary symptoms
- Large tumor size (>3 cm)
- Nonsquamous histology
- Metastases to multiple lymph nodes within a TNM-defined nodal station[8-18]
- Vascular invasion[19-21]

Similarly, conflicting results regarding the prognostic importance of aberrant expression of a number of proteins within lung cancers have been reported. For patients with inoperable disease, prognosis is adversely affected by weight loss of more than 10%. In multiple retrospective analyses of clinical trial data, advanced age alone has not been shown to influence response or survival with therapy.[22]

IV. Cellular Classification

Before a patient begins lung cancer treatment, an experienced lung cancer pathologist must review the pathologic material. This is critical because small cell lung cancer (SCLC), which responds well to chemotherapy and is generally not treated surgically, can be confused on microscopic examination with non-small cell carcinoma.[23] Malignant non-small cell epithelial tumors of the lung are classified by the World Health Organization (WHO)/International Association for the Study of Lung Cancer (IASLC). There are three major types of NSCLC, including squamous cell carcinoma (25% of lung cancers), adenocarcinoma (40% of lung cancers) and large cell carcinoma (10% of lung cancers). There are also additional subtypes of decreasing frequency.

Squamous cell carcinoma

Most squamous cell carcinomas of the lung are centrally located, in the larger bronchi of the lung. Squamous cell carcinomas are linked more strongly with smoking than other forms of NSCLC, and the incidence has been decreasing in recent years. The WHO/IASLC classification of squamous cell carcinoma includes the following subtypes:

- Papillary.
- Clear cell.
- Small cell.
- Basaloid.

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Adenocarcinoma

Adenocarcinoma is the predominant histologic subtype in many countries, and issues relating to subclassification of adenocarcinoma are very important. One of the biggest problems with lung adenocarcinomas is the frequent histologic heterogeneity. In fact, mixtures of adenocarcinoma histologic subtypes are more common than tumors consisting purely of a single pattern of acinar, papillary, bronchioloalveolar, and solid adenocarcinoma with mucin formation. In 2011, significant changes were made in the pathological classification of lung adenocarcinoma from the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society lung adenocarcinoma classification.[24] There are several major differences in the new classification system compared to those previously published by the WHO. The new classification system was revised not only on pathology, but on an integrated multidisciplinary approach involving pathologists, oncologists, pulmonologists, radiologists, molecular biologists and surgeons. It is recognized that molecular characteristics play a role in lung cancer diagnosis, response to treatment and clinical outcomes. Changes in the classification system now reflect molecular characteristics of the disease (EGRF mutations and ALK rearrangements).[25] It is also now recognized that 70% of lung cancer patients are diagnosed at advanced staged-disease on the basis of small biopsies and cytology. Prior WHO classifications focused on diagnosis from surgical specimens, which are obtained in only 30% of patients. The new classification system addresses both resection specimens and small biopsies and cytology and is divided into two components based on the procedure of diagnosis: 1) small biopsy and cytology for advanced staged-patients 2) resection specimens for early-stage patients. A major point in the new classification system is the concept of personalized medicine which is determined by histology and genetics, as well as providing a classification system to provide uniform terminology and diagnostic criteria. The following lists the major changes to the classification system for lung adenocarcinoma and full details can be found in The Journal of Thoracic Oncology, Volume 6,(2), 244 – 285, 2011:

- The revised classification system addresses both resection specimens and small biopsies and cytology
- The terms BAC (bronchioloalveolar carcinoma) and mixed subtype adenocarcinoma are no longer recommended
- For resection specimens, new concepts are introduced including adenocarcinoma in situ and minimally invasive adenocarcinoma for small solitary adenocarciomas
- Invasive adenocarcinomas are classified by predominant pattern after using comprehensive histological subtyping with lepidic, acinar, papillay and solid patterns
- Micropapillary is added as a new histologic subtype
- Variants include invasive mucinous adenocarcinoma, colloid, fetal and enteric adenocarcinoma
- NSCLC not otherwise specified (NOS) should be avoided and further classification based on histological staining is recommended

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Large cell carcinoma

Large cell carcinoma has previously been called large cell anaplastic carcinoma and large cell undifferentiated carcinoma. Large cell carcinomas, except basaloid carcinomas, preferentially occur in the lung periphery. In addition to the general category of large cell carcinoma, several uncommon variants are recognized, including:

- Large cell neuroendocrine carcinoma (LCNEC)
- Basaloid carcinoma.
- Lymphoepithelioma-like carcinoma.
- Clear cell carcinoma.
- Large cell carcinoma with rhabdoid phenotype.

Basaloid carcinoma is also recognized as a variant of squamous cell carcinoma, and rarely, adenocarcinomas may have a basaloid pattern; however, in tumors without either of these features, they are regarded as a variant of large cell carcinoma.

Neuroendocrine tumors

A substantial evolution of concepts of neuroendocrine lung tumor classification has occurred. LCNEC is recognized as an histologically high-grade non-small cell carcinoma. It has a very poor prognosis similar to that of SCLC. Atypical carcinoid is recognized as an intermediate-grade neuroendocrine tumor with a prognosis that falls between typical carcinoid and the high-grade SCLC and LCNEC. Neuroendocrine differentiation can be demonstrated by immunohistochemistry or electron microscopy in 10% to 20% of common NSCLC that do not have any neuroendocrine morphology. These tumors are not formally recognized within the WHO/IASLC classification scheme since the clinical and therapeutic significance of neuroendocrine differentiation in NSCLC is not firmly established. These tumors are referred to collectively as NSCLC with neuroendocrine differentiation.

Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements

This is a group of rare tumors. Spindle and giant cell carcinomas and carcinosarcomas comprise only 0.4% and 0.1% of all lung malignancies, respectively. In addition, this group of tumors reflects a continuum in histologic heterogeneity as well as epithelial and mesenchymal differentiation. Biphasic pulmonary blastoma is regarded as part of the spectrum of carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements based on clinical and molecular data.

Additional histological subtypes of NSCLC include:

- Adenosquamous carcinoma.
- Carcinoid tumor.

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    - Typical carcinoid.
    - Atypical carcinoid.
- Carcinomas of salivary-gland type.
    - Mucoepidermoid carcinoma.
    - Adenoid cystic carcinoma.
    - Others.
- Unclassified carcinoma.

V. Staging

In non-small cell lung cancer (NSCLC), the determination of stage is important in terms of therapeutic and prognostic implications. Careful initial diagnostic evaluation to define the location and to determine the extent of primary and metastatic tumor involvement is critical for the appropriate care of patients.

Stage has a critical role in the selection of therapy. The stage of disease is based on a combination of clinical factors (i.e., physical examination, radiology, and laboratory studies) and pathological factors (i.e., biopsy of lymph nodes, bronchoscopy, mediastinoscopy, or anterior mediastinotomy).[26] The distinction between clinical stage and pathologic stage should be considered when evaluating reports of survival outcome.

The procedures used to determine staging include the following:

- History.
- Physical examination.
- Routine laboratory evaluations.
- Chest x-ray.
- Chest-computed tomography (CT) scan with infusion of contrast material.

The CT scan should extend inferiorly to include the liver and adrenal glands. Magnetic resonance imaging (MRI) scans of the thorax and upper abdomen do not appear to yield advantages over CT scans.[27]

In general, symptoms, physical signs, laboratory findings, or perceived risk of distant metastasis lead to an evaluation for distant metastatic disease. Additional tests such as bone scans and CT/MRI of the brain may be performed if initial assessments suggest metastases or if patients with stage III disease are under consideration for aggressive local and combined modality treatments. Surgical staging of the mediastinum is considered standard if accurate evaluation of the nodal status is needed to determine therapy. The wider availability and use of fluorodeoxyglucose-positron emission tomography (FDG-PET) for staging has modified this approach to staging mediastinal lymph nodes and distant metastases.

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A systematic review of the medical literature relating to the accuracy of CT scanning for noninvasive staging of the mediastinum in patients with lung cancer has been conducted.[28] In the 35 studies published from 1991 through June, 2006, 5,111 evaluable patients were identified. The median prevalence of mediastinal metastasis was 28% (range, 18%–56%). Almost all studies specified that CT scanning was performed following the administration of IV contrast material and that a positive test result was defined as the presence of one or more lymph nodes that measured larger than 1 cm on the short-axis diameter. The pooled sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastasis were 51% (95% confidence interval [CI], 47%–54%) and 86% (95% CI, 84%–88%), respectively. The corresponding positive and negative likelihood ratios were 3.4 and 0.6, respectively. These results are similar to those of a large meta-analysis that reported the median sensitivity and specificity of CT scanning for identifying malignant mediastinal nodes as 61% and 79%, respectively. An earlier meta-analysis reported average sensitivity and specificity of 64% and 74%, respectively.[29]

Another systematic review, an expansion of a health technology assessment conducted in 2001 by the Institute for Clinical and Evaluative Sciences, evaluated the accuracy and utility of FDG-PET in the diagnosis and staging of lung cancer.[30] Through a systematic search of the literature, 12 evidence summary reports and 15 prospective studies of the diagnostic accuracy of positron emission tomography (PET) were identified. PET appears to have high sensitivity and reasonable specificity for differentiating benign from malignant lesions as small as 1 cm. PET also appears superior to CT imaging for mediastinal staging in NSCLC. Randomized trials evaluating the utility of PET in potentially resectable NSCLC report conflicting results in terms of the relative reduction in the number of noncurative thoracotomies.

Although the current evidence is conflicting, PET may improve results of early-stage lung cancer by identifying patients who have evidence of metastatic disease that is beyond the scope of surgical resection and that is not evident by standard preoperative staging procedures.

If there is no evidence of distant metastatic disease on CT scan, FDG-PET scanning complements CT scan staging of the mediastinum. The combination of CT scanning and PET scanning has greater sensitivity and specificity than CT scanning alone.[31] Numerous nonrandomized studies of FDG-PET have evaluated mediastinal lymph nodes using surgery (i.e., mediastinoscopy and/or thoracotomy with mediastinal lymph node dissection) as the gold standard of comparison.

A systematic review of the medical literature relating to the accuracy of FDG-PET scanning for noninvasive staging of the mediastinum in patients with lung cancer identified 44 studies published between 1994 and 2006 with 2,865 evaluable patients.[28] The median prevalence of mediastinal metastases was 29% (range, 5% to 64%). Pooled estimates of sensitivity and specificity for identifying mediastinal metastasis were 74% (95% CI, 69%–79%) and 85% (95% CI, 82%–88%), respectively. Corresponding positive and negative likelihood ratios for mediastinal staging with PET scanning were

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4.9 and 0.3, respectively. These findings demonstrate that PET scanning is more accurate than CT scanning for staging of the mediastinum in patients with lung cancer. In a meta-analysis evaluating the conditional test performance of FDG-PET and CT scanning, the median sensitivity and specificity of PET scans were reported as 100% and 78%, respectively, in patients with enlarged lymph nodes.[29] PET scanning is considered very accurate in identifying malignant nodal involvement when nodes are enlarged. However, PET scanning will falsely identify a malignancy in approximately one-fourth of patients with nodes that are enlarged for other reasons, usually as a result of inflammation or infection.[32, 33]

The median sensitivity and specificity of PET scanning in patients with normal-sized mediastinal lymph nodes were 82% and 93%, respectively.[29] These data indicate that nearly 20% of patients with normal-sized nodes but with malignant involvement had falsely negative PET scan findings. For patients with clinically operable NSCLC, the recommendation is for a biopsy of mediastinal lymph nodes that were found on chest CT scan to be larger than 1 cm in shortest transverse axis or were found to be positive on FDG-PET scanning. Negative FDG-PET scanning does not preclude biopsy of radiographically enlarged mediastinal lymph nodes. Mediastinoscopy is necessary for the detection of cancer in mediastinal lymph nodes when the results of the CT scan and FDG-PET do not corroborate each other.

Numerous nonrandomized, prospective and retrospective studies have demonstrated that FDG-PET seems to offer diagnostic advantages over conventional imaging in staging distant metastatic disease; however, standard FDG-PET scans have limitations. FDG-PET scans may not extend below the pelvis and may not detect bone metastases in the long bones of the lower extremities. Because the metabolic tracer used in FDG-PET scanning accumulates in the brain and urinary tract, FDG-PET is not reliable for detection of metastases in these sites.[34]

Decision analyses demonstrate that FDG-PET may reduce the overall costs of medical care by identifying patients with falsely negative CT scans in the mediastinum or otherwise undetected sites of metastases.[35, 36] Studies concluded that the money saved by forgoing mediastinoscopy in FDG-PET–positive mediastinal lesions was not justified because of the unacceptably high number of false-positive results. A randomized study found that the addition of FDG-PET to conventional staging was associated with significantly fewer thoracotomies.[37] A second randomized trial evaluating the impact of PET on clinical management found that PET provided additional information regarding appropriate stage but did not lead to significantly fewer thoracotomies.[38]

Accurate staging of the mediastinal lymph nodes provides important prognostic information. The association between survival and the number of examined lymph nodes during surgery for patients with stage I NSCLC treated with definitive surgical resection was assessed from the population-based Surveillance, Epidemiology and End Results database for the period from 1990 to 2000.[39] A total of 16,800 patients were included in the study. The overall survival analysis for patients without radiation therapy

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demonstrated that in comparison to the reference group (1 to 4 lymph nodes), patients with 5 to 8 lymph nodes examined during surgery had a modest but statistically significant increase in survival, with a proportionate hazard ratio (HR) of 0.90 (95% CI, 0.84–0.97). For patients with 9 to 12 lymph nodes and 13 to 16 lymph nodes examined, HRs were 0.86 (95% CI, 0.79–0.95) and 0.78 (95% CI, 0.68–0.90), respectively, there appeared to be no incremental improvement after evaluating more than 16 lymph nodes. The corresponding results for lung cancer-specific mortality and for patients receiving radiation therapy were not substantially different. These results indicate that patient survival following resection for NSCLC is associated with the number of lymph nodes evaluated during surgery. Because this is most likely the result of a reduction of staging error, namely, a decreased likelihood of missing positive lymph nodes with an increasing number of lymph nodes sampled, it suggests that an evaluation of nodal status should include between 11 to 16 lymph nodes.

Patients at risk for brain metastases may be staged with CT or MRI scans. One study randomly assigned 332 patients with potentially operable NSCLC but without neurological symptoms to brain CT or MRI imaging to detect occult brain metastasis before lung surgery. MRI showed a trend toward a higher preoperative detection rate than CT (P = .069), with an overall detection rate of approximately 7% from pretreatment to 12 months after surgery.[34] Patients with stage I or stage II disease had a detection rate of 4% (i.e., eight detections out of 200 patients); however, individuals with stage III disease had a detection rate of 11.4% (i.e., 15 detections out of 132 patients). The mean maximal diameter of the brain metastases was significantly smaller in the MRI group. Whether the improved detection rate of MRI translates into improved outcome remains unknown. Not all patients are able to tolerate MRI, and for these patients contrast-enhanced CT scan is a reasonable substitute.

Pathological staging requires:

- Examination of the tumor
- Resection margins
- Lymph nodes

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Prognostic and treatment decisions are based on some of the following factors:

- Knowledge of histologic type
- Tumor size and location
- Involvement of pleura
- Surgical margins
- Status and location of lymph nodes by station
- Tumor grade
- Lymphovascular invasion

The Revised International Staging System for Lung Cancer

The Revised International System for Staging Lung Cancer, based on information from a clinical database of more than 5,000 patients, was adopted in 1997 by the American Joint

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Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer.[40] In 2010, an updated review of 10,000 patients from the clinical database resulted in a revision of the TNM classification system which were published in the seventh edition of the TNM Classification System for Lung Cancer by the International Association for the Study of Lung Cancer.[41] Theses revisions were subsequently accepted by the Union for International Cancer Control and the AJCC.[42] In the seventh edition, significant changes were made to the T and M descriptors, which include the following:

- T1 has been subclassified into T1a (≤ 2 cm in size) and T1b (> 2 cm – 3 cm)
- T2 has been subclassified into T2a (> 3 cm – 5 cm in size) and T2b (> 5- 7 cm)
- T2 (> 7 cm in size) has been reclassified as T3
- Multiple tumor nodules in the same lobe as the primary lesion have been reclassified from T4 to T3
- Multiple tumor nodules in the same lung but different lobe have been reclassified from M1 to T4
- Multiple tumor nodules in the contralateral lung are M1a
- M1 has been subdivided into M1a and M1b
- Malignant pleural and pericardial effusions have been reclassified from T4 to M1a
- M1b designates distant metastasis

A detailed description of these changes and the possible impacts on clinical care and research have been described by Peter Goldstraw, MD, FRCS, Imperial College, London, UK. [42]

The AJCC has designated staging by TNM classification. Definitions of the TNM classification for lung cancer, from the AJCC seventh edition are described below: [41, 43]

TNM Definitions

Primary tumor (T)

- TX: Primary tumor cannot be assessed, or tumor is proven by the presence of malignant cells in sputum or bronchial washings but is not visualized by imaging or bronchoscopy
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1a: A tumor that is 2 cm or smaller in greatest dimension, is surrounded by lung or visceral pleura, and is without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus).
- T1b: A tumor is > 2 cm but ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus).
- T2a: Tumor > 3 cm but ≤ 5 cm in greatest dimension, or tumor with any of the following features: involves main bronchus, ≥ 2 cm distal to the carina; invades

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visceral pleura; or is associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.

- T2b: A tumor > 5 cm but ≤ 7 cm in greatest dimension, or tumor with any of the following features: involves main bronchus, ≥ 2 cm distal to the carina; invades visceral pleura; or is associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.
- T3: Tumor > 7 cm or a one that invades any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or, tumor in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or, associated atelectasis or obstructive pneumonitis of the entire lung; or separate tumor nodule(s) in the same lobe.
- T4: A tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; or, separate tumor nodule(s) in a different ipsilateral lobe

[Note: The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.]

Regional lymph nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes including involvement by direct extension of the primary tumor
- N2: Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
- N3: Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant metastasis (M)

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis
    - M1a: Separate tumor nodule(s) in a contralateral lobe, tumor with pleural nodules or malignant pleural (or pericardial) effusion
    - M1b: Distant metastasis (in extrathoracic organs)

[*Note: Most pleural (and pericardial) effusions associated with lung cancer are due to tumor; however, in a few patients multiple cytopathologic examinations of pleural and pericardial fluid are negative for tumor and the fluid is nonbloody and is not an exudant. Where these elements and clinical judgement dictate that*

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the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

AJCC Stage Groupings

Occult carcinoma

- TX, N0, M0

Stage 0

- Tis, N0, M0

Stage IA

- T1a, N0, M0
- T1b, N0, M0

Stage IB

- T2a, N0, M0

Stage IIA

- T2b, N0, M0
- T1a, N1, M0
- T1b, N1, M0
- T2a, N1, M0

Stage IIB

- T2b, N1, M0
- T3, N0, M0

Stage IIIA

- T1a, N2, M0
- T1b, N2, M0
- T2a, N2, M0
- T2b, N2, M0
- T3, N1, M0
- T3, N2, M0
- T4, N0, M0
- T4, N1, M0

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Stage IIIB

- Any T, N3, M0
- T4, N2, M0

Stage IV

- Any T, any N, M1a
- Any T, any N, M1b

VI. Treatment Options for Non-Small Cell Lung Cancer by Stage

In non-small cell lung cancer (NSCLC), results of standard treatment are poor except for the most localized cancers. All newly diagnosed patients with NSCLC are potential candidates for studies evaluating new forms of treatment.

Surgery is the most potentially curative therapeutic option for this disease. Adjuvant chemotherapy may provide an additional benefit to patients with resected NSCLC. Radiation therapy combined with chemotherapy can produce a cure in a small number of patients and can provide palliation in most patients. Prophylactic cranial irradiation (PCI) may reduce the incidence of brain metastases, but there is no evidence of a survival benefit and the effect of PCI on quality of life is not known.[44, 45] In patients with advanced-stage disease, chemotherapy offers modest improvements in median survival, though overall survival is poor.[46, 47]

Chemotherapy has produced short-term improvement in disease-related symptoms. Several clinical trials have attempted to assess the impact of chemotherapy on tumor-related symptoms and quality of life. In total, these studies suggest that tumor-related symptoms may be controlled by chemotherapy without adversely affecting overall quality of life;[48, 49] however, the impact of chemotherapy on quality of life requires more study. In general, medically fit elderly patients with good performance status obtain the same benefits from treatment as younger patients.

Current areas under evaluation include:

- Combining local treatment (surgery).
- Regional treatment (radiation therapy).
- Systemic treatments (chemotherapy, immunotherapy, and targeted agents).
- Developing more effective systemic therapy.

Chemoprevention of second primary cancers of the upper aerodigestive tract is undergoing clinical evaluation in patients with early stage lung cancer.

Treatment for Occult Non-Small Cell Lung Cancer

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Occult non-small cell lung cancer (NSCLC) is defined by the following clinical stage grouping:

- TX, N0, M0

In occult lung cancer, a diagnostic evaluation often includes chest x-ray and selective bronchoscopy with close follow-up (e.g., computed tomographic scan), when needed, to define the site and nature of the primary tumor; tumors discovered in this fashion are generally early stage and curable by surgery.

After discovery of the primary tumor, treatment involves establishing the stage of the tumor. Therapy is identical to that recommended for other NSCLC patients with similar stage disease.

Treatment for Stage 0 Non-Small Cell Lung Cancer

Stage 0 non-small cell lung cancer (NSCLC) is defined by the following clinical stage grouping:

- Tis, N0, M0

Stage 0 NSCLC is carcinoma *in situ* of the lung. Carcinoma *in situ* frequently progresses to invasive cancer.[50-52] Patients may be offered surveillance bronchoscopies and, if lesions are detected, potentially curative therapies. Because these tumors are by definition noninvasive and incapable of metastasizing, they should be curable with surgical resection; however, such lesions, when identified, are often centrally located and may require a lobectomy.

Patients with central lesions may be candidates for curative endobronchial therapy. Endobronchial therapies that preserve lung function include photodynamic therapy, electrocautery, cryotherapy, and Nd-YAG laser therapy.[53-55] Small case series have reported high complete response rates and long-term survival in selected patients.[56, 57]Efficacy of these treatment modalities in the management of patients with early NSCLC remains to be proven in definitive randomized controlled trials.

There is a high incidence of second primary cancers developing.

Standard treatment options:

1. Surgical resection using the least extensive technique possible (segmentectomy or wedge resection) to preserve maximum normal pulmonary tissue because these patients are at high risk for second lung cancers.
2. Endoscopic photodynamic therapy.
3. Other endobronchial therapies, including electrocautery, cryotherapy, and Nd-YAG laser therapy.

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Treatment for Stage I Non-Small Cell Lung Cancer

Stage I non-small cell lung cancer (NSCLC) is defined by the following clinical stage groupings:

- T1, N0, M0
- T2, N0, M0

Surgery is the treatment of choice for patients with stage I NSCLC. Careful preoperative assessment of the patient's overall medical condition, especially the patient's pulmonary reserve, is critical in considering the benefits of surgery. The immediate postoperative mortality rate is age related, but a 3% to 5% mortality rate with lobectomy can be expected.[58] Patients with impaired pulmonary function are candidates for segmental or wedge resection of the primary tumor.

The Lung Cancer Study Group conducted a randomized study (LCSG-821) to compare lobectomy with limited resection for patients with stage I lung cancer. Results of the study showed a reduction in local recurrence for patients treated with lobectomy compared with those treated with limited excision, but the outcome showed no significant difference in overall survival (OS).[59] Similar results have been reported from a non-randomized comparison of anatomic segmentectomy and lobectomy.[60] A survival advantage was noted with lobectomy for patients with tumors larger than 3 cm but not for those with tumors smaller than 3 cm; however, the rate of locoregional recurrence was significantly less after lobectomy, regardless of primary tumor size.

Patients with inoperable stage I disease and with sufficient pulmonary reserve may be candidates for radiation therapy with curative intent. In a single report of patients older than 70 years who had resectable lesions smaller than 4 cm but who had medically inoperable disease or who refused surgery, survival at 5 years after radiation therapy with curative intent was comparable with an historical control group of patients of similar age who were resected with curative intent.[61] In the two largest retrospective radiation therapy series, patients with inoperable disease treated with definitive radiation therapy achieved 5-year survival rates of 10% and 27%.[62] Both series found that patients with T1, N0 tumors had better outcomes, and 5-year survival rates of 60% and 32% were found in this subgroup.

Primary radiation therapy should consist of approximately 60 Gy delivered with megavoltage equipment to the midplane of the known tumor volume using conventional fractionation. A boost to the cone down field of the primary tumor is frequently used to enhance local control. Careful treatment planning with precise definition of target volume and avoidance of critical normal structures to the extent possible is needed for optimal results; this requires the use of a simulator.

Many patients treated surgically subsequently develop regional or distant metastases.[7] Such patients are candidates for entry into clinical trials evaluating adjuvant treatment with chemotherapy or radiation therapy following surgery. At present, neither

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chemotherapy nor radiation therapy has been found to improve the outcome of patients with stage I NSCLC that has been completely resected.

The value of postoperative radiation therapy (PORT) has been evaluated.[63] The meta-analysis, based on the results of ten randomized controlled trials and 2,232 individuals, reported an 18% relative increase in the risk of death for patients who received PORT compared to surgery alone (hazard ratio [HR] = 1.18; *P* = .002). This is equivalent to an absolute detriment of 6% at 2 years (95% CI, 2%–9%), reducing OS from 58% to 52%. Exploratory subgroup analyses suggested that this detrimental effect was most pronounced for patients with stage I/II, N0–N1 disease, whereas for stage III, N2 patients there was no clear evidence of an adverse effect. Results for local (HR = 1.13; *P* = .02), distant (HR = 1.14; *P* = .02) and overall (HR = 1.10; *P* = .06) recurrence-free survival similarly show a detriment of PORT. Further analysis is needed to determine whether these outcomes can potentially be modified with technical improvements, better definitions of target volumes, and limitation of cardiac volume in the radiation portals.

Several randomized controlled trials and meta-analyses have evaluated the use of adjuvant chemotherapy in patients with stage I, II, and IIIA NSCLC.[64-68]In the largest meta-analysis based on individual patient outcomes, data were collected and pooled from the five largest trials (4,584 patients) that were conducted after 1995 of cisplatin-based chemotherapy in patients with completely resected NSCLC. With a median follow-up time of 5.2 years, the overall HR of death was 0.89 (95% CI, 0.82–0.96; *P* = .005), corresponding to a 5-year absolute benefit of 5.4% from chemotherapy. The benefit varied with stage (test for trend, *P* = 0.04; HR for stage IA = 1.40; 95% CI, 0.95–2.06; HR for stage IB = 0.93; 95% CI, 0.78–1.10; HR for stage II = 0.83; 95% CI, 0.73–0.95; and HR for stage III = 0.83; 95% CI, 0.72–0.94). The effect of chemotherapy did not vary significantly (test for interaction, *P* = .11) with the associated drugs, including vinorelbine (HR = 0.80; 95% CI, 0.70–0.91), etoposide or vinca alkaloid (HR = 0.92; 95% CI, 0.80–1.07), or other (HR = 0.97; 95% CI, 0.84–1.13). The apparent greater benefit seen with vinorelbine should be interpreted cautiously as vinorelbine and cisplatin combinations generally required that a higher dose of cisplatin be given. Chemotherapy effect was higher in patients with better performance status.

There was no interaction between chemotherapy effect and any of the following:

- Sex.
- Age.
- Histology.
- Type of surgery.
- Planned radiation therapy.
- Planned total dose of cisplatin.

A significant number of patients cured of their smoking-related lung cancer may develop a second malignancy. In the Lung Cancer Study Group trial of 907 patients with stage T1, N0 resected tumors, the rate was 1.8% per year for nonpulmonary second cancers and 1.6% per year for new lung cancers.[69] Others have reported even higher risks of

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second tumors in long-term survivors, including rates of 10% for second lung cancers and 20% for all second cancers.

Because of the persistent risk of developing second lung cancers in former smokers, various chemoprevention strategies have been evaluated in randomized control trials. None of the phase III trials with the agents beta carotene, retinol, 13-cis-retinoic acid, [alpha]-tocopherol, N-acetylcysteine, or acetylsalicylic acid has demonstrated beneficial, reproducible results.[70-73]**Treatment options:**

1. Lobectomy or segmental, wedge, or sleeve resection as appropriate.
2. Radiation therapy with curative intent (for potentially resectable tumors in patients with medical contraindications to surgery).
3. Clinical trials of adjuvant chemoprevention (as evidenced in the ECOG-5597 trial, for example).
4. Endoscopic photodynamic therapy and other endobronchial therapies (under clinical evaluation in highly selected patients with T1, N0, M0 tumors).

Treatment for Stage II Non-Small Cell Lung Cancer

Stage II non-small cell lung cancer (NSCLC) is defined by the following clinical stage groupings:

- T1, N1, M0
- T2, N1, M0
- T3, N0, M0

Surgery is the treatment of choice for patients with stage II NSCLC. Careful preoperative assessment of the patient's overall medical condition, especially the patient's pulmonary reserve, is critical in considering the benefits of surgery. Despite the immediate and age-related postoperative mortality rate, a 5% to 8% mortality rate with pneumonectomy or a 3% to 5% mortality rate with lobectomy can be expected.[74]

Patients with inoperable stage II disease and with sufficient pulmonary reserve are candidates for radiation therapy with curative intent. Among patients with excellent performance status (PS) a 3-year survival rate of 20% may be expected if a course of radiation therapy with curative intent can be completed. In the largest retrospective series reported to date, 152 patients with medically inoperable NSCLC, who were treated with definitive radiation therapy, achieved a 5-year OS rate of 10%; however, the 44 patients with T1 tumors achieved an actuarial disease-free survival (DFS) rate of 60%. This retrospective study also suggested that improved DFS was obtained with radiation therapy doses larger than 60 Gy.

After surgery, many patients develop regional or distant metastases. Chemotherapy should be used. The benefit of chemotherapy varies with stage (test for trend, $P = .04$; HR for stage IA = 1.40; 95% CI, 0.95–2.06; HR for stage IB = 0.93; 95% CI, 0.78–1.10; HR for stage II = 0.83; 95% CI, 0.73–0.95; and HR for stage III = 0.83; 95% CI, 0.72–

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0.94). The effect of chemotherapy did not vary significantly (test for interaction, *P* = .11) with the associated drugs, including vinorelbine (HR = 0.80; 95% CI, 0.70–0.91), etoposide or vinca alkaloid (HR = 0.92; 95% CI, 0.80–1.07), or other (HR = 0.97; 95% CI, 0.84–1.13). The greater effect on survival observed with the doublet of cisplatin plus vinorelbine compared with other regimens should be interpreted with caution as the total dose of cisplatin received was significantly higher in patients treated with vinorelbine. However, the meta-analysis as well as the individual studies support the administration of adjuvant cisplatin-based chemotherapy in combination with vinorelbine.[75] For these studies, the LACE pooled analysis (NCT00576914), ANITA (NCT00238849), and NCIC-CTG JBR.10 (CAN-NCIC-BR10) trials all reported superior OS for the trial population as well as for the patients with stage II disease (pooled HR = 0.83, 95% CI, 0.73–0.95; HR = 0.71, 95% CI, 0.49–1.03; HR = 0.59, 95% CI, 0.42–0.85, respectively). Chemotherapy effect was higher in patients with better PS.

There was no interaction between chemotherapy effect and any of the following:

- Sex.
- Age.
- Histology.
- Type of surgery.
- Planned radiation therapy.
- Planned total dose of cisplatin.

In a retrospective analysis of a phase III trial of adjuvant cisplatin and vinorelbine, patients older than 65 years were found to benefit from treatment. Chemotherapy significantly prolonged OS for elderly patients (HR = 0.61; 95% CI, 0.38–0.98; *P* = .04). There were no significant differences in toxic effects, hospitalization, or treatment-related death by age group, although elder patients received less treatment. Based on these data, patients with completed resected stage II lung cancer may benefit from adjuvant cisplatin-based chemotherapy.[76]

The role of chemotherapy prior to surgery has been tested in clinical trials. The proposed benefits of preoperative chemotherapy are a reduction in tumor size that may facilitate surgical resection, early eradication of micrometastases, and better tolerability. Preoperative chemotherapy may, however, delay potentially curative surgery. The Cochrane Collaboration Review group reported a systematic review and meta-analysis of seven randomized controlled trials including 988 patients evaluating the addition of preoperative chemotherapy to surgery versus surgery alone. Included trials evaluated patients with stages I, II, and IIIa NSCLC.[77] Preoperative chemotherapy provided an absolute benefit in survival of 6% across all stages of disease from 14% to 20% at 5 years (HR = 0.82; 95% CI, 0.69–0.97; *P* = .022). This analysis was unable to address questions such as whether particular types of patients may benefit more or less from preoperative chemotherapy.

Although the Cochrane Collaboration group's analysis indicates an OS advantage for preoperative chemotherapy, in the largest trial reported to date, no survival advantage

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was seen.[78] In that trial, 519 patients were randomized to receive either surgery alone or three cycles of platinum-based chemotherapy followed by surgery. Most patients (61%) had clinical stage I disease; 31% had stage II disease, and 7% had stage III disease. Postoperative complications were similar between groups, and no impairment of quality of life was observed. There was no evidence of a benefit in terms of OS (HR = 1.02; 95% CI, 0.80–1.31, *P* = .86). Updating the systematic review by addition of the present result suggests a 12% relative survival benefit with the addition of neoadjuvant chemotherapy (1,507 patients; HR = 0.88, 95% CI, 0.76–1.01, *P* = .07), equivalent to an absolute improvement in survival of 5% at 5 years.

In summary, the preponderance of evidence indicates that adjuvant cisplatin combination chemotherapy provides a significant survival advantage to patients with resected stage II NSCLC. Preoperative chemotherapy may also provide survival benefit. The optimal sequence of surgery and chemotherapy and the benefits and risks of adjuvant radiation therapy in patients with resectable NSCLC remain to be determined.

Treatment options:

1. Lobectomy; pneumonectomy; or segmental, wedge, or sleeve resection as appropriate.
2. Radiation therapy with curative intent (for potentially operable tumors in patients with medical contraindications to surgery).
3. Adjuvant chemotherapy after curative surgery.
4. Clinical trials of radiation therapy after curative surgery.

Treatment for Stage IIIA Non-Small Cell Lung Cancer

Stage IIIA non-small cell lung cancer (NSCLC) is defined by the following clinical stage groupings:

- T1, N2, M0
- T2, N2, M0
- T3, N1, M0
- T3, N2, M0

Patients with stage IIIA NSCLC are a heterogenous group. Patients may have metastases to ipsilateral mediastinal nodes or potentially resectable T3 tumors invading chest wall or mediastinal involvement with metastases to peribronchial or hilar lymph nodes (N1). Presentations of disease range from resectable tumors with microscopic metastases to lymph nodes to unresectable, bulky disease involving multiple nodal stations.

Patients with clinical stage IIIA-N2 disease have a 5-year survival rate of 10% to 15% overall; however, patients with bulky mediastinal involvement (i.e., visible on chest radiography) have a 5-year survival rate of 2% to 5%. Depending on clinical circumstances, the principal forms of treatment that are considered for patients with stage

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IIIA NSCLC are radiation therapy, chemotherapy, surgery, and combinations of these modalities.

Resected/Resectable Stage IIIA N2 Disease

Despite careful preoperative staging, some patients will be found to have metastases to mediastinal N2 lymph nodes at thoracotomy. Preoperative staging typically includes the following:

- Computed tomography (CT) scan.
- Positron emission tomography (PET).
- Mediastinoscopy.

If complete resection of tumor and lymph nodes is possible, such patients may benefit from surgery followed by postoperative adjuvant chemotherapy. The Cochrane Collaboration group reviewed 11 randomized trials with a total of 1,910 patients who underwent surgical interventions for early stage (I–IIIA) lung cancer. From a pooled analysis of three trials, 4-year survival was superior in patients with resectable stage I to IIIA NSCLC who underwent resection and complete ipsilateral mediastinal lymph node dissection (CMLND) compared with those who underwent resection and lymph node sampling; the hazard ratio (HR) was estimated to be 0.78 (95% confidence interval [CI], 0.65–0.93, *P* = .005).[77]

There was no interaction between the chemotherapy effect and any of the following:

1. Sex.
2. Age.
3. Histology.
4. Type of surgery.
5. Planned radiation therapy.
6. Planned total dose of cisplatin.

The role of chemotherapy prior to surgery in patients with stage III-N2 NSCLC has been extensively tested in clinical trials. The proposed benefits of preoperative chemotherapy are:

- A reduction in tumor size that may facilitate surgical resection.
- Early eradication of micrometastases.
- Better tolerability.

The value of postoperative radiation therapy (PORT) has been assessed.[63] Although some studies suggest that PORT can improve local control for node-positive patients whose tumors were resected, it remains controversial whether it can improve survival. A meta-analysis of 10 randomized trials that evaluated PORT versus surgery alone showed no difference in OS for the entire PORT group or for the subset of N2 patients.

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The optimal dose of postoperative thoracic radiation therapy is not known at this time. Further analysis is needed to determine whether these outcomes can be modified with technical improvements, better definitions of target volumes, and limitation of cardiac volume in the radiation portals.

As referred to in the National Cancer Institute of Canada and Intergroup Study JBR.10 study (CAN-NCIC-BR10 and JBR.10), PORT may be considered in selected patients to reduce the risk of local recurrence, if there is:

- Involvement of multiple nodal stations.
- Extracapsular tumor spread.
- Close or microscopically positive resection margins.

Five randomized trials have assessed the value of adjuvant combination chemoradiation therapy versus radiation following surgical resection.[79] Only one trial reported improved disease-free survival (DFS) and no trial reported improved OS. Combination chemotherapy and radiation administered before or following surgery should be viewed as investigational and requiring evaluation in future clinical trials.

In summary, the preponderance of evidence indicates that adjuvant cisplatin combination chemotherapy provides a significant survival advantage to patients with resected NSCLC with occult N2 disease discovered at surgery. The optimal sequence of surgery and chemotherapy and the benefits and risks of adjuvant radiation therapy in patients with resectable NSCLC are yet to be determined.

Treatment options for patients with resected/resectable disease:

1. Surgery followed by postoperative adjuvant chemotherapy.
2. Clinical trials of combined modality therapy.

Unresectable Stage IIIA N2 NSCLC

Radiation therapy alone, administered sequentially with chemotherapy and concurrently with chemotherapy, may provide benefit to patients with locally advanced unresectable stage III NSCLC. However, combination chemoradiation therapy delivered concurrently provides the greatest benefit in survival with increase in toxic effects. Radiation therapy with traditional dose and fractionation schedules (1.8–2.0 Gy per fraction per day to 60–70 Gy in 6 to 7 weeks) results in reproducible long-term survival benefit in 5% to 10% of patients and significant palliation of symptoms.[47] One prospective randomized clinical study showed that radiation therapy given continuously (including weekends) as three daily fractions (CHART) improved OS compared with radiation therapy given as one daily fraction.[80] Patterns of failure for patients treated with radiation therapy alone included both locoregional and distant failures.

Although patients with unresectable stage IIIA disease may benefit from radiation therapy, long-term outcomes have generally been poor because of local and systemic

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relapse. The addition of sequential and concurrent chemotherapy to radiation therapy has been evaluated in prospective randomized trials.[81] A meta-analysis of patient data from 11 randomized clinical trials showed that cisplatin-based combinations plus radiation therapy resulted in a 10% reduction in the risk of death compared with radiation therapy alone.[82] Meta-analysis of the 13 trials (based on 2,214 evaluable patients) showed that the addition of concurrent chemotherapy to radical radiation therapy reduced the risk of death at 2 years (RR = 0.93; 95% CI, 0.88–0.98, *P* = .01). For the 11 trials with platinum-based chemotherapy, RR was 0.93 (95% CI, 0.87–0.99, *P* = .02).[83] In a meta-analysis of individual data from 1,764 patients, which was based on nine trials, the HR of death among patients treated with radiation chemotherapy compared to radiation therapy alone was 0.89 (95% CI, 0.81–0.98; *P* = .02) corresponding to an absolute benefit of chemotherapy of 4% at 2 years. The combination of platinum with etoposide seemed more effective than platinum alone. Concomitant platinum-based radiation chemotherapy may improve survival of patients with locally advanced NSCLC. However, the available data are insufficient to accurately define the size of such a potential treatment benefit and the optimal schedule of chemotherapy.[81] The results of two randomized trials (including RTOG-9410) and a meta-analysis (NPC 95-01) indicate that concurrent chemotherapy and radiation therapy provide greater survival benefit albeit with more toxic effects than sequential chemotherapy and radiation therapy.[84-86] In the first trial, the combination of mitomycin C, vindesine, and cisplatin were given concurrently with split-course daily radiation therapy to 56 Gy compared to chemotherapy followed by continuous daily radiation therapy to 56 Gy. Five-year OS favored concurrent therapy (27% vs. 9%). Myelosuppression was greater among patients in the concurrent arm, but treatment-related mortality was less than 1% in both arms.

Several small series have reported that reduction in fluorodeoxyglucose-positron emission tomography (FDG-PET) after chemotherapy, radiation therapy, or chemoradiation therapy correlate with pathological complete response and favorable prognosis.[87-91]Series have used different timing of assessments, positron emission tomography (PET) parameters, and cutpoints to define PET response. Reduction in maximum standardized uptake value (SUV) of more than 80% predicted for complete pathological response with a sensitivity of 90%, specificity of 100%, and accuracy of 96%.[92] Median survival after resection was greater for patients with tumor SUV values of less than 4 (56 months vs. 19 months). Patients with complete metabolic response following radiation therapy were reported to have median survivals of 31 months versus 11 months. PET may be more sensitive and specific than the CT scan in assessing response to induction therapy.

Radiation therapy may be effective in palliating symptomatic local involvement with NSCLC, such as tracheal, esophageal, or bronchial compression; pain; vocal cord paralysis; hemoptysis; or superior vena cava syndrome. In some cases, endobronchial laser therapy and/or brachytherapy has been used to alleviate proximal obstructing lesions. [93] A systematic review identified six randomized trials of high-dose rate brachytherapy (HDREB) alone or with external-beam radiation therapy (EBRT) or laser therapy.[94] Better overall symptom palliation and fewer retreatments were required in previously untreated patients using EBRT alone. HDREB did provide palliation of

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symptomatic patients with recurrent endobronchial obstruction previously treated by EBRT, providing it is technically feasible. Although EBRT is frequently proscribed for symptom palliation, there is no consensus about when the fractionation scheme should be used. Although different multifraction regimens appear to provide similar symptom relief,[95-100] single-fraction radiation may be insufficient for symptom relief compared with hypofractionated or standard regimens, as evidenced in the NCIC Clinical Trials' Group trial NCIC-CTG-SC15. Evidence is available of a modest increase in survival in patients with better PS given high-dose radiation therapy.

Treatment options for patients with unresectable disease:

1. Surgery followed by adjuvant cisplatin-based combination chemotherapy for patients incidentally found to have occult N2 disease following complete resection.
2. Chemoradiation therapy for patients with stage IIIA-N2 disease.
3. Radiation therapy alone for patients medically unfit for combined modality therapy.

Superior sulcus tumors (T3, N0 or N1, M0)

NSCLC of the superior sulcus, frequently termed Pancoast tumors, occurs in less than 5% of patients.[101-103] Superior sulcus tumors (SST) usually arise from the apex of the lung and are challenging to treat because of their proximity to structures at the thoracic inlet. At this location, tumors may invade the parietal pleura, chest wall, brachial plexus, subclavian vessels, stellate ganglion, and adjacent vertebral bodies. However, Pancoast tumors are amenable to curative treatment, especially in patients with T3, N0 disease.

Adverse prognostic factors include the presence of mediastinal nodal metastases (N2 disease), spine, or subclavian-vessel involvement (T4 disease), and limited resection (R1 or R2).

While radiation therapy is an integral part of the treatment of Pancoast tumors, variations in dose, treatment technique, and staging that was used in various published series make it difficult to determine its effectiveness.[103] In the preoperative setting, a dose of 45 Gy over 5 weeks is generally recommended, while a dose of approximately 61 Gy is required when using definitive radiation therapy as the primary modality. Small retrospective series of radiation therapy of patients who were only clinically staged have reported 5-year survival rates of 0% to 40% depending on T stage, total radiation dose, and other prognostic factors. Induction radiation therapy and en-bloc resection was shown to be potentially curative. Retrospective case series have reported complete resection was achieved in only 64% of tumor stage (T) 3, nodal stage (N) 0, and 39% of T4, N0 tumors.

Two large, prospective, multicenter phase II trials have evaluated induction chemoradiation therapy followed by resection.[102, 104] In the trial (SWOG-9416), 110 eligible patients were enrolled with mediastinoscopy negative, clinical T3–4 N0–1

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tumors of the superior sulcus. Induction treatment was two cycles of etoposide and cisplatin with 45 Gy of concurrent radiation therapy. The induction regimen was well tolerated and only five participants had grade 3 or higher toxic effects. Induction chemoradiation therapy could sterilize the primary lesion. Induction therapy was completed by 104 (95%) patients. Of 95 patients eligible for surgery, 88 (80%) underwent thoracotomy, two (1.8%) died postoperatively, and 83 (76%) had complete resections. Pathologic complete response or minimal microscopic disease was seen in 61 (56%) resection specimens. Five-year survival was 44% for all patients and 54% after complete resection, with no difference between T3 and T4 tumors. Pathologic complete response led to better survival than when any residual disease was present (P = .02). Disease progression occurred mainly in distant sites.

Treatment options for patients with superior sulcus tumors:

1. Radiation therapy and surgery.
2. Radiation therapy alone.
3. Surgery alone (selected cases).
4. Concurrent chemotherapy with radiation therapy and surgery.
5. Clinical trials of combined modality therapy.

Chest wall tumor (T3, N0 or N1, M0)

Selected patients with bulky primary tumors that directly invade the chest wall can obtain long-term survival with surgical management provided that their tumor is completely resected.

Treatment options for patients with chest wall tumors:

1. Surgery.[105, 106]
2. Surgery and radiation therapy.
3. Radiation therapy alone.
4. Chemotherapy combined with radiation therapy and/or surgery.

Treatment for Stage IIIB Non-Small Cell Lung Cancer

Stage IIIB non-small cell lung cancer (NSCLC) is defined by the following clinical stage groupings:

- Any T, N3, M0
- T4, any N, M0

Based on the Surveillance, Epidemiology, and End registry the estimated incidence of stage IIIB NSCLC is 17.6%.[1] The anticipated 5-year survival for the vast majority of patients who present with clinical stage IIIB NSCLC is 3% to 7%.[107] In general, patients with stage IIIB NSCLC do not benefit from surgery alone and are best managed by initial chemotherapy, chemotherapy plus radiation therapy, or radiation therapy alone,

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depending on the sites of tumor involvement and the performance status (PS) of the patient. In small case series, selected patients with T4, N0-1 solely due to satellite tumor nodule(s) within the primary lobe have been reported to have 5-year survival rates of 20%.[108, 109] Selected patients with T4 N0 disease may be treated with combined modality therapy and surgery similar to patients with superior sulcus tumors. Patients with T4 disease caused by malignant pleural effusions are treated similarly to patients with stage 4 disease. With the above exceptions, most patients with excellent PS are candidates for combined modality chemotherapy and radiation therapy. Many randomized studies of patients with unresectable stage III NSCLC show that treatment with neoadjuvant or concurrent cisplatin-based chemotherapy and radiation therapy to the chest is associated with improved survival compared with treatment that uses radiation therapy alone. A meta-analysis of patient data from 11 randomized clinical trials showed that cisplatin-based combinations plus radiation therapy resulted in a 10% reduction in the risk of death compared with radiation therapy alone.

Patients with stage IIIB disease with poor PS are candidates for chest radiation therapy to palliate pulmonary symptoms (e.g., cough, shortness of breath, hemoptysis, or pain).[110]

T4 or N3, M0

Radiation therapy alone, administered sequentially or concurrently with chemotherapy, may provide benefit to patients with locally advanced unresectable stage III NSCLC. However, combination chemoradiation therapy delivered concurrently provides the greatest benefit in survival with increase in toxic effects. Radiation therapy with traditional dose and fractionation schedules (1.8 Gy to 2.0 Gy per fraction per day to 60 Gy to 70 Gy in 6 to 7 weeks) results in reproducible long-term survival benefit in 5% to 10% of patients and significant palliation of symptoms.[47] One prospective randomized clinical study showed that radiation therapy given as three daily fractions improved OS compared with radiation therapy given as one daily fraction.[81] Patterns of failure for patients treated with radiation therapy alone included both loco-regional and distant failures.

Although patients with unresectable stage IIIB disease may benefit from radiation therapy, long-term outcomes have generally been poor, often due to local and systemic relapse. The addition of sequential and concurrent chemotherapy to radiation therapy has been evaluated in prospective randomized trials. A meta-analysis of patient data from 11 randomized clinical trials showed that cisplatin-based combinations plus radiation therapy resulted in a 10% reduction in the risk of death compared with radiation therapy alone.[47] A meta-analysis of the 13 trials (based on 2,214 evaluable patients) showed that the addition of concurrent chemotherapy to radical radiation therapy reduced the risk of death at 2 years (relative risk [RR] = 0.93; 95% confidence interval [CI], 0.88–0.98, *P* = .01). For the 11 trials with platinum-based chemotherapy, RR was 0.93 (95% CI, 0.87–0.99, *P* = .02).[81]

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In a meta-analysis of individual data from 1,764 patients, based on nine trials, the hazard ratio of death among patients treated with radiation chemotherapy compared to radiation therapy alone was 0.89 (95% confidence interval, 0.81–0.98; *P* = .02) corresponding to an absolute benefit of chemotherapy of 4% at 2 years. The combination of platinum with etoposide seemed more effective than platinum alone. Concomitant platinum-based radiation chemotherapy may improve survival of patients with locally advanced NSCLC. However, the available data are insufficient to accurately define the size of such a potential treatment benefit and the optimal schedule of chemotherapy.[82]

Because of the poor overall results, these patients are candidates for clinical trials that examine new fractionation schedules, radiosensitizers, and combined modality approaches, which may lead to improvement in the control of disease.

Treatment options:

1. Chemotherapy combined with radiation therapy.
2. Radiation therapy alone.

Treatment for Stage IV Non-Small Cell Lung Cancer

Stage IV non-small cell lung cancer (NSCLC) is defined by the following clinical stage grouping:

- Any T, any N, M1

Forty percent of patients with newly diagnosed NSCLC have stage IV disease. Randomized controlled trials of patients with stage IV disease and stage IIIB disease with malignant pleural effusions and good performance status (PS) have shown that cisplatin-based chemotherapy improves survival and palliates disease-related symptoms. Patients with nonsquamous cell histology, good PS, no history of hemoptysis or other bleeding or recent history of cardiovascular events may benefit from the addition of bevacizumab to paclitaxel carboplatin. The role of chemotherapy in patients with poor PS was less certain. Second-line chemotherapy with docetaxel, pemetrexed, or erlotinib also improves survival patients with good PS.[111]

Several randomized trials have evaluated various drugs combined with either cisplatin or carboplatinum in previously untreated patients with advanced NSCLC. Based on meta-analyses of the trials the following conclusions can be drawn:

1. Platinum combinations with vinorelbine, paclitaxel, docetaxel, gemcitabine, irinotecan, and pemetrexed yield similar improvements in survival. Types and frequencies of toxic effects differ, and these may determine the preferred regimen for an individual patient.
2. Cisplatin and carboplatinum yield similar improvements in outcome, although some but not all trials and meta-analyses of trials suggest that outcomes with

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cisplatin may be superior, although with a higher risk of certain toxicities such as nausea and vomiting.
3. Nonplatinum combinations offer no advantage to platinum-based chemotherapy, and some studies demonstrate inferiority.
4. Three-drug combinations of the commonly used chemotherapy drugs do not result in superior survival and are more toxic than two-drug combinations.
5. Certain three-drug combinations that add so-called targeted agents may result in superior survival.

In a randomized study of 878 patients with recurrent or advanced stage IIIB or stage IV NSCLC, 444 received paclitaxel and carboplatin alone, and 434 patients received paclitaxel and carboplatin plus bevacizumab.[112] Chemotherapy was administered every 3 weeks for six cycles, and bevacizumab was administered every 3 weeks until disease progression was evident or toxic effects were intolerable. Patients with squamous cell tumors, brain metastases, clinically significant hemoptysis, or inadequate organ function or PS (ECOG PS >1) were excluded. The median survival was 12.3 months in the group assigned to chemotherapy plus bevacizumab, as compared with 10.3 months in the chemotherapy-alone group (hazard ratio [HR] for death, 0.79; $P = .003$). The median progression-free survival in the two groups was 6.2 months and 4.5 months, respectively (HR for disease progression, 0.66; $P < .001$), with corresponding response rates of 35% and 15% ($P < .001$). Rates of clinically significant bleeding were 4.4% and 0.7%, respectively ($P < .001$). There were 15 treatment-related deaths in the chemotherapy-plus-bevacizumab group, including five from pulmonary hemorrhage. For this subgroup of patients with NSCLC, the addition of bevacizumab to paclitaxel and carboplatin may provide survival benefit.

The type and number of chemotherapy drugs to be used for the treatment of patients with advanced NSCLC has been extensively evaluated in randomized controlled trials and meta-analyses. The Cochrane Collaboration group reviewed data from all randomized controlled trials published between January 1980 and June 2006, comparing a doublet regimen with a single-agent regimen or comparing a triplet regimen with a doublet regimen in patients with advanced NSCLC.[113] Sixty-five trials (13,601 patients) were identified. In the trials comparing a doublet regimen with a single-agent regimen, a significant increase was observed in tumor response (OR = 0.42; 95% confidence interval [CI], 0.37– 0.47, $P < .001$) and 1-year survival (OR = 0.80; 95% CI, 0.70–0.91, $P < .001$) in favor of the doublet regimen. The absolute benefit in 1-year survival was 5%, which corresponds to an increase in 1-year survival from 30% with a single-agent regimen to 35% with a doublet regimen. The rates of grades 3 and 4 toxic effects caused by doublet regimens were statistically increased compared with rates following single-agent therapy, with ORs ranging from 1.2 to 6.2. There was no increase in infection rates in doublet regimens. There was no increase in 1-year survival (OR = 1.01; 95% CI, 0.85–1.21; $P = .88$) for triplet regimens versus doublet regimens. The median survival ratio was 1.00 (95% CI, 0.94–1.06, $P = .97$).

Several meta-analyses have evaluated whether cisplatin or carboplatin regimens are superior with variable results.[65, 114, 115] One meta-analysis reported individual

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patient data for 2,968 patients entered in nine randomized trials. The objective response rate was higher for patients treated with cisplatin than for patients treated with carboplatin (30% vs. 24%, respectively; OR = 1.37; 95% CI, 1.16–1.61; *P* < .001). Carboplatin treatment was associated with a nonstatistically significant increase in the hazard of mortality relative to treatment with cisplatin (HR = 1.07; 95% CI, 0.99–1.15; *P* = .100). In patients with nonsquamous tumors and those treated with third-generation chemotherapy, carboplatin-based chemotherapy was associated with a statistically significant increase in mortality (HR = 1.12; 95% CI, 1.01–1.23 and HR = 1.11; 95% CI, 1.01–1.21, respectively). Treatment-related toxic effects were also assessed in the meta-analysis. More thrombocytopenia was seen with carboplatin than with cisplatin (12% vs. 6%; OR = 2.27; 95% CI, 1.71–3.01; *P* < .001), while cisplatin caused more nausea and vomiting (8% vs. 18%; OR = 0.42; 95% CI, 0.33–0.53; *P* < .001) and renal toxic effects (0.5% vs. 1.5%; OR = 0.37; 95% CI, 0.15–0.88; *P* = .018). The authors concluded that treatment with cisplatin was not associated with a substantial increase in the overall risk of severe toxic effects. This comprehensive individual-patient meta-analysis is consistent with the conclusions of other meta-analyses, which were based on essentially the same clinical trials but which used only published data.

Three literature-based meta-analyses have trials comparing platinum to nonplatinum combinations.[116-118] The first meta-analysis identified 37 assessable trials that included 7,633 patients. A 62% increase in the OR for response was attributable to platinum-based therapy (OR = 1.62; 95% CI, 1.46–1.8; *P* < .001). The 1-year survival rate was increased by 5% with platinum-based regimens (34% vs. 29%; OR = 1.21; 95% CI, 1.09–1.35; *P* = .003). No statistically significant increase in 1-year survival was found when platinum therapies were compared to third-generation-based combination regimens (OR = 1.11; 95% CI, 0.96–1.28; *P* = .17). The toxic effects of platinum-based regimens was significantly higher for hematologic toxic effects, nephrotoxic effects, and nausea and vomiting, but not for neurologic toxic effects, febrile neutropenia rate, or toxic death rate. These results are consistent with the second literature-based meta-analysis.

The second meta-analysis identified 17 trials that included 4,920 patients. The use of platinum-based doublet regimens was associated with a slightly higher survival at 1 year (RR = 1.08; 95% CI, 1.01–1.16, *P* = .03), better partial response (RR = 1.11, 95% CI, 1.02–1.21; *P* = .02), with a higher risk of anemia, nausea, and neurologic toxic effects. However, in subanalyses, cisplatin-based doublet regimens improved survival at 1 year (RR = 1.16; 95% CI, 1.06–1.27; *P* = .001), complete response (RR = 2.29; 95% CI, 1.08–4.88; *P* = .03), partial response (RR = 1.19; 95% CI, 1.07–1.32; *P* = .002) with an increased risk of anemia, neutropenia, neurologic toxic effects, and nausea. Conversely, carboplatin-based doublet regimens did not increase survival at 1 year (RR = 0.95; 95% CI, 0.85–1.07; *P* = .43).

The third meta-analysis of phase III trials randomizing platinum-based versus nonplatinum combinations as first-line chemotherapy identified 14 trials. Experimental arms were gemcitabine and vinorelbine (n = 4), gemcitabine and taxane (n = 7), gemcitabine and epirubicin (n = 1), paclitaxel and vinorelbine (n = 1), and gemcitabine

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and ifosfamide (n = 1). This meta-analysis was limited to the set of 11 phase III studies that used a platinum-based doublet (2,298 and 2,304 patients in platinum-based and nonplatinum arms, respectively). Patients treated with a platinum-based regimen benefited from a statically significant reduction in the risk of death at 1 year (odds ratio [OR] = 0.88; 95% CI, 0.78–0.99; *P* = .044) and a lower risk of being refractory to chemotherapy (OR = 0.87; 0.73–0.99; *P* = .049). Forty-four (1.9%) and 29 (1.3%) toxic-related deaths were reported for platinum-based and nonplatinum regimens, respectively (OR = 1.53; 0.96–2.49; *P* = 0.08). An increased risk of grade 3 to 4 gastrointestinal and hematological toxic effects for patients receiving platinum-based chemotherapy was statistically demonstrated. There was no statistically significant increase in risk of febrile neutropenia (OR=1.23; 0.94–1.60; *P* = .063).

Among the active combinations, definitive recommendations regarding drug dose and schedule cannot be made. However, there has been one meta-analysis of seven trials that included 2,867 patients to assess the benefit of docetaxel versus vinorelbine.[119] Docetaxel was administered with a platinum agent in three trials, with gemcitabine in two trials, or as monotherapy in two trials. Vinca alkaloid (vinorelbine in six trials and vindesine in one trial) was administered with cisplatin in six trials or alone in one trial. The pooled estimate for OS showed an 11% improvement in favor of docetaxel (HR = 0.89; 95% CI, 0.82–0.96; *P* = .004). Sensitivity analyses considering only vinorelbine as a comparator or only the doublet regimens showed similar improvements. Grade 3 and 4 neutropenia and grade 3–4 serious adverse events were less frequent with docetaxel-based regimens versus vinca alkaloid-based regimens (OR = 0.59; 95% CI, 0.38–0.89; *P* = .013 and OR = 0.68; 95% CI, 0.55–0.84; *P* < .001, respectively). There have been two randomized trials comparing weekly versus every 3 weeks' dosing of paclitaxel carboplatin, which reported no significant difference in efficacy and better tolerability for weekly administration.[120, 121] Although meta-analyses of randomized controlled trials suggest that cisplatin combinations may be superior to carboplatin or nonplatinum combinations, the clinical relevance of the differences in efficacy must be balanced against the anticipated tolerability, logistics of administration, and familiarity of the medical staff for treatment decisions for individual patients.

Platinum-containing combination chemotherapy regimens provide clinical benefit when compared with supportive care or single-agent therapy; however, such treatment may be contraindicated in some older patients because of the age-related reduction in the functional reserve of many organs and/or comorbid conditions. Approximately two-thirds of patients with NSCLC are 65 years or older and approximately 40% are 70 years or older.[122] Surveillance, Epidemiology, and End Results (SEER) data suggest that the percentage of patients who are older than 70 years is closer to 50%. A review of the SEER Medicare data from 1994 to 1999 found a much lower rate of chemotherapy use than expected for the overall population. It also suggested that the elderly may have more comorbidities or a higher rate of functional compromise that would make study participation difficult, if not contraindicated, and lack of clinical trial data may influence decisions to treat individual patients with standard chemotherapy.

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Single-agent chemotherapy and combination chemotherapy clearly benefit at least some elderly patients. In the Elderly Lung Cancer Vinorelbine Italian Study, 154 patients who were older than 70 years were randomized to vinorelbine or supportive care.[123] Patients who were treated with vinorelbine had a 1-year survival rate of 32%, compared with 14% for those who were treated with supportive care alone. Quality-of-life parameters were also significantly improved in the chemotherapy arm, and toxic effects were acceptable. A more recent trial from Japan compared single-agent docetaxel with vinorelbine in 180 elderly patients with good PS.[124, 125] Response rates and progression-free survival were significantly better with docetaxel (22% vs. 10%; 5.4 months vs. 3.1 months, respectively), whereas median and 1-year survival rates did not reach statistical significance (14.3 months vs. 9.9 months; 59% vs. 37%, respectively). Retrospective data analyzing and comparing younger (<70 years old) with older (≥70 years old) patients who participated in large, randomized trials of doublet combinations have also shown that elderly patients may derive the same survival benefit although with a higher risk of toxic effects in the bone marrow.[126-130]Evidence supports that elderly patients with good PS and limited comorbidity may benefit from combination chemotherapy.

In summary, age alone should not dictate treatment-related decisions in patients with advanced NSCLC. Elderly patients with a good PS enjoy longer survival and a better quality of life when treated with chemotherapy compared with supportive care alone. Caution should be exercised when extrapolating data for elderly patients (70–79 years old) to patients who are 80 years or older because only a very small number of patients greater than 80 years of age have been enrolled on clinical trials, and the benefit in this group is uncertain.

A phase II randomized trial (ECOG-1599) of attenuated dosages of cisplatin plus gemcitabine and carboplatin plus paclitaxel included 102 patients with a PS of 2. Response rates were 25% and 16%, median survival times were 6.8 months and 6.1 months, and 1-year survival rates were 25% and 19%, respectively. None of these differences was statistically significant, but the survival figures were longer than expected on the basis of historical controls. Results from two trials suggest that patients with a PS of 2 may experience symptom improvement.[131, 132]

The results support further evaluation of chemotherapeutic approaches for both metastatic and locally advanced NSCLC; however, the efficacy of current platinum-based chemotherapy combinations is such that no specific regimen can be regarded as standard therapy. Outside of a clinical trial setting, chemotherapy should be given only to patients with good PS and evaluable tumor lesions, who desire such treatment after being fully informed of its anticipated risks and limited benefits.

Treatment options:

1. EBRT, primarily for palliative relief of local symptomatic tumor growth.
2. Doublet of chemotherapy with platinum (cisplatin or carboplatin) and paclitaxel, gemcitabine, docetaxel, vinorelbine, irinotecan, and pemetrexed.

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3. Paclitaxel, carboplatin, and bevacizumab for patients with non-squamous histology, no brain metastases, or no hemoptysis.
4. Clinical trials evaluating the role of new chemotherapy regimens and other systemic agents.
5. Endobronchial laser therapy and/or brachytherapy for obstructing lesions.

Recurrent Non-Small Cell Lung Cancer

Many patients with recurrent non-small cell lung cancer (NSCLC) are eligible for clinical trials. Radiation therapy may provide excellent palliation of symptoms from a localized tumor mass.

Patients who present with a solitary cerebral metastasis after resection of a primary NSCLC lesion and who have no evidence of extracranial tumor can achieve prolonged disease-free survival with surgical excision of the brain metastasis and postoperative whole-brain radiation therapy (WBRT).[133, 134] Unresectable brain metastases in this setting may be treated with radiation surgery.[135] Because of the small potential for long-term survival, radiation therapy should be delivered by conventional methods in daily doses of 1.8 Gy to 2.0 Gy. Because of the high risk of toxic effects observed with such treatments, higher daily doses over a shorter period of time (i.e., hypofractionated schemes) should be avoided.[136] Most patients who are not suitable for surgical resection should receive conventional WBRT. Selected patients with good performance status (PS) and small metastases can be considered for stereotactic radiation surgery.[137]

Approximately 50% of patients treated with resection and postoperative radiation therapy will develop recurrence in the brain; some of these patients will be suitable for additional treatment.[138] For most patients, additional radiation therapy can be considered; however, the palliative benefit of this treatment is limited.[139]

A solitary pulmonary metastasis from an initially resected bronchogenic carcinoma is unusual. The lung is frequently the site of second primary malignancies in patients with primary lung cancers. Whether the new lesion is a new primary cancer or a metastasis may be difficult to determine. Studies have indicated that in most patients the new lesion is a second primary tumor, and after its resection some patients may achieve long-term survival. Thus, if the first primary tumor has been controlled, the second primary tumor should be resected, if possible.[140, 141] The use of chemotherapy has produced objective responses and small improvement in survival for patients with metastatic disease.[142] In studies that have examined symptomatic response, improvement in subjective symptoms has been reported to occur more frequently than objective response.[143] Informed patients with good PS and symptomatic recurrence can be offered treatment with a platinum-based chemotherapy regimen for palliation of symptoms. For patients who have relapsed after platinum-based chemotherapy, second-line therapy can be considered. Two prospective randomized studies have shown an improvement in survival with the use of docetaxel compared with vinorelbine, ifosfamide, or best supportive care;[144, 145] however, criteria for the selection of

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appropriate patients for second-line treatment are not well defined.[146] A meta-analysis of five trials of 865 patients assessing the efficacy and safety of docetaxel administered weekly or every 3 weeks has been reported.[147] In that analysis, median survival was 27.4 weeks for patients treated with every 3 weeks and 26.1 weeks for patients treated weekly (P = .24, log-rank test). Significantly less severe and febrile neutropenia was reported with weekly docetaxel (P < .001 for both), whereas no significant differences were observed for anemia, thrombocytopenia, and nonhematologic toxic effects.

A randomized phase III trial of 571 patients designed to demonstrate the noninferiority of pemetrexed compared with docetaxel showed no difference in response rates, progression-free survival (PFS), or overall survival (OS).[148]

A report of a randomized, placebo-controlled trial indicated that erlotinib prolongs survival and time to deterioration in symptoms in NSCLC patients after first-line or second-line chemotherapy compared with placebo.[149, 150] In this trial of 731 patients, 49% had received two prior chemotherapy regimens, and 93% had received platinum-based chemotherapy. OS was 6.7 months and 4.7 months, respectively (hazard ratio (HR) = 0.70; P < .001), in favor of erlotinib. When used in combination with carboplatin and paclitaxel,[151] or cisplatin and gemcitabine,[152] erlotinib was not found to improve response rates, DFS, or OS in previously untreated patients with advanced or metastatic NSCLC.

A randomized phase III trial evaluating gefitinib versus placebo in 1,692 previously treated NSCLC patients showed that gefitinib does not improve OS, median survival did not differ significantly between the groups in the overall population (5.6 months for gefitinib and 5.1 months for placebo; HR = 0.89; 95% CI, 0.77–1.02], P = .087) or among the 812 patients with adenocarcinoma (6.3 months vs. 5.4 months; HR = 0.84; 0.68–1.03] P = .089). Preplanned subgroup analyses showed significantly longer survival in the gefitinib group than in the placebo group for never-smokers (n = 375; 0.67 [0.49–0.92], P = .012; median survival 8.9 months vs. 6.1 months) and patients of Asian origin (n = 342; 0.66 [0.48–0.91], P = .01; median survival 9.5 mo vs. 5.5 mo).[153] In addition, in two randomized trials comparing the addition of gefitinib with standard platinum combination chemotherapy, no improvement in response rates, PFS, or OS was shown.[151, 154]Objective response rates to erlotinib and gefitinib are higher in patients who have never smoked, in females, in East Asians, and in patients with adenocarcinoma and bronchioloalveolar carcinoma.[155-161] Survival benefit may be greater in patients with EGFR protein expression by immunohistochemistry or increased EGFR gene copy number by FISH, although the clinical utility of EGFR testing by immunohistochemistry has been questioned.[162]

Treatment options:

1. Palliative radiation therapy.
2. Chemotherapy alone.

For patients who have received platinum chemotherapy previously:

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- Docetaxel.
- Pemetrexed.
- Erlotinib after failure of both platinum-based and docetaxel chemotherapies.[150][2]

3. Surgical resection of isolated cerebral metastasis (highly selected patients).
4. Laser therapy or interstitial radiation therapy for endobronchial lesions.[93]
5. Stereotactic body radiotherapy (highly selected patients).[135, 137]

VII. SBRT Literature Review

This section reviews the literature on treatment of non-small cell lung cancer with stereotactic body radiotherapy (SBRT). All types of non-small cell lung cancer may be considered for radiosurgical management, but biologic differences must be recognized. Tumor margins may be less distinct in bronchoalveolar carcinoma, and adenocarcinoma may have a higher tendency to metastasize to regional lymph nodes. The primary concern with SBRT is high doses of radiation to nearby organs. The principle organs at risk in lung tumor treatment are the lung itself, the esophagus, the spinal cord, the skin, and the pleura. Esophageal tolerance is also not well defined for radiosurgical doses and fractionation. Skin and pleura are other organs at risk not commonly considered when planning radiation treatment with standard fractionation. Inattention to skin doses can result in hot spots and skin ulceration. Pleura can also be affected by high dose per fraction radiation. When tumors near the chest wall are treated, several days of pleuritic pain is not uncommon. Neuropathic pain from treatment of intercostal nerves has also been reported.

The standard of care for stage I NSCLC is generally accepted to be surgery. In patients who are not candidates for lobectomy, various treatment strategies are available, including SBRT. Local control is a main step to cure NSCLC because at least 30-40% of patients die due to local or regional progression of their disease. Radiation therapy is the only treatment that can cure patients with T1-T2 lesions if they are not suitable for or refuse surgery. In general, doses higher than 60 Gy must be given to improve tumor control but such doses pose a greater threat to the organs at risk. In the last ten years many new techniques have been made available for treating NSCLC more accurately with SBRT and respiratory gating systems are now available from several manufactures.

SBRT uses high doses per each faction, on the order of 10 to 20 Gy per fraction (up to a total of 5 fractions) rather than 2 to 3 Gy per fraction used in conventional radiotherapy. In addition, the overall period of treatment is much shorter, 1 to 2 weeks rather than 5 to 6 weeks with conventional radiation. These characteristics make SBRT much more potent (i.e., radioablative) than conventional radiotherapy, but also potentially much more damaging to normal tissues. The first use of extracranial stereotactic radiotherapy was in 1991, started at the Karolinska University hospital, in Sweden with treatment for tumors in the liver and lung.[163] In this study, an analytical method was used to calculate the dose distributions of an isocentric treatment and the potential advantages of a heterogeneous target dose was proposed. Since then groups in Japan, Europe and North

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America have refined the use of SBRT for the treatment of lung cancer, with emerging treatment methods and regimes.

Lax *et al*. reported on the results of SBRT treatment of 138 patients with medically inoperable stage I NSCLC treated from 1996 to 2003, at five different centers in Sweden and Denmark. The mean patient age was 74 years (range 56 to 90) with 69 men and 72 women. SBRT was delivered using a 3D conformal multi-field technique and a stereotactic body frame. Doses delivered were 30 to 48 Gy in 2 to 4 fractions. Overall response rate was 61% (84/138). During a median follow-up period of 33 months (1-107), 16 (12%) local failures occurred, ten of which also included distant metastases. Local failure was associated with tumor size, target definition and central or pleura proximity. Distant metastases occurred in 25% (35/138) of the patients. Ninety-one (65%) patients died during follow-up of which 55 patients (60%) died of causes other than lung cancer. Three- and 5-year overall survival was 52 and 26% respectively. Lung cancer specific 3- and 5-year overall survival was 66 and 40% respectively. Fifty nine percent (83/138) of the patients had no side effects. Fourteen patients experienced grade 3-4 toxicity according to Radiation Therapy Oncology Group (RTOG). This early study led the authors to conclude that SBRT for stage I NSCLC resulted in favorable local control with acceptable toxicity.[164]

In Japan, beginning in the early 1990's, results looked promising for higher doses of radiation for treatment of NSCLC.[165] Five year experience from October 1994 to June 1999, in 50 patients with pathologically proven T1-2N0 M0 NSCLC treated by CT-guided frameless SBRT was reported. Of these, 21 patients were medically inoperable and the remainder refused surgery. In most patients, SBRT was given at 50 to 60 Gy in 5 to 10 fractions for 1 to 2 weeks. Eighteen patients also received conventional radiotherapy of 40 to 60 Gy in 20 to 33 fractions before SBRT. With a median follow-up period of 36 months (range 22 to 66), 30 patients were alive and disease free, 3 were alive with disease, 6 had died of disease, and 11 had died due to other causes. Local progression was not observed on follow-up CT scans in 47 (94%) of 50 patients. The 3-year overall survival rate was 66% in all 50 patients and 86% in the 29 medically operable patients. The 3-year cause-specific survival rate of all 50 patients was 88%. No definite adverse effects related to SBRT were noted, except for 2 patients with minor bone fractures and 6 patients with temporary pleural pain. This study led the authors to conclude that SBRT is a safe and effective treatment for stage I NSCLC.[166]

A later study in Japan from 2002, was performed to evaluate the clinical outcomes of 3D conformal SBRT for one or two lung tumors using a stereotactic body frame. Forty patients that were treated between July 1998 and November 2000, and were followed for >10 months were included in this study. Of the 40 patients, 31 had primary lung cancer and 9 had metastatic lung cancer. The primary lung cancer was staged as T1N0M0, T2N0M0, and T3N0M0 in 19, 8, and 4 patients, respectively. All patients received 10 to 12 Gy in four fractions during a period of 5 to 13 days (median 12). The initial 3 patients received 40 Gy, and the remaining 37 patients received 48 Gy after dose escalation. Of the 33 tumors followed > 6 months, 6 tumors (18%) disappeared completely after treatment. Twenty-five tumors (76%) decreased in size by 30% or more after treatment

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and 31 tumors (94%) showed a local response. During the follow-up period of 4 to 37 months (median 19), no pulmonary complications greater than National Cancer Institute-Common Toxicity Criteria Grade 2 were noted. Of the 16 patients with primary lung cancer who received 48 Gy, all tumors were locally controlled during the follow-up of 6 to 36 months (median = 19). In 9 tumors with lung metastases that were irradiated with 48 Gy in total, 2 tumors did not show a local response. Finally, 3 tumors (33%) with lung metastases relapsed locally at 6-12 months (median 7) after treatment during the follow-up of 3 to 29 months (median 18).[167]

Another study from Japan in 2006, investigated the treatment effects and morbidities of single-fraction stereotactic radiosurgery (SRS) for 59 lung tumors (11 primary tumors, 48 metastases) treated between August 1998 and December 2004.[168] Nine tumors received a minimal dose of < 30 Gy, and 50 tumors received a minimal dose of > or = 30 Gy. The 1-year and 2-year local progression-free rates were 93% and 78%, respectively. The overall survival rate was 76.5% at 1 year and 41% at 2 years. Local re-growth of the irradiated tumor was a direct cause of death in two patients. The 2-year local progression-free rate for patients who received irradiation doses of ≥30 Gy and < 30 Gy were 83% and 52%, respectively. With regard to toxicity, Grade 3 respiratory symptoms were noted in one patient.

Onishi *et al.* reported on the treatment outcomes of SBRT for stage I NSCLC treated in a Japanese multi-institutional study. This was a retrospective review of 257 patients with stage I NSCLC (median age, 74 years: 164 T1N0M0, 93 T2N0M0) that were treated with SBRT at 14 institutions. A total dose of 18 to 75 Gy was administered in 1 to 22 fractions. During follow-up (median 38 months), pulmonary complications above grade 2 arose in 14 patients (5.4%). Local progression occurred in 36 patients (14.0%), and the local recurrence rate was 8.4%. The 5-year overall survival rate of medically operable patients was 70.8% among those treated with higher doses compared with 30.2% among those treated with less than 100 Gy ($p < 0.05$). The authors concluded that the local control and overall survival rates at 5 years were superior to the reported results for conventional radiotherapy. Furthermore, local control and survival rates were better with BED ≥ 100 Gy compared to < 100 Gy.[169]

In Europe in 2001, Wulf *et al.* evaluated the use of SRS to achieve local control of lung and liver cancer and its relation to treatment toxicity. Treatment was performed in 3 fractions of 10 Gy each with patient fixation in a stereotactic body frame. Targets were circumscribed tumors in the lung (n = 27) and liver (n = 24) with primary lung cancer (n = 12), local recurrences of lung cancer (n = 4) and lung metastases (n = 11). Local control was defined as complete or partial remission and stable disease, as measured by repeated CT scans after 6 weeks and in 3 months intervals. Treatment toxicity was evaluated according to WHO score. Local control was 85% for pulmonary targets with actuarial local control after 1 and 2 years at 76% for lung tumors. Actuarial overall patient survival was 48% after 1 year and 21% after 2 years for targets in the lung. No acute grade 3-5 side effects were observed. Serious late toxicity occurred in two patients consisting of a chronic ulceration of the esophagus at a target close to the mediastinum after 3 months (grade 3) and fatal bleeding from the pulmonary artery after 9 months

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(grade 5) in a previously irradiated patient, however it was unclear, whether the bleeding was a side effect of treatment or due to tumor infiltration. The authors concluded that severe late toxicity could be avoided if targets close to the mediastinum were avoided.[170]

This same group reported on the dose-response for local tumor control after SBRT in patients with lung cancer. In this study from 2005, there were a total of 92 pulmonary tumors, 36 were NSCLC and 56 were metastases. SBRT was delivered in 1 to 8 fractions with different doses was used. After a median follow-up of 14 months (2 to 85 months) 11 local recurrences were observed with significant advantage found for the higher treatment doses. It was found that when a dose of 94 Gy at the isocenter and 50 Gy at the margins was used there was demonstrated a 50% probability of tumor control.[171] In 2007, this same group reported on the results of tumor response and pulmonary injury after SBRT for early stage NSCLC and pulmonary metastases. Seventy patients with a total of 86 lesions of which 48 were pulmonary metastases and 38 were primary early stage NSCLC were treated. Patients were treated with SBRT as follows: 56 were treated with 3 to 8 fractions of 6 Gy to 12.5 Gy and 30 were treated with SBRT at 26 Gy. The pattern and sequence of pulmonary injury and of tumor response was evaluated in 346 follow-up CT studies (average= 4.9). Symptomatic pneumonitis was observed in 10% of the patients after a median interval of 5 months. No pulmonary reaction was observed in most patients 6 weeks after treatment. CT scans showed dense consolidation and retraction started after 9 months and the fibrotic remodelling process continued for years. At 12 months complete response was seen in 43% of patients. All in all there was a typical sequence of pulmonary reactions that was observed and characterized in this study.[172]

Hof *et al*. reported on the results of SBRT for lung metastasis on patients treated between May 1997 and December 2005, where 61 patients received SBRT treatment for 71 pulmonary metastases. Doses ranged from 12 to 30 Gy in a single fraction. After a median follow-up period of 14 months the actuarial overall survival was 78.4%, 65.1%, and 47.8% at 12, 24, and 36 months, respectively. The actuarial local progression-free rate was 88.6%, 73.7%, and 63.1% 12, 24, and 36 months, respectively. Although the majority of patients (70.4%) developed perifocal normal-tissue changes, these were not related to clinically relevant toxicities. The authors concluded that SBRT was a feasible, safe and effective local treatment option for solitary pulmonary metastases in patients with contraindications to surgery or for palliation of symptomatic pulmonary metastases.

This same group reported on the clinical results after single dose SRS for stage I and II NSCLC in 2007. Forty-two patients with biopsy-proven NSCLC received stereotactic SRS with a stereotactic body frame. The single doses ranged between 19 and 30 Gy. After a median follow-up period of 15 months (range, 1.5 to 72 months) the actuarial overall survival rates and disease-free survival rates were 74.5%, 65.4%, 37.4%, and 70.2%, 49.1%, 49.1% at 12, 24, and 36 months after therapy, respectively. The actuarial local tumor control rates were 89.5%, 67.9%, and 67.9% at 12, 24, and 36 months after therapy, respectively. A significant difference ($p = .032$) in local tumor control was found for patients receiving 26 to 30 Gy ($n = 32$) compared with doses of less than 26 Gy

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(n = 10). Thirteen (31%) patients developed metastases during follow-up, whereas isolated regional lymph node recurrence was only encountered in 2 patients. No clinically significant treatment-associated side effects were documented. The authors concluded that single-dose SRS is a safe and effective treatment option for patients with early stage NSCLC not suitable for surgery.[173]

A phase I trial in 2003, from Timmerman *et al.* reported on patients with stage I NSCLC who were medically inoperable. Eligible patients included those with clinically staged T1 or T2N0M0 biopsy confirmed NSCLC. SBRT was administered in 3 fractions over 2 weeks. Three to five patients were treated within each dose cohort starting at 8 Gy per fraction (total of 24 Gy) followed by successive dose escalations of 2 Gy per fraction (total increase per cohort, 6 Gy). Waiting periods occurred between dose cohorts to observe toxicity. Patients with T1 vs. T2 tumors underwent separate independent dose escalations. One patient experienced grade 3 pneumonitis, and another patient had grade 3 hypoxia. For the entire population, there was no appreciable decline in cardiopulmonary function as measured by symptoms, physical examination, need for oxygen supplementation, pulmonary function testing, arterial blood gas determinations, or regular chest imaging. Both groups ultimately reached and tolerated 20 Gy per fraction for three fractions (total of 60 Gy) with the maximum tolerated dose unreached in this study. Tumors responded to treatment in 87% of patients (complete response, 27%). After a median follow-up period of 15.2 months, six patients experienced local failure, all of whom had received doses of < 18 Gy per fraction. [174]

This same group reported on a second study, which was a prospective phase II trial using SBRT in medically inoperable patients with NSCLS. Eligible patients included clinically staged T1 or T2, N0, M0, biopsy-confirmed NSCLC. All patients had co-morbid medical problems that precluded lobectomy. SBRT treatment was a total of 60 to 66 Gy in three fractions during 1 to 2 weeks. A total of 70 patients enrolled and completed therapy as planned and median follow-up was 17.5 months. The 3-month major response rate was 60%. Kaplan-Meier local control at 2 years was 95%. Altogether, 28 patients died as a result of cancer (n = 5), treatment (n = 6), or other co-morbid illnesses (n = 17). Median overall survival was 32.6 months and 2-year overall survival was 54.7%. Grade 3-5 toxicity occurred in a total of 14 patients. Among patients experiencing toxicity, the median time to observation was 10.5 months. Patients treated for tumors in the peripheral lung had 2-year freedom from severe toxicity of 83% compared with only 54% for patients with central tumors. Tumor location was a strong predictor of toxicity with hilar or pericentral tumors showing an 11-fold increase in Grade 3-5 adverse events compared to more peripheral tumors. The authors concluded that high rates of local control were achieved with SBRT however, this regimen (60-66 Gy in 3 fractions) should not be used for patients with tumors near the central airways due to excessive toxicity.[175]

McGarry et al conducted a Phase I dose escalation study of SBRT to assess toxicity and local control rates for patients with medically inoperable stage I lung cancer in 2005. All patients had NSCLC, stage T1a or T1b N0, M0. Patients were immobilized in a stereotactic body frame and treated in escalating doses beginning at 24 Gy total (3 x 8 Gy fractions). Cohorts were then dose escalated by 6 Gy with appropriate observation

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periods. The maximum tolerated dose was not achieved in the T1 stratum (maximum dose = 60 Gy), but within the T2 stratum, the maximum tolerated dose was realized at 72 Gy for tumors larger than 5 cm. Dose-limiting toxicity included bronchitis, pericardial effusion, hypoxia, and pneumonitis. Local failure occurred in 4 of 19 T1 and 6 of 28 T2 patients. Nine local failures occurred at doses < or =16 Gy and only 1 at higher doses. Local failures occurred between 3 and 31 months from treatment. Within the T1 group, 5 patients had distant or regional recurrence as an isolated event, whereas 3 patients had both distant and regional recurrence. Within the T2 group, 2 patients had solitary regional recurrences, and the 4 patients who failed distantly also failed regionally.[176]

A group in Miami reported on their experience with SBRT for patients with stage I NSCLC starting in 2004. All patients had co-morbid conditions that precluded lobectomy. A 60 to 67.5 Gy dose was given in 3 to 5 fractions. Patients were followed every 3 months for a median of 27.5 months (range 24 to 53 months). Of the 67 patients with NSCLC stage IA or IB treated between January 2004 and December 2008, there was a cohort of 31 patients with peripheral stage I tumors which showed no grade 3 or above toxicity. Four cases of radiation induced pneumonitis and one case of esophagitis was observed. In those patients whose pre- and post-treatment results were available, no change in pulmonary function tests was observed. Actuarial local control was 93.2% for 1 year and 85.8% for up to 4.5 years. One-year overall survival was 93.6% and 83.5% for up to 4.5 years, as projected by Kaplan-Meier analyses. The authors concluded that in this small cohort of patients with stage I peripheral NSCLC, SBRTappears to be a superior alternative to conventionally fractionated radiotherapy, with results that may be approaching those obtained with lobectomy without the associated morbidity.[177]

Coon *et al.* studied the outcomes of patients treated with SBRT who had primary, recurrent, or metastatic lung lesions, with a focus on positron emission tomography (PET)/computed tomography (CT)–based management. Fifty-one patients with primary stage I NSCLC (n = 26), recurrent lung cancer after definitive treatment (n = 12), or solitary lung metastases (n = 13) were treated with SBRT between 2005 and 2007. A dose of 60 Gy was delivered in 3 fractions. All patients had CT or PET/CT performed at approximately 3-month intervals after treatment. The median follow-up was 12 months. Local control at median follow-up was 85% in patients with stage I NSCLC, 92% in patients with recurrent lung cancer, and 62% in the patients with solitary lung metastasis. Analysis of the 28 patients with pre- and post-treatment PET/CT scans demonstrated that those with stable disease (n = 4) had a mean standardized uptake value (SUV) decrease of 28%, partial responders (n = 11) had a decrease of 48%, and patients with a complete response (n = 11) had a decrease of 94%. Patients with progressive disease (n = 2) had an SUV decrease of only 0.4%. No correlations were found between pretreatment SUV and tumor response, disease progression, or survival. Overall 1-year survival rates were 81%, 67%, and 85% among the patients with primary NSCLC, recurrent lung cancer, and solitary lung metastases, respectively. The authors concluded that SBRT is an effective treatment for patients with medically inoperable recurrent or metastatic lung cancer and that PET/CT is valuable in staging, planning, and evaluating treatment response and may predict long-term outcome.[178]

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The Radiation Therapy Oncology Group (RTOG) 0236 was the first North American multicenter, cooperative group study to investigate SBRT in treating medically inoperable patients with early stage NSCLC.[179] Eligible patients included T1-T2N0M0 NSCLC tumors measuring < 5 cm in diameter and medical conditions precluding surgical treatment. The SBRT dose delivered was 54 Gy delivered in 3 fractions. In 2010, the 3-year outcomes were reported from 55 evaluable patients with a median of 34.4 months (4.8 – 49.9 months). One patient had a primary tumor failure thus resulting in a 3-year primary tumor control rate of 97.6%. Three patients had recurrence within the involved lobe, 2 patients had regional failure and 11 patients had distant failure. The rates for disease-free survival and overall survival at 3 years was 48.3 % and 55.8%, respectively. Grade 3 adverse events were reported in 7 patients and Grade 4 events were reported in 2 patients. The authors concluded that SBRT treatment of early stage NSCLC in medically inoperable patients resulted in a high rate of primary tumor control, with acceptable toxicities.

In the largest series to date, 505 Stage I-IIB NSCLC patients were treated with SBRT at five institutions from 1998 to 2010.[180] Of these cases, 87% were medically inoperable and staging included 63% stage 1A, 33% stage IB, 2% stage IIA and 1% recurrent. The median dose was 54 Gy (range 20-64 Gy) in three fractions (range 1-15) over 8 days with a median BED of 132 Gy. The 2-year Kaplan-Meier local control, regional control and distant metastases rates were 94%, 89% and 20%, respectively. Overall survival was 60% and cause-specific survival was 87%. Stage, gross-tumor volume size (≥ 2.7 cm) and BED predicted local relapse and distant metastasis with BED ≥ 105 Gy resulting in decreased local relapse and decreased distant metastases. Toxicities were minimal with Grade 2 or higher pneumonitis, rib fracture, myositis and dermatitis were 7%, 3%, 1% and 2%, respectively. The authors concluded the high rate of local control was achieved when BED was ≥ 105 Gy with minimal severe toxicities.
On the basis of the Indiana University experience[175], SBRT using 60 Gy in three fractions for centrally located tumors is not considered an acceptable practice due to excessive toxicity. Several groups have investigated the optimal SBRT fractionation schedule for the treatment of centrally located lung tumors. Chang et al delivered either 40 Gy or 50 Gy in 4 fractions to 27 patients with stage I and recurrent centrally located lung tumors.[181] With a median of 17 months, local control was 100% with 50 Gy and only 57% with 40 Gy. Toxicities were acceptable for both treatment groups. Four patients developed Grade 2 pneumonitis and 3 patients developed Grade 2-3 dermatitis and chest wall pain. One patient who received 40 Gy developed brachial plexus neuropathy and partial arm paralysis. The authors suggested that 50 Gy in 4 fractions was needed to achieve sufficient local control for centrally and superiorly located T1-T2N0M0 lesions.

Rowe et al treated 47 patients with 51 centrally located NSCLC tumors with 3 to 5 fractions with the majority of patients receiving 50 Gy in 4 fractions of 12.5 Gy. With a median follow up of 11.3 months (4.8 – 40.8 months), 4 patients had Grade 3 dyspnea and 1 patient developed hemoptysis, respiratory failure and died. The 2-year local control rate was 94% for the entire group and when stratified by dose, the local control rate for patients receiving BED > 100 Gy was 100% and BED < 100 Gy was 80%. These

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results suggest that SBRT for central lung tumors is safe, although efforts to decrease toxicity by decreasing the BED resulted in reduced local control.[182]

Nuyttens et al reported on 58 central lesions (39 primary lesions and 17 metastatic tumors) treated with SBRT.[183] Tumors located near the esophagus were treated with 54 Gy delivered in 6 fractions. The remaining tumors were treated according to a dose escalation scheme of 5 fractions of 9 Gy, 10 Gy and 12 Gy. With a median follow-up of 23 months, the actuarial 2-year local tumor control rate was 85% for tumors treated with a BED > 100 Gy and 60% for tumor treated with a BED ≤ 100 Gy. Minimal toxicities were reported with 11% of patients having acute Grade 1-2 toxicities and no Grade 4-5 toxicities. The authors concluded that SBRT could be safely delivered to centrally located lung tumors.

In efforts to explore the role of SBRT for the treatment of centrally located lung tumors, the RTOG launched a phase I/II multicenter study (0618) in 2009. The primary objective is to determine the maximum tolerated dose (MTD) of a SBRT schedule of 5 fractions for stage I NSCLC tumors that are touching or within the zone of the proximal bronchial tree or adjacent to the mediastinal or pericardial pleura. The starting dose is 10 Gy x 5 fractions and will escalate dose by 0.5 Gy per fraction to a maximum dose of 12 Gy x 5. Results of this study are pending.

A study from Germany reviewed response rates, local control, survival and side effects after single-dose SRS for lung tumors. In this study, 40 patients with stage I non-small cell lung cancer (NSCLC) underwent SRS with a single dose of 30 Gy. Follow-up periods varied from 6.0 to 61.5 months with a median of 20 months. There were three local tumor recurrences, resulting in an actuarial local tumor control of 81% at 3 years. With the exception of two rib fractures, no serious late toxicities were observed. The overall survival probability rates were 66% at 2 years and 53% at 3 years with a median overall survival of 37 months. Cancer-specific survival probability was 71% at 2 years and 57% at 3 years. The authors concluded that single-dose SRS for NSCLC is more convenient for the patient and less time-consuming than hypofractionated SRS, but that data dealing with this new method are still scanty and more research is necessary.[184]

Ngyun *et al.* published a paper entitled "Can stereotactic fractionated radiation therapy become the standard of care for early stage non small cell lung cancer" where the authors compared SRS treatment with video assisted thoracic surgery (VATS).[185] Overall the authors concluded that SRS was very well tolerated with minimal toxicity. Among studies that used a total biologic equivalent dose of 100 Gy, local control rates between 80 and 90%were observed. Six reported patient deaths came from a single institution using 20 to 22 Gy per a day.[176]

Some have postulated that SBRT is now the treatment of choice for patients with early stage NSCLC who both are and are not candidates for surgery. In 2010, Grills et al. published outcomes after SBRT vs. wedge resection for stage I NSCLC in patients that were ineligible for lobectomy.[186] In this nonrandomized trial, patients that were

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borderline surgical candidates with limited pulmonary reserve or medical morbidities underwent either limited wedge surgical resection (n = 69) or SBRT (n = 58). SBRT was delivered in either 48 Gy in 4 fractions or 60 Gy in 5 fractions. At a median of 30 months follow-up, there were no statistical differences in regional recurrences, loco-regional recurrences or distant metastasis between the two treatment groups. SBRT did reduce the risk of local recurrence after SBRT (4%) compared to wedge resection (20%). Overall survival was higher in surgical patients, however, cause-specific survival was equivalent between the two groups. The authors concluded that SBRT is a reasonable treatment option for patients with stage I NSCLC who are ineligible for lobectomy.

Crabtree et al. reported on the outcomes of 538 patients with clinical stage I NSCLC treated with either SBRT or surgical resection (lobar or sublobar).[187] Differences in baseline factors of the two patient cohorts were reported, with surgically-treated patients being younger, having better baseline pulmonary function and lower baseline co-morbidity scores compared to patients treated with SBRT. Final pathology resulted in upstaging of 35% of the surgical patients. In an unmatched comparison, the 5-year overall survival rate was 55% for surgically-treated patients vs a 3-year overall survival rate of 35% for SBRT patients. For patients with stage IA disease, 3-year local control was better for surgical patients compared SBRT (96% and 89% for surgery vs SBRT, respectively). Because of the significant differences in patient age and baseline co-morbidities between the surgery and SBRT cohorts, a propensity analysis was performed and matched 57 high-risk surgical patients to 57 SBRT patients. In the matched analysis, there was no difference in local recurrence, disease-free survival and overall survival at 3 years. The authors concluded that similar rates of local recurrence and disease-specific survival were detected in the propensity-matched high risk patients, however extrapolation of these results regarding the efficacy of SBRT should not be applied to healthier patients with operable disease outside of approved clinical trials.

There are several ongoing clinical trials assessing the role of SBRT in the treatment of patients with operable stage I NSCLC. RTOG 0618 launched a phase II single arm multicenter study in 2009, to determine whether SBRT delivered in 20 Gy x 3 fractions achieves acceptable primary tumor control in operable patients with early-stage NSCLC. Results of this study are pending. In 2012, a group from the Netherlands reported on SBRT treatment of 177 potentially operable stage I NSCLC cases. A dose of 60 Gy was delivered in 3, 5 or 8 fractions depending on tumor size and location. With a median follow-up of 31.5 months, the 1- and 3-year survival rates were 94.7% and 84.7%, respectively. Overall survival did not significantly differ in patients with and without histological diagnosis. The 1- and 3-year local control rates were 98% and 93%, respectively and regional and distant failure rates were 9.7% each at 3 years. Toxicities were minimal with Grade 3 and higher pneumonitis and rib fractures in 2% and 3%, respectively. The authors concluded that SBRT can provide excellent overall survival and local control in patients with potentially operable disease.[188] In another study, the same group conducted a matched-pair analysis of overall survival after surgery vs SBRT for 120 elderly patients (≥ 75 years).[189] The median follow-up was 43 months. The 30 day mortality rate was 8.3% for surgery and 1.7% for SBRT. One- and 3-year overall survival was 75% and 60% after surgery and 87% and 42% after SBRT, respectively.

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The authors concluded similar overall survival rates are achieved with surgery and SBRT for stage I NSCLC in elderly patients. In 2013, this group compared outcomes of lobectomy by video-assisted thoracoscopic surgery (VATS) vs SBRT for Stage I-II NSCLC using propensity score-matched analysis.[190] Patients were matched based on cTNM stage, age, gender, co-morbidity scores, lung function and performance score. Local control rates were superior for SBRT patients at 1 and 3 years compared to VATS patients (96.8% and 93.3% vs 86% and 82.6%, respectively). Distant recurrences and overall survival were not significantly different. The authors findings support the need for randomized controlled clinical trials assessing outcomes of SBRT vs surgery for stage I NSCLC. Randomized trials are underway to compare SRS to surgery in Japan and in North America.[191-193]

Zimmermann *et al* published an excellent review on SBRT including definitions of treatment, pre-procedure staging, comparison of techniques and clinical response including local tumor response and survival data.[194] The authors conclude that SBRT could offer a less toxic, less costly and more convenient alternative then surgical resection.
Some authors have suggested that SBRT should represent a new standard of care, while others contend that more study is needed. Early comparisons suggest that use of SBRT achieves a rate of local control double that obtained with conventional radiotherapy and comparable to or better results as compared to surgically treated patients.[186] Long-term data from such studies will help to document the incidence and significance of late radiation effects. It is recommended that clinical treatment emphasize adequate training, rigorous quality assurance and robust clinical process to emulate the results obtained in these trials. It is possible that SBRT may become standard of care for all patients with early stage lung cancer.

In addition to early stage lung cancer, SBRT may play a role in the setting of re-irradiation for NSCLC, however, only a few studies with small patient numbers have been published. Coon et al evalulated 12 patients with recurrent disease after definitive treatment treated with SBRT (20 Gy x 3 fractions). No information describing the initial radiation treatment dose, schedule or treatment interval was provided. The local control and overall survival rates one year after re-irradiation was 92% and 67%, respectively.[178]

The MDACC group recently reported their experience with SBRT to treat lung cancer patients previously treated with thoracic radiation. In this study, 36 patients who had received prior standard fractionation radiation therapy to the thorax for lung cancer subsequently received SBRT to recurrent or second lung cancers within the thorax.[195] The median dose delivered during the initial treatment was 61.5 Gy (range 30 – 79.2 Gy) and the median time between the initial treatment and SRS was 22 months (0 – 92 months). The most common SBRT dose and fractionation schedule was 50 Gy in four fractions. The 2-year overall survival rate was 59% and the 2-year progression-free survival rate was 26%. Twenty-two patients had intra-thoracic relapse, however only 3 of the 22 failures occurred within the SBRT field resulting in a 92% local control rate. The most common side effect was pneumonitis, including 11 patients with Grade 2

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pneumonitis and 7 patients with Grade 3 pneumonitis. Three patients had Grade 3 esophagitis, 2 patients with Grade 3 chest wall ulcers and 2 patients with Grade 3 cough. No patients experienced Grade 4 or 5 toxicity. Chest wall pain was reported in 31% of patients. The authors concluded that toxicity was significant but manageable, in-field tumor control rate was excellent, but the high rate of intrathoracic recurrences requires further study to identify which patients previously treated with radiation to the thorax would best benefit from SBRT treatment to recurrent and secondary thoracic tumors.

VIII. Clinical Indications and Guidelines for SBRT

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