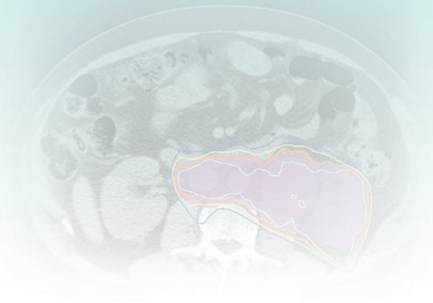
Overview



Jeffrey A. Bogart

Primary thoracic neoplasms are reviewed in detail in the chapters of this section. In this overview, we consider developments and controversies in the diagnosis and treatment of non–small cell lung cancer (NSCLC), small cell lung cancer (SCLC), esophageal cancer, thymic tumors, pulmonary carcinoid, and mesothelioma.

EPIDEMIOLOGY

Lung Cancer

Lung cancer is the most common and deadliest thoracic malignancy, accounting for approximately 3000 deaths each week in the United States.[1] Exposure to tobacco smoke is the most common cause of lung cancer, with 85% to 90% of cases directly linked to active or passive tobacco exposure.[2] Lung cancer mortality rates have been trending downward in men because of reductions in smoking prevalence dating back to the mid-1960s, whereas mortality rates in women started to stabilize only in 2003. There is substantial geographic variation in the United States, with California the only state with decreasing lung cancer incidence and death rates in women.[3] Exposures to several occupational respiratory carcinogens have been controlled in developed nations, but environmental exposure to radon, the second-leading cause of lung cancer death, remains problematic.[4] Lung cancer in never-smokers is increasingly recognized as a distinct entity, described in greater detail in Chapter 44, and is the seventh-most common cause of cancer worldwide. Most of these cancers occur in women, and geographic, cultural, and genetic differences and hormonal factors have been implicated.[5]

The median age of patients who present with lung cancer is 70 years.[6] Lung cancer is broadly separated into SCLC and NSCLC types, and NSCLC accounts for approximately 80% to 85% of cases. Less than 50% of patients with NSCLC have resectable disease on initial presentation, and 25% of patients present with locally advanced (regional lymph node involvement without distant metastases) disease. Approximately 30% of patients with SCLC have limited-stage disease on presentation.[7]

Esophageal Cancer

In 2013, an estimated 17,990 patients Americans were diagnosed with esophageal cancer, and the incidence of esophageal cancer has increased approximately 15% during the past two decades.[8] Patients with esophageal cancers often present with advanced-stage disease, and most eventually die of their disease. Approximately 50% of patients present with locally advanced disease, and another 30% to 40% present with systemic metastases.[9]

Esophageal carcinomas are divided into squamous cell carcinoma and adenocarcinoma, each of which has a distinct epidemiology. Adenocarcinoma is associated with gastroesophageal reflux disease, Barrett's esophagus, obesity, and male gender. Squamous cell carcinoma is associated with alcohol and tobacco exposure, nutritional deficits, and lower socioeconomic status.[10] Although the incidence of squamous cell carcinoma has remained stable in the United States, the incidence of esophageal adenocarcinoma has increased dramatically over the past several decades, surpassing squamous cell carcinoma as the most common esophageal cancer in the United States.

Thymic Neoplasms

Thymoma is the most common tumor in the anterior mediastinum. Most thymic neoplasms arise in the epithelial cells of the thymus. The incidence of thymoma in the United States is estimated to be 0.13 to 0.15 per 100,000 people.[11] The median age of patients with thymoma is older than 50 years, and thymomas are diagnosed equally in men and women.[12] Thymic carcinomas account for a minority of all thymic neoplasms,[13] and they are more aggressive than thymomas.[14] Thymic carcinoids represent less than 5% of anterior mediastinal tumors, but they have a higher rate of regional lymph node metastases on presentation compared with carcinoids found in other locations in the body.[15]

Pulmonary Carcinoid

Pulmonary or bronchial carcinoid tumors are often low-grade neoplasms that arise from bronchial mucosal cells known as enterochromaffin cells or Kulchitsky cells.[16] These specialized cells are capable of producing bioactive amines, which cause carcinoid syndrome if released into the blood stream by the tumor. The respiratory tract is the second-most common site for carcinoids (after the gastrointestinal tract). Pulmonary carcinoid tumors are often centrally located and confined to the main or lobar bronchi.[17]

The incidence of bronchopulmonary carcinoids in the United States is estimated to be 0.6 per 100,000 people.[17] Carcinoid tumors tend to occur at a younger age than other lung cancers, with a median age ranging from 50 to 56 at diagnosis. In contrast to NSCLC and SCLC, bronchial carcinoids are more common in women.

Mesothelioma

The incidence of mesothelioma in the United States is estimated to be 10 per 1 million people,[18] or approximately 3000 patients per year, and the rate is expected to increase to about 4000 cases per year by 2025. Approximately 90% of mesotheliomas can be attributed to prior occupational asbestos exposure, and a lag of 20 to 40 years between asbestos exposure and diagnosis is typical.[19] Mesothelioma occurs predominantly in men, but secondary asbestos exposure from a spouse or parent can be as significant as environmental exposure. Major histologic subtypes of mesothelioma include epithelioid, biphasic, and sarcomatoid. Although epithelioid tumors are most common and have a better prognosis than other histologic types, the prognosis for most patients with mesothelioma remains poor.[20]

BIOLOGY

Lung Cancer

Lung cancers have a propensity to disseminate early and have a high rate of relapse despite aggressive treatment with surgery, chemotherapy, radiotherapy (RT), or combinations of these modalities. Molecular characteristic of NSCLC and SCLC are described in Chapters 43 and 44. Although NSCLC has traditionally been treated as a single disease, there is increasing recognition that histologic and molecular characteristics may help direct therapy, and targeted drugs are now considered first-line therapy for advanced NSCLC with specific epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) gene rearrangements.[21,22] Efforts to take advantage of molecular abnormalities in small cell lung cancer in developing more effective treatment have been less successful.

Esophageal Cancer

Esophageal cancer is characterized by early locoregional and distant spread of disease. Although the biologic characteristics of squamous cell carcinoma and adenocarcinoma of the esophagus differ, implications for therapeutic approach are unclear at this time. Molecular targets of interest identified in carcinoma of the esophagus include EGFR, Her2-neu, vascular endothelial growth factor (VEGF), cyclin D1, and cyclooxygenase-2.[23] Alterations in p53 may be important in the development of esophageal cancer, although mutations for squamous cell carcinoma differ from adenocarcinoma, and p15 and p16 have been found to be involved in the pathogenesis of esophageal cancer.[24]

Thymus Tumors

The cause of thymic neoplasms is unclear. Environmental factors that contribute to the development of thymic neoplasms may include Epstein-Barr virus infection[25] and exposure to ionizing irradiation.[26] The translocation of chromosomes 15 and 19 has been observed in thymic carcinoma.[27] Benign thymoma has been associated with deletion of the short arm of chromosome 6. Abnormalities in TP53, epidermal growth factor, and EGFR may contribute to the development of thymoma.[28,29]

Thymic carcinoma displays features that are similar to features of carcinoma arising in other body sites. It has a higher rate of capsular invasion, involvement of the regional lymph nodes, and systemic metastases compared with invasive thymomas.[30] Features of thymic carcinomas may include expression of high levels of EGFR, VEGF, and basic fibroblast growth factor.[31,32] CD70 positivity may serve as a marker for thymic carcinoma.[33] In contrast to lung cancer, thymic carcinomas usually do not express transcription termination factor-1.[34]

Pulmonary Carcinoid

Although most pulmonary carcinoids are nonfunctional, some can secrete various substances, which can lead to paraneoplastic syndromes, including carcinoid and Cushing's syndrome.[35] Serotonin is the most common substance released by carcinoid tumors, but corticotropin, histamine, dopamine, substance P, neurotensin, prostaglandins, and kallikrein may also be involved.[36]

Typical carcinoids usually display an indolent clinical course, but atypical carcinoids have a higher rate of regional and systemic involvement on presentation.[37] Most familial pulmonary carcinoids have been reported in patients with multiple endocrine neoplasia type I.[38] In atypical carcinoids, there seems to be a higher rate of inactivation of TP53.[39] Other genetic alterations in lung carcinoids include losses of 3p, 5p, 9p, 10q, and 13q.[40]

STAGING AND WORKUP

Lung Cancer

As with other medical conditions, the workup begins with a careful history and physical examination. There should be an emphasis on the duration of symptoms and signs related to the thoracic neoplasm and the overall baseline medical condition of the patient.

Diagnosis and staging should be accomplished in an orderly and cost-effective manner. Although sputum cytology reveals a diagnosis in only a small percentage of patients, it is a simple and noninvasive evaluation that should be considered for patients with respiratory symptoms and a suspicious lung mass. Traditionally, bronchoscopy has been employed for biopsy of central lesions, whereas transthoracic needle biopsy is often the first consideration for peripheral lesions. Endobronchial ultrasound is increasingly used to obtain tissue from mediastinal lymph nodes or parenchymal lung lesions; esophageal ultrasound may be used for biopsy of paraesophageal lymph nodes.

Staging evaluation is often initiated before a definitive pathologic diagnosis has been established. Positron emission tomography with ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) combined with computed tomography (CT) imaging is indicated in most patients with localized NSCLC and SCLC and can replace the traditional workup that included CT imaging of the chest and abdomen plus a bone scan. The use of ^{18}F-FDG-PET imaging has been shown to reduce the number of futile thoracotomies for patients with NSCLC and has a substantial impact on the radiation treatment plan for NSCLC and SCLC, particularly when an approach of involved field RT is used.[41-43] Generally, biopsy of suspected distant metastatic sites should be considered in lieu of biopsy of the primary lung lesion because this would confirm both histology and stage. ^{18}F-FDG-PET imaging is typically not warranted in patients presenting with evidence of distant metastases (on other imaging studies) because treatment would not likely be altered by the PET results. Magnetic resonance imaging (MRI) of the brain should be obtained in patients with localized SCLC and patients with clinical stage III NSCLC, in addition to patients presenting with neurologic symptoms.

The TNM (primary tumor, regional nodes, metastases) staging system for bronchogenic cancer has undergone substantial revision to correlate stage better with clinical outcome

(see Tables 44-2 and 44-3). Changes in T stage include subclassifying T1 into T1a and T1b and T2 into T2a and T2b, reclassifying T2c and additional nodules in the same lobe as T3, and reclassifying nodules in the ipsilateral nonprimary lobe as T4. Malignant pleural or pericardial effusions have been reclassified from T4 to M1.[44] Although the American Joint Committee on Cancer (AJCC) system has been proposed for use in staging patients with both SCLC and NSCLC, it is more common to use the 1973 Staging System of the Veterans Administration Lung Cancer Study Group for staging SCLC. It distinguishes disease extent as limited versus extensive,[45] with limited-stage SCLC often described as one that can be treated with a "reasonable" RT portal to encompass the known disease.

Mediastinal staging is indicated for most patients with early-stage clinical node-negative NSCLC because CT and ^{18}F-FDG-PET imaging have a false-negative rate (in the mediastinum) ranging from 10% to greater than 25%.[46] Combined anatomic and functional imaging is generally sufficient to assess mediastinal lymph node involvement for the subset of patients with peripheral stage I NSCLC.[47] Whether comprehensive mediastinal lymph node sampling with endobronchial ultrasound can replace mediastinoscopy is an area of active investigation.

Esophageal Cancer

The staging of esophageal cancer underwent substantial revision in the most recent version (seventh edition) of the AJCC Staging Manual (see Box 45-1). Staging groups are now divided according to histology, acknowledging the difference in biology between squamous cell carcinoma and adenocarcinoma. The staging system has also been amended to account for the influence of tumor grade on prognosis. Regional lymph nodes have been redefined, and N has been subdivided according to the number of lymph nodes involved. In addition, the previous division between M1a and M1b has been abandoned because it was not found to be useful.

Clinical staging is typically based on findings of endoscopy with biopsy, endoscopic esophageal ultrasound, and anatomic CT imaging. Endoscopic ultrasound can assess the depth of invasion with up to 90% accuracy once the tumor has gone through the submucosa and can detect abnormal or enlarged lymph nodes.[48] Assessment with ^{18}F-FDG-PET/CT has become commonplace in the workup of esophageal carcinoma and is particularly helpful in detection of unsuspected distant or regional disease, although the sensitivity of ^{18}F-FDG-PET imaging in defining regional lymph node metastases seems to be improved with integrated ^{18}F-FDG-PET/CT imaging.[49-51] A randomized prospective trial from the American College of Surgeons Oncology Group showed that ^{18}F-FDG-PET after conventional staging evaluation identified confirmed metastatic disease in approximately 5% of patients. This study was performed before routine availability of integrated ^{18}F-FDG-PET/CT.[52] Thoracoscopic or laparoscopic assessment may be helpful in certain cases to help determine disease extent and resectability.

Thymic Tumors

Approximately 10% to 15% of patients with myasthenia gravis have thymoma, and 30% to 45% of patients with thymomas have myasthenia gravis.[53] Serum alpha-fetoprotein and beta-human chorionic gonadotropin levels should be obtained in young men to exclude nonseminomatous germ cell tumors.[54] Thymic carcinoids may also be associated with Cushing's syndrome, Eaton-Lambert syndrome, syndrome of inappropriate secretion of antidiuretic hormone, and hypercalcemia.[55]

TABLE C-1 Masaoka Staging System for Thymoma

Stage	Criteria
I	Completely encapsulated macroscopically and no microscopic capsular invasion
II-1	Macroscopic invasion into surrounding fatty tissue or mediastinal pleura
II-2	Microscopic invasion into capsule
III	Microscopic invasion into adjacent organs
IVA	Pleural or pericardial implants
IVB	Lymphatogenous or hematogenous metastasis

Symptoms of classic carcinoid syndrome are rare in patients with thymic carcinoids.

A routine chest x-ray examination can detect 30% to 40% of patients with thymic neoplasms.[56] CT is the most valuable radiologic study in the workup of thymic tumors.[57] It can establish the initial clinical staging and response to treatment. MRI has not been shown to be more accurate than CT in assessing anterior mediastinal tumors.[58] ^{18}F-FDG-PET has not been established as routine in the workup of thymic neoplasms. The risk of tumor spillage and pleural seeding during biopsy of thymoma is uncertain, although current guidelines suggest biopsy may be avoided for resectable tumors if thymoma is strongly suspected by clinical and radiographic features.

Thymomas histologically display epithelial and lymphatic cell types. They can be classified according to the degree of the epithelial and lymphatic cell combination. The neoplastic cells are the epithelial cells, but there is no consistent correlation between the histology of thymomas and their malignant potential or systemic syndromes. The degree of invasion of the capsule and adjacent tissues defines malignancy.[59] The Masaoka staging system[60] is used widely and is based on the anatomic extent of disease at the time of surgery (Table C-1). Thymic carcinoma histology is cytologically not different from carcinomas in other sites. Thymic carcinomas often involve the pleura and locoregional lymph nodes. Distant metastases to the lungs, liver, brain, and bone can also develop.[61]

Pulmonary Carcinoid

Pulmonary carcinoids are often located centrally within the tracheobronchial tree, and approximately 10% to 20% are in the peripheral lung parenchyma.[62] The AJCC lung staging system (TNM) is commonly used for lung carcinoids. Most patients with typical carcinoid present with early-stage disease, and less than 5% have evidence of distant spread. Approximately 20% of patients with atypical carcinoids have stage IV disease at presentation.

Functioning carcinoids may be diagnosed by showing an increase in urinary excretion of the serotonin metabolite, 5-hydroxyindoleacetic acid. In addition to anatomic CT imaging, targeted radioactive octreotide or pentetreotide has been used to stage carcinoids.[63] Such targeted imaging against type 2 somatostatin receptors may be useful in 80% of carcinoids. The utility of ^{18}F-FDG-PET imaging is controversial, although PET imaging using alternative tracers seems promising.[64,65]

Mesothelioma

A detailed history of asbestos exposure should be investigated for any patient with mesothelioma. Thoracentesis and percutaneous fine-needle aspiration biopsy have a low diagnostic

sensitivity because mesothelioma can be difficult to differentiate from benign pleural disease and other malignancies.[66] Video-assisted thoracoscopic biopsy seems to be the most accurate means to establish a pathologic diagnosis.[67]

Contrast-enhanced CT imaging of the chest is indicated as part of initial staging but can underestimate the extent of the disease. MRI may be more accurate in predicting the extent of chest wall and diaphragm invasion. Additional invasive studies such as laparoscopy and peritoneal lavage may be indicated to document resectability. The AJCC staging system, which is based on the International Mesothelioma Interest Group staging system, is commonly used, and the most common sites of metastatic disease are the peritoneum, contralateral pleura, and lung.[68]

NORMAL TISSUE TOXICITY CONSIDERATIONS

The spinal cord, lung, esophagus, and heart are the dose-limiting structures in RT for thoracic malignancy. Generally, functioning subunits of an organ may be arranged as an in-series or in-parallel structure. Normal tissue such as the lung is an example of an in-parallel structure in which critical numbers of functioning units must be damaged before the organ is impaired.[69] Organ failure occurs when functional subunits are damaged beyond a critical level. The gastrointestinal tract and spinal cord represent in-series structures in which a loss of a single functioning subunit may lead to organ impairment or development of clinical symptoms. Current grading systems for toxicities include Common Terminology Criteria for Adverse Events version 4.0 (CTCAEv4) from the National Cancer Institute.

Although many reports suggest limited toxic effects after stereotactic body radiotherapy (SBRT) for early-stage NSCLC, mature prospective results are just starting to appear in the literature.[70] Phase II data from Indiana University initially showed an increased risk of toxic deaths after SBRT for centrally located lesions, although a statistically significant difference in severe toxicity was not seen between central and peripheral lesions with longer follow-up.[71,72] Nevertheless, central tumors were excluded from the subsequent multiinstitutional RTOG Phase II study (RTOG 0236), and caution should be used in treating central lesions with SBRT outside of a clinical study.[73] No treatment-related deaths were reported on RTOG 0236, which was reported with 34-month median follow-up, although 14% grade 3 and 4% grade 4 *protocol-specified* toxicity was observed, and six additional patients had severe toxicity that was not classified prospectively as protocol specified. Rigorous quality assurance was mandated. In addition to tumor location, size of the gross tumor volume was a significant predictor of severe toxicity in the Indiana University trial.[74] In other experience, fatalities have been observed secondary to fistula (tracheoesophageal or bronchopulmonary), pneumonitis, pleural effusion, and hemoptysis.[75] Several more recent SBRT reports have also shown higher than expected skin, rib, soft-tissue, and brachial plexus toxicity.[76-78] Specific dose constraints for SBRT regimens have been suggested by the RTOG and National Comprehensive Cancer Network (NCCN).

The following sections are generally based on data derived with conventionally fractionated RT and may not apply when large doses per fractions are used, such as in SBRT. Routine integration of conformal RT planning has facilitated the assessment of dose-volume relationships for conventionally fractionated RT. A systematic review of the literature found that an ideal dose-volume parameter predicting for pulmonary toxicity has not been identified,[79] although the most widely used measures are the total lung volume receiving at least 20 Gy (i.e., V20) and the mean lung dose.[80-82] Other metrics, including baseline pulmonary function and perfusion abnormalities, have also been used, and it is likely that multiple physical and biologic factors are important in predicting the risk of pulmonary toxicity.[83,84] Barriers to describing accurately the relationship between treatment and its resultant toxicity include the use of imperfect metrics and the inaccurate reporting of toxic effects. The latter may be particularly relevant for patients with underlying pulmonary toxicity, where it may be difficult to determine whether a functional decline is attributable to the effects of therapy.

The dose-volume relationship may also be affected by the integration of systemic chemotherapy, and the sequencing of therapies may have a significant impact on the toxic effects of therapy.[85] Most current prospective combined modality trials have adopted V20 as a treatment planning parameter and limit V20 to a maximum 30% to 40% of the total lung volume. Current NCCN guidelines recommend limiting the V20 lung to less than 37% and the mean lung dose to less than 20 Gy. There is increasing recognition of the potential impact of exposing relatively large volumes of lung to low doses of 5 Gy or 7 Gy, which is particularly relevant when intensity-modulated radiotherapy (IMRT) techniques are employed for lung cancer, esophageal cancer, or mesothelioma.[86]

Esophageal toxicity is generally the major clinically relevant acute toxicity during thoracic RT. The implementation of conformal techniques may affect esophageal toxicity by reducing the volume of esophagus irradiated, particularly for patients without extensive mediastinal adenopathy. The risk of radiation-induced acute esophageal toxicity varies according to fractionation, and increased acute toxicity has been observed with hyperfractionated and accelerated RT regimens.[87] The integration of concurrent chemotherapy with thoracic RT results in significantly increased severe esophagitis compared with primary RT or sequential therapy. Dosimetric parameters that may correlate with esophageal toxicity include the length of esophagus treated to greater than 40 Gy to 50 Gy, the volume of esophagus receiving greater than 50 Gy, and the mean esophageal dose.[88-90] Current NCCN guidelines recommend keeping the mean esophageal dose less than 34 Gy if possible, but esophageal dose guidelines are not absolute, and acute esophagitis should be managed aggressively with measures including pain management and nutritional support.

It is crucial that the patient's treatment plan not be compromised because of a (generally) temporary toxic effect of therapy. The role of "radioprotective" agents is unclear; the RTOG conducted a randomized trial to test the ability of amifostine to reduce esophagitis in locally advanced NSCLC treated with concurrent RT and chemotherapy.[91] The rate of grade 3 esophagitis did not differ between arms (34% versus 30%), although subjective swallowing function was apparently better with the addition of amifostine. Amifostine was associated with higher rates of acute nausea, vomiting, cardiovascular toxicity, and infection or febrile neutropenia. Amifostine is not recommended in combination with thoracic RT outside of a clinical trial.

Spinal cord radiation injury, covered in detail in Chapter 30, is a serious but rare complication of thoracic RT. Most contemporary clinical trials of concurrent fractionated RT and chemotherapy for thoracic malignancies limit the maximum point dose to the spinal cord to 45 Gy to 50 Gy.

The risk of radiation-induced cardiovascular disease is difficult to define for patients treated for locally advanced lung cancer and esophageal cancer as there are relatively few long-term survivors, though a recent analysis of RTOG 0617 demonstrated a negative impact of increasing heart dose (V50) on overall survival in patients with locally advanced NSCLC

(ASCO 2013).[92] Most data relating to cardiovascular toxicity is derived from patients with Hodgkin's disease and breast cancer. Multiple studies have shown that patients with Hodgkin's disease are at higher risk for the development of cardiovascular disease after mediastinal irradiation, and fatal myocardial infarction is the leading cause of noncancer death in this population.[93] Although the total dose used to treat Hodgkin's disease has been reduced over the years, it is not yet clear whether this results in a reduced risk of myocardial infarctions.

The increased risk of cardiac mortality for patients treated with RT for breast cancer has been defined by the Early Breast Cancer Trialists' Collaborative Group meta-analyses of randomized clinical trials, which showed patients treated with RT have a 1.27 relative risk of mortality from cardiac disease compared with patients not receiving RT.[94] The treatment of left-sided breast cancer and the treatment of internal mammary lymph nodes seem to increase the risk of cardiac morbidity further.[95] There seems to be a decline in RT-induced cardiac disease with modern RT planning. The implementation of advanced treatment techniques including conformal therapy, IMRT, image guidance, and respiratory gating should reduce the risk of cardiac toxicity, through improved sparing of cardiac structures, in treating thoracic cancers. Current NCCN guidelines suggest that no more than 50% of the heart should receive 4000 cGy when combined RT and chemotherapy is given.

TREATMENT CONSIDERATIONS

Non–Small Cell Lung Cancer

The standard of care for fit patients with early-stage I NSCLC is anatomic resection (lobectomy). Patients with borderline cardiopulmonary function should be assessed for rehabilitation and smoking cessation before being deemed to be medically inoperable. In a Phase III trial conducted during the 1980s for fit patients with peripheral stage I (<3 cm) NSCLC, limited resection was associated with a substantially higher risk of local tumor relapse and increased risk of death from cancer compared with lobectomy.[96] Evidence has emerged supporting the use of limited resection for peripheral NSCLC smaller than 2 cm, although most experience comes from Asia where the biology of small peripheral lesions may differ from the biology in North America and Europe.[97] An ongoing North American Phase III trial studying limited resection for lesions less than 2 cm should soon complete accrual.[98] Alternatively, provocative results with SBRT have been reported in certain *fit* patients with early-stage NSCLC. Prospective Phase II trials of SBRT in operable patients have been completed in North America and Japan and mature outcomes are pending. Phase III trials comparing SBRT and surgery in this population have not successfully met accrual goals.[99-101]

Treatment of patients with early-stage NSCLC and cardiopulmonary dysfunction has rapidly evolved during the past decade. Fractionated RT has been the most frequent treatment, but approaches including sublobar resection, SBRT, and radiofrequency ablation are increasingly used.[102,103] Local tumor control approaching 90% has been reported in several trials of SBRT for stage I NSCLC, although some trials with aggressive SBRT regimens restrict entry to lesions in the lung periphery owing to concerns about severe toxicity.[75] Accelerated hypofractionated RT regimens, with daily fractions given over 3 to 4 weeks, also seem promising.[104,105] Although traditional dose escalation is feasible with modern treatment planning, protracted regimens do not seem to be as effective as accelerated regimens and are more burdensome for patients.[106-108] Although pilot experience suggested the addition of I-125 brachytherapy might reduce local relapse for high-risk patients treated with sublobar resection for stage I NSCLC, an initial report of a Phase III American College of Surgeons Oncology Group (ACOSOG) trial failed to show a benefit with intraoperative I-125.[109] The relative merit of SBRT and sublobar resection in high-risk early stage NSCLC remains unclear. A randomized Phase III trial comparing SBRT and sublobar resection for high-risk peripheral stage I NSCLC was closed prematurely because of poor accrual, and it is not likely that level 1 evidence will emerge in the foreseeable future. Large randomized studies show that adjuvant chemotherapy improves survival for patients with resected NSCLC, although the benefit diminishes over time.[110] The role of adjuvant chemotherapy for early-stage node-negative NSCLC is controversial. A Cancer and Leukemia Group B (CALGB) trial did not show a benefit for adjuvant chemotherapy for T2 NSCLC, although there was a suggestion of improved survival for tumors larger than 4 cm.[111] Whether chemotherapy should be given to patients treated with primary RT for node-negative NSCLC has not been well studied.

The role of surgery for patients with stage IIIA NSCLC is unclear despite the reporting of mature results of a Phase III trial comparing concurrent chemotherapy and definitive RT (61 Gy) with induction concurrent chemotherapy and RT (45 Gy) followed by surgical resection.[112] Improved relapse-free survival, but not overall survival, was observed for patients assigned to receive surgery. Nevertheless, surgical resection is currently used in certain patients with stage IIIA NSCLC, although it is recognized that induction therapy should be administered. Whether induction therapy should consist of chemotherapy or combined chemotherapy and RT is controversial, and a randomized trial assessing the question closed prematurely because of poor accrual.

The cornerstone of treatment for patients with "unresectable" locally advanced NSCLC is concurrent systemic doublet chemotherapy and thoracic RT as described in Chapter 42. There are several controversies regarding the optimal treatment of this population, as described next.

Chemotherapy Regimen and Schedule During Radiotherapy

The landmark Phase III studies supporting concurrent chemotherapy and RT over a sequential approach used cisplatin-based chemotherapy in a schedule similar to that administered when chemotherapy is given for systemic disease.[113] Nevertheless, several Phase III trials have adopted a regimen of weekly paclitaxel and carboplatin as standard of care despite a lack of level 1 evidence.[114] Whether the weekly chemotherapy schedule or the substitution of carboplatin for cisplatin affects outcomes is unknown, though the excellent results from the standard (60 Gy) arm of RTOG 0617 lend support to the considering weekly concurrent paclitaxel and carboplatin as an acceptable standard therapy.[92]

Sequencing and Timing of RT and Chemotherapy

Trials conducted in the 1980s first showed that giving cisplatin-based chemotherapy before thoracic RT improved overall survival compared with RT alone, and subsequent trials showed that concurrent administration of chemotherapy and RT was better than sequential treatment.[115] Additional chemotherapy is frequently given in clinical practice either before or after concurrent therapy, although more recent Phase III randomized trials failed to show benefit for either induction chemotherapy or consolidation chemotherapy.[116,117] Toxicity was enhanced in the cohorts receiving longer duration chemotherapy. Further research assessing consolidation chemotherapy is likely given more recent reports favoring "maintenance" chemotherapy for patients with metastatic NSCLC treated with primary chemotherapy.[118]

Radiation Dose Escalation and Fractionation

The standard RT regimen for NSCLC, 60 Gy in daily 2-Gy fractions, was defined by an RTOG trial conducted in the 1970s.[119] The emergence of conformal RT planning ushered in several dose escalation studies, and encouraging outcomes of Phases I-II studies led to development of a Phase III trial, RTOG 0617, testing 74 Gy compared with 60 Gy with weekly carboplatin and paclitaxel chemotherapy.[120,121] Unexpectedly, results of this seminal trial demonstrate that higher doses of RT result in significantly worse survival and provides strong evidence against dose-escalated RT outside of a clinical trial.[92]

Altered fractionation has been tested in several Phase III trials of locally advanced NSCLC. Regimens that accelerate the time to complete therapy by giving multiple daily treatments have shown promise, although the utility of these regimens is limited by difficulty in integrating concurrent chemotherapy and the logistic challenge for many centers to treat patients up to three times a day.[122,123] The use of hyperfractionated RT seems to have no benefit if the time to complete treatment is not shortened.[124-126] The emergence of advanced treatment technologies, which facilitate limiting radiation dose to critical normal tissue, has resulted in increased interest in studying accelerated hypofractionted regimens, and ongoing cooperative group studies are assessing hypofractionated RT concurrent with chemotherapy.

Although there is limited experience treating locally advanced NSCLC with proton therapy, the increase in proton facilities in the United States and worldwide has resulted in the development of a Phase III RTOG trial comparing photon and proton radiotherapy concurrent with chemotherapy. A planned total dose of 7000 cGy is recommended in both arms, although there is allowance for dose reduction if normal tissue constraints cannot be met.[127]

Radiation Target Volumes

The role of elective nodal irradiation (ENI) is controversial; current practice has generally evolved such that clinically uninvolved lymph node regions are not intentionally targeted.[128,129] Studying the impact of ENI and accurately documenting sites of relapse in locally advanced NSCLC is challenging, although a modest-sized Chinese study showed less toxicity without a detriment in survival with involved field treatment compared with ENI.[130]

The potential influence of ENI may be lessened in the era of routine ^{18}F-FDG-PET staging, and most ongoing prospective trials do not include ENI.

Integration of Molecular Targeted Agents

A Phase III trial conducted by SWOG from 2001 to 2005 demonstrated worse survival with maintenance EGFR inhibitor gefitinib after chemoradiotherapy in locally advanced NSCLC,[131] curbing enthusiasm for large-scale study of targeted agents in potentially curable populations. Pilot data from CALGB showed gefitinib concurrent with chemoradiotherapy results in poor outcomes, although encouraging results were observed with concurrent administration of gefitinib with RT if concurrent chemotherapy was not given.[132] A subsequent Phase II trial assessing erlotinib and RT for patients who were a poor risk with stage III NSCLC failed to reach the primary survival endpoint although the median survival of 17 months was reasonable for a poor-risk population.[133] Additionally, although Phase II studies showed that combining cetuximab (a monoclonal antibody against EGFR) with concurrent chemotherapy and RT yielded encouraging outcomes,[134,135] cetuximab did not improve survival in the recently reported Phase III RTOG 0617 trial.[92] Routine administration of targeted agents do not appear to have a role in the treatment of unselected patients, but a recently activated randomized RTOG study is assessing the role of induction targeted therapy in patients with locally advanced NSCLC harboring either an EGFR mutation or an ALK gene rearrangement.

The addition of the VEGF inhibitor bevacizumab to doublet chemotherapy improves survival for patients with advanced non–squamous cell carcinoma.[136] Although there was initial enthusiasm for studying bevacizumab in locally advanced disease, an increased risk of tracheoesophageal fistula has been shown when bevacizumab is given with chemoradiotherapy for both NSCLC and SCLC. Administration of bevacizumab months to years after completion of thoracic RT has been linked to fistula formation.[137] These agents should not be used in combination with RT outside of a clinical trial.

Prophylactic Cranial Irradiation

The role of prophylactic cranial irradiation was assessed in four early trials for locally advanced NSCLC,[138-141] with the general conclusion that prophylactic cranial irradiation reduces brain metastases but does not improve overall survival. Results of an RTOG-led an intergroup study confirm this observation, although the trial was terminated prematurely because poor accrual.[142]

Postoperative Radiotherapy

Meta-analyses of postoperative RT has been roundly criticized on many counts, including the use of outdated technology, inclusion of patients with early-stage disease, and administration of excessive RT doses.[143] Nevertheless, a survival detriment was shown for postoperative RT in early-stage node-negative NSCLC, with an unclear benefit in patients who are node positive. Current efforts have generally focused on assessing postoperative RT for resected N2 disease, and a more recent Surveillance, Epidemiology, and End Results (SEER) analysis supports the contention that postoperative RT may be beneficial in N2 disease when delivered with modern technology in appropriate doses (e.g., 50 Gy in 2-Gy fractions).[144] A Phase III European study assessing postoperative RT is ongoing.[145]

Small Cell Lung Cancer

Treatment of limited stage SCLC includes the concurrent administration of RT and chemotherapy. Standard practice includes delivery of full dose cisplatin-based systemic chemotherapy during accelerated hyperfractionated thoracic RT (1.5 Gy twice daily to 45 Gy over 3 weeks). Prophylactic cranial irradiation is indicated after completion of thoracic RT and chemotherapy in patients with a good tumor response. Several issues that remain unresolved in the standard treatment of limited SCLC are described next.

Thoracic Radiotherapy Dose and Fractionation

Although high clinical response rates are expected with combined-modality therapy, durable local tumor control is poor when modest dose, conventionally fractionated thoracic RT is employed. Intensifying the RT course by accelerating the time to complete treatment seems to be an effective strategy in limited stage SCLC. Intergroup trial 0096 randomly assigned patients to receive 4500 cGy in either conventional (180 cGy daily fractions) or hyperfractionated, accelerated (150 cGy twice daily fractions) regimens.[146] Thoracic RT was initiated with the first cycle of etoposide and cisplatin chemotherapy. Mature results favored accelerated RT. With accelerated RT, 5-year survival was 26% compared with 16% for patients receiving conventional RT. The major increased toxicity of the accelerated regimen was a doubling of the grades 3 to 4 acute esophagitis rate (e.g., 16% versus 32%). Despite this result, the

regimen of 45 Gy twice daily has not been well accepted in clinical practice. The Patterns of Care Study published in 2003 noted that less than 10% of patients with limited stage SCLC received this regimen, whereas more than 80% were treated with daily RT.[147] Reluctance to accept accelerated RT may be in part as a result of the increased acute toxicity and practical issues involved with treating patients twice each day. However, the results of the study have also been questioned because of the inclusion of relatively low dose (45 Gy) daily RT as the standard treatment.

The CALGB studied high dose daily thoracic RT. CALGB 8837,[148] a Phase I study, assessed the maximum tolerated dose of RT given in standard daily and accelerated twice daily schedules. The maximum tolerated dose of twice daily RT was determined to be 45 Gy in 30 fractions over 3 weeks, whereas it was judged to be at least 70 Gy in 35 fractions for daily RT. The median survival for patients receiving daily RT was 29.8 months compared with 24 months for patients receiving twice daily RT. A subsequent Phase II study suggested encouraging survival with less apparent toxicity than was observed on studies using twice-daily fractions to 45 Gy.[149] Alternatively, the RTOG studied a concomitant boost strategy in limited stage SCLC. A Phase II study, RTOG 0239, employing a 61.2-Gy concomitant boost regimen demonstrated excellent local tumor control although 2-year overall survival fell well short of expectations.[150] An ongoing Phase III trial, CALGB 30610/RTOG 0538, initially compared standard thoracic RT (1.5 Gy twice daily) with the CALGB 70-Gy once daily and the RTOG 61.2-Gy concomitant boost regimens, but the 61.2-Gy cohort was discontinued in 2013 after an interim analysis of acute toxicity.[151] A Phase III study in Europe for limited small cell lung cancer, assessing 45-Gy twice-daily RT compared with 66-Gy once-daily RT, recently completed accrual and results should be reported in the next few years.[152]

Timing of Radiotherapy

The optimal timing of thoracic RT relative to chemotherapy is controversial. CALGB 8083 randomly assigned patients to receive initial RT plus chemotherapy, delayed RT plus chemotherapy, or chemotherapy alone. Mature results showed that survival with chemotherapy alone was inferior to both thoracic RT arms. A significant difference was not observed between early and delayed RT, although there was a trend favoring delayed thoracic RT ($p = 0.14$).[153] Conversely, a Phase III trial from the National Cancer Institute of Canada showed a benefit for initiating RT, 40 Gy in 3 weeks, with the second chemotherapy cycle compared with the sixth cycle of chemotherapy.[154] In the early thoracic RT cohort, 5-year survival was 20% compared with 11% in the late thoracic RT arm; the difference was ascribed to a reduction in brain metastases because local tumor control did not differ between arms. Additional studies have attempted to address the timing of thoracic RT. Meta-analyses have been published addressing this issue.[155,156] Although definitive conclusions cannot be reached, there is general consensus that the early initiation of thoracic RT (e.g., first through third cycle) may be beneficial, particularly in the context of intensive thoracic RT.

Treatment Volume

The issue of optimal thoracic RT volume in limited stage SCLC therapy has not been well studied in comparative trials. Investigators from the Southwest Oncology Group found that targeting the postchemotherapy tumor volume instead of the tumor volume on presentation did not result in increased failure rates.[157] More recent prospective trials using delayed (e.g., third or fourth cycle) chemotherapy incorporated reduced volume thoracic RT for all patients.[158,159] Mature patterns of failure data from the North Central Cancer Treatment Group, showing that only 2 of 90 local relapses may have occurred outside the postinduction volume but inside the preinduction volume, indicate that reduced field thoracic RT may be an acceptable strategy.[159]

Data attesting to the role of ENI for limited stage SCLC are lacking. Most prospective trials have included selected bilateral mediastinal stations as part of the initial target volume, although elective inclusion of the supraclavicular regions and the contralateral hilum is not indicated. Whether implementation of ^{18}F-FDG-PET imaging can reduce the role of ENI for SCLC has not been well studied, though small trials from the Netherlands suggest that promising results can be obtained with FDG-PET–guided involved field radiotherapy.[160]

Prophylactic Cranial Irradiation

The meta-analysis by the Prophylactic Cranial Irradiation Overview Collaborative Group[161] showed a convincing survival benefit (5.4% at 3 years) for the addition of prophylactic cranial irradiation following a complete response to therapy. A Phase III trial compared standard dose (25 Gy in 10 fractions) and high dose (36 Gy in either once-daily or twice-daily fractions) in limited stage SCLC. Higher doses of prophylactic cranial irradiation did not further reduce brain metastases, but increased mortality was observed on the patients receiving high doses.[162]

Chemotherapy Regimen

SCLC is exquisitely sensitive to systemic chemotherapy. The combination of cisplatin and etoposide became standard frontline therapy in the 1980s because of its clinical activity and tolerability in combination with concurrent thoracic irradiation. Efforts to improve outcomes by adding a third chemotherapy agent have been disappointing. A Phase III trial showed increased severe toxicity without a survival benefit when paclitaxel was added to etoposide and cisplatin for first-line therapy in extensive SCLC.[163] The RTOG conducted a Phase II study of paclitaxel, etoposide, and cisplatin chemotherapy with 45-Gy twice-daily RT in limited stage SCLC. Although the regimen was active, the authors of the study concluded that the addition of paclitaxel was unlikely to improve survival in patients with limited stage SCLC.[164] Topotecan and irinotecan, topoisomerase I inhibitors, are active agents against SCLC. Topotecan has been studied in combination with paclitaxel in both extensive and limited SCLC, but Phase II results did not warrant study in a Phase III setting.[165] In contrast, chemotherapy with irinotecan and cisplatin was superior to cisplatin and etoposide in a Phase III study for extensive SCLC conducted by the Japanese Cooperative Oncology Group.[166] Nevertheless, confirmatory trials conducted in North America failed to show improved survival for irinotecan and cisplatin chemotherapy over cisplatin and etoposide chemotherapy.[167,168]

Esophageal Cancer

There is no universally agreed on standard treatment for many patients with esophageal cancer, due in large part to the difficulty conducting large-scale randomized trials. Surgical resection alone is considered curative therapy for the few patients with early stage disease, with the potential for a minimally invasive approach (endoscopic mucosal resection) in certain patients.[169]

Treatment of locally advanced disease with primary RT is inappropriate for patients able to receive combined-modality therapy. This point is best illustrated by the results of RTOG 85-01, which showed a statistically and clinically significant survival benefit for concurrent chemotherapy[170] and RT compared with primary RT. In that experience, none of the patients

assigned to receive primary RT survived at least 5 years compared with a 5-year survival of 27% of patients receiving chemoradiotherapy.

Whether induction therapy improves outcomes for surgically treated patients has been debated extensively, and recently reported studies contribute substantially to evidence supporting multimodality therapy. The Phase III Chemoradiotherapy for Oesophageal Cancer followed by Surgery Study (CROSS) included 366 patients, and overall survival was significantly improved with preoperative radiotherapy (41.4 Gy) with concurrent weekly paclitaxel and carboplatin. Median survival was 24 months for patients assigned to surgery and 49.4 months in the preoperative chemoradiotherapy group.[171] A North American Intergroup trial also demonstrated improved survival with the addition of neoadjuvant chemoradiotherapy to surgery, even though the study was closed because of poor accrual after only 56 patients were randomized.[172] The impact of induction chemotherapy (without RT) on survival for surgically treated esophageal cancer is likewise controversial, and the two largest studies addressing the question reached different conclusions.[173,174]

The role of surgical resection after concurrent RT and chemotherapy remains unclear. Two European Phase III trials, the French FFCD 9102 trial[175] and the German Esophageal Cancer Study Group trial,[176] did not find a significant difference in survival between patients who received preoperative chemoradiotherapy or chemoradiotherapy alone, although the local recurrence rate was higher without surgery. On the other hand, locoregional tumor relapse was only 14% with trimodality therapy in the recently reported CROSS study, which is far less than would be expected with either definitive chemoradiotherapy or surgery alone, suggesting trimodality therapy should be considered for fit patients with locally advanced disease.[177] Additional studies suggest reduced local relapse with the addition of surgery. The possible benefit of surgical resection needs to be weighed against the risk of perioperative morbidity and mortality.

The standard RT dose regimen for patients treated with definitive RT and concurrent chemotherapy is 5040 cGy in 180-cGy fractions, and prospective studies have demonstrated that higher doses of radiotherapy result in increased toxicity without improving outcomes.[178] When neoadjuvant chemoradiotherapy is used, radiation doses typically range between 4500 cGy and 5040 cGy, similar to nonsurgical treatment, although a slightly reduced dose of 4140 cGy was used in the CROSS trial. Whether the integration of advanced technology, including ^{18}F-FDG-PET imaging, image-guided RT, and motion management, might alter the therapeutic radio of delivering more intense doses of RT remains open to study.

The combination of cisplatin and 5-fluorouracil, which had been considered standard chemotherapy for esophageal cancer in the United States (before the CROSS trial was reported), has resulted in pathologic complete response rates of approximately 20% to 30%. Although no chemotherapy regimen has proven superior to cisplatin and 5-fluorouracil in combination with RT, the regimen of weekly paclitaxel and carboplatin resulted in encouraging outcomes in the CROSS study and is increasingly used in clinical practice and clinical trials. An active CALGB Phase II trial is assessing the role of FDG-PET response directed chemotherapy and should complete accrual in the near future.[179] Despite overexpression of EGFR in esophageal cancer, several trials assessing agents that inhibit the EGFR pathway have reported disappointing results.[180] An active RTOG Phase III trial specific to Her2-overexpressing esophageal adenocarcinoma is evaluating trastuzumab in patients treated with trimodality therapy.[181]

RT guidelines have been published for gastroesophageal junction adenocarcinoma, and these tumors are sometimes managed similarly to gastric adenocarcinoma with initial surgical resection followed by adjuvant chemotherapy and RT as pathologically indicated.[182-185]

Thymoma

The initial treatment of choice for thymic tumors is surgery. Adjuvant RT or chemotherapy should be considered for patients at high risk for recurrence. Complete en bloc surgical resection is the standard of care for resectable thymomas. The primary determinants of clinical outcome are surgical-pathologic staging, tumor size, histology, and extent of surgical resection.

Complete resection of thymoma can lead to low recurrence and excellent survival rates.[186] Although prospective, randomized data on the value of adjuvant RT after resection of invasive thymoma are lacking, certain retrospective studies have shown improvements in local tumor control and survival in patients receiving RT for invasive disease.[187-189] However, conflicting results regarding the utility of adjuvant RT have been reported from analyses of large multiinstitutional series, including the SEER database. A more recent analysis of SEER data showed postoperative RT had no advantage in patients with localized thymoma (Masaoka stage I), but a possible survival benefit was suggested in patients with regional disease (Masaoka stage II-III).[190] The strongest data supporting postoperative RT were in the population of patients with non-extirpative surgery. In contrast, Kondo and Monden[13] reported a large multiinstitutional, retrospective study of 1320 patients with stage II or III thymic epithelial tumors for whom no significant benefit of adjuvant irradiation after surgery was found.

Primary RT has been administered to certain patients with unresectable thymoma with reasonable results, including approximately 65% local control and 5-year survival rate of 40% to 50%.[191] Likewise, salvage RT for patients with recurrent thymoma may achieve a 7-year survival rate of approximately 70%.[192]

Similar to the treatment for thymomas, surgery remains the predominant treatment for patients with thymic carcinomas, which are treated similarly to carcinomas found in other body sites. Adjuvant RT is commonly administered after surgery.[193] There may be a trend toward improved survival and local control with adjuvant therapy, but it is difficult to show.[194] There are reports of promising 5-year overall survival rates of more than 50% for patients who received irradiation after surgery.[195]

Pulmonary Carcinoid

Surgery is the primary treatment for typical and atypical pulmonary carcinoids, and long-term results after complete resection are excellent.[196] Clinical symptoms such as flushing can be relieved with ondansetron, a serotonin 5-HT$_3$ antagonist. Somatostatin analogs, inhibitors of neuropeptide release, relieve the symptoms of carcinoids by binding to somatostatin receptors.[197] Long-acting analogs of somatostatin, such as octreotide and lanreotide, are used to control diarrhea and flushing, and they have an approximately 70% chance of improving symptoms.

Typical carcinoids do not require adjuvant therapy after curative resection.[198] Patients with a tumor greater than 3 cm in diameter, lymph node metastasis, atypical histology, or residual disease may benefit from RT.[199]

Tumor targeting with radioactive somatostatin analogs has been used in patients with carcinoids with inconclusive results.[200] Interferon-α, alone or in combination with octreotide, has resulted in symptomatic relief in some patients.[201]

Chemotherapy results have been inconclusive, with a possible role for cisplatin and etoposide in patients with atypical carcinoids.[202] RT may palliate symptoms in patients with locally advanced or metastatic disease.[203]

Mesothelioma

Because mesothelioma usually involves the visceral and parietal pleural surfaces of the lung and extends into the pleural-lined pulmonary fissures, it can be difficult to perform a complete resection without an extrapleural pneumonectomy (EPP). EPP includes en bloc removal of tissues in the hemithorax, including the parietal and visceral pleura, involved lung, mediastinal lymph nodes, diaphragm, and pericardium. Given the aggressive nature of the surgery, EPP is considered only for patients with localized disease who have minimal comorbid medical problems. Even with EPP, R0 resections cannot be accomplished, and the relative value of EPP compared with lesser resection has been questioned.[204]

The value of RT in patients with unresectable mesothelioma is controversial. A report from Cancer Care Ontario's Program in Evidence-based Care suggested there was little evidence in the published literature to support a role for RT in the management of mesothelioma.[205] A more recent review of the SEER database identified epithelioid histology, pneumonectomy, and RT as predictive of increased survival.[206] Median survival for patients treated with pneumonectomy with and without RT was 19 months and 13 months ($p = 0.01$). Additional studies have suggested improved local tumor control when RT is administered after EPP.

The combination of pemetrexed and cisplatin is considered standard of care for patients with advanced (unresectable) mesothelioma,[207] and the expected median survival in patients treated with the regimen approaches 12 months. Carboplatin is frequently substituted for cisplatin, often owing to medical comorbidity, without an apparent decrease in efficacy. Chemotherapy has now routinely been integrated as part of trimodality therapy for patients with resectable mesothelioma based primarily on promising results in select series.[208]

Treatment of the ipsilateral hemithorax with IMRT after EPP has been associated with a high rate of toxic deaths in several single-institution experiences.[209,210] Fatal pneumonitis has been related to radiation exposure of the contralateral lung, and NCCN guidelines suggest that the mean lung dose be limited to 8.5 Gy and the V5 lung be kept as low as possible. Recent series suggest IMRT can be used with acceptable toxicity if normal tissue dose constraints are strictly followed.

CRITICAL REFERENCES

A full list of cited references is published online at www.expertconsult.com.

7. Warde P, Payne D: Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. J Clin Oncol 10:890–895, 1992.
21. Robinson BW, Lak RA: Advances in malignant mesothelioma. N Engl J Med 353:1591–1603, 2005.
22. Mok TS, Wu YL, Thongprasert S, et al: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361:947–957, 2009.
43. Fischer B, Lassen U, Mortensen J, et al: Preoperative staging of lung cancer with combined PET-CT. N Engl J Med 361:32–39, 2009.
46. Rami-Porta R, Ball D, Crowley J, et al: The IASLC lung cancer staging project: Proposal for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for the lung cancer. J Thorac Oncol 2:593–602, 2007.
54. Meyers BF, Downey RJ, Decker PA, et al: Surgeons Oncology Group Z0060 trial carcinoma of the thoracic esophagus: Results of the American College of the utility of positron emission tomography in staging of potentially operable. J Thorac Cardiovasc Surg 133:738–745, 2007.
72. Chi A, Liao Z, Nguyen NP, et al: Systemic review of the patterns of failure following stereotactic body radiation therapy in early-stage non–small-cell lung cancer: Clinical implications. Radiother Oncol 94:1–11, 2010.
73. Timmerman R, McGarry R, Yiannoutsos C, et al: Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 24:4833–4839, 2006.
75. Timmerman R, Paulus R, Galvin J, et al: Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 303:1070–1076, 2010.
80. Graham MV, Purdy JA, Emami B, et al: Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non–small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 45:323–329, 1999.
89. Rose J, Rodrigues G, Yaremko B, et al: Systematic review of dose-volume parameters in the prediction of esophagitis in thoracic radiotherapy. Radiother Oncol 91:282–287, 2009.
91. Movsas B, Scott C, Langer C, et al: Randomized trial of amifostine in locally advanced non- small-cell lung cancer patients receiving chemotherapy and hyperfractionated radiation: Radiation Therapy Oncology Group trial 98-01. J Clin Oncol 23:2145–2154, 2005.
92. Bradley JD, Paulus R, Komaki R, et al: A randomized phase III comparison of standard-dose (60GY) versus high-dose (74Gy) conformal chemoradiotherapy with or without cetuximab for stage III non–small lung cancer: Results on radiation dose in RTOG. J Clin Oncol 31(7501):2013.
96. Ginsberg RJ, Rubinstein LV: Randomized trial of lobectomy versus limited resection for T1 N0 non–small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 60:615–622, 1995.
104. Bogart JA, Hodgson L, Seagren SL, et al: Phase I study of accelerated conformal radiotherapy for stage I non–small-cell lung cancer in patients with pulmonary dysfunction: CALGB 39904. J Clin Oncol 28:202–206, 2010.
108. Bradley J, Graham MV, Winter K, et al: Toxicity and outcome results of RTOG9311: A phase I-II dose escalation study using three-dimensional conformal radiotherapy in patients with inoperable non–small-cell lung cancer. Int J Radiat Oncol Biol Phys 61:318–328, 2005.
109. Fernando HC, Landreneau RJ, Mandrekar SJ, et al: Impact of brachytherapy on local recurrence after sublobar resection: Results from ACOSOG Z40322 (Alliance), a phase III randomized trial for high-risk operable non–small cell lung cancer (NSCLC). J Clin Oncol 31(7502):2013.
110. Arriagada R, Dunant A, Pignon JP, et al: Long-term results of the international adjuvant lung cancer trial evaluating adjuvant cisplatin-based chemotherapy in resected lung cancer. J Clin Oncol 28:35–42, 2010.
112. Albain KS, Swann RS, Rusch VW, et al: Radiotherapy plus chemotherapy with or without surgical resection for stage III non–small-cell lung cancer: A phase III randomised controlled trial. Lancet 374:379–386, 2009.
113. Curran WJ, Scott C, Langer CJ, et al: Long-term benefits is observed in a phase III comparison of sequential vs. concurrent chemo-radiation for patients with unresectable stage III NSCLC: RTOG 9410 [abstract 2499]. Proc Am Soc Clin Oncol 22:621, 2003.
116. Vokes EE, Herndon JEII, Kelley MJ, et al: Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non–small-cell lung cancer: Cancer and Leukemia Group B. J Clin Oncol 25:1698–1704, 2007.
117. Hanna N, Neubauer M, Ansari R, et al: Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (D) in patients (pts) with inoperable stage III non–small cell lung cancer (NSCLC) HOG LUN01-24/USO-023. Proc Am Soc Clin Oncol 25:2007.
119. Perez CA, Stanley K, Rubin P, et al: A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung: Preliminary report by the Radiation Therapy Oncology Group. Cancer 45:2744–2753, 1980.
122. Saunders M, Dische S, Barrett A, et al: Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non–small-cell lung cancer: A randomised multicentre trial. Chart Steering Committee. Lancet 350:161–165, 1997.
123. Belani CP, Wang W, Johnson DH, et al: Phase III study of the Eastern Cooperative Oncology Group (ECOG 2597): Induction chemotherapy followed by either standard thoracic radiotherapy or hyperfractionated accelerated radiotherapy for patients with unresectable stage IIIA and B non–small-cell lung cancer. Eastern Cooperative Oncology Group. J Clin Oncol 23:3760–3767, 2005.
124. Sause W, Kolesar P, Taylor S, IV, et al: Final results of phase III trial in regionally advanced unresectable non–small cell lung cancer. Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Chest 117:358–364, 2000.
130. Yuan SP, Sun XMD, Li MP, et al: A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III non small cell lung cancer. Am J Clin Oncol 30:239–244, 2007.
137. Spigel DR, Hainsworth JD, Yardley DA, et al: Tracheoesophageal fistula formation in patients with lung cancer treated with chemoradiation and bevacizumab. J Clin Oncol 1:43–48, 2010.
143. PORT Meta-analysis Trialists Group: Postoperative radiotherapy in non–small-cell lung cancer: Systematic review and meta-analysis of individual patient data from nine randomized controlled trials. Lancet 352:257–263, 1998.
146. Turrisi AT, 3rd, Kim K, Blum R, et al: Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 340:265–271, 1999.

149. Bogart JA, Herndon JE, 2nd, Lyss AP, et al: 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: Analysis of Cancer and Leukemia Group B study 39808. Int J Radiat Oncol Biol Phys 59:460–468, 2004.
153. Perry MC, Herndon JE, 3rd, Eaton WL, et al: Thoracic radiation therapy added to chemotherapy for small-cell lung cancer: An update of Cancer and Leukemia Group B Study 8083. J Clin Oncol 16:2466–2467, 1998.
154. Murray N, Coy P, Pater JL, et al: Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 11:336–344, 1993.
158. Bonner JA, Sloan JA, Shanahan TG, et al: Phase III comparison of twice-daily split-course irradiation versus once-daily irradiation for patients with limited stage small-cell lung carcinoma. J Clin Oncol 17:2681–2691, 1999.
160. Aupérin A, Arriagada R, Pignon JP, et al: Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 341:476–484, 1999.
162. Le Pechoux C, Dunant A, Senan S, et al: Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): A randomised clinical trial. Lancet Oncol 10:467–474, 2009.
164. Ettinger DS, Berkey BA, Abrams RA, et al: Study of paclitaxel, etoposide, and cisplatin chemotherapy combined with twice-daily thoracic radiotherapy for patients with limited-stage small-cell lung cancer: A Radiation Therapy Oncology Group 9609 phase II study. J Clin Oncol 23:4991–4998, 2005.
168. Lara PN, Jr, Natale R, Crowley J, et al: Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: Clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol 15:2530–2535, 2009.
170. Herskovic A, Martz K, al-Sarraf M, et al: Combined chemotherapy and radiotherapy compared with radiotherapy alone. N Engl J Med 26:1593–1598, 1992.
173. Gebski V, Burmeister B, Smithers BM, et al: Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: A meta-analysis. Lancet Oncol 8:226–234, 2007.
174. Allum WA, Stenning SP, Bancewicz J, et al: Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol 27:5062–5067, 2009.
175. Bedenne L, Michel P, Bouche O, et al: Randomized phase III trial in locally advanced esophageal cancer: Radiochemotherapy followed by surgery versus radiochemotherapy alone (FFCD 9102) [abstract]. Proc Am Soc Clin Oncol 21:130a, 2002.
176. Stahl M, Stuschke M, Lehmann N, et al: Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 23:2310–2317, 2005.
178. Minsky BD, Pajak TF, Ginsberg RJ, et al: INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: High-dose versus standard-dose radiation therapy. J Clin Oncol 20:1167–1174, 2002.
183. Macdonald JS, Smalley SR, Benedetti J, et al: Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 345:725–730, 2001.
190. Forquer JA, Rong N, Fakiris AJ, et al: Postoperative radiotherapy after surgical resection of thymoma: Differing roles in localized and regional disease. Int J Radiat Oncol Biol Phys 76:440–445, 2010.
193. Eng TY, Fuller CD, Jagirdar J, et al: Thymic carcinoma: State of the art review. Int J Radiat Oncol Biol Phys 59:654–664, 2004.
199. Carretta A, Ceresoli GL, Arrigoni G, et al: Diagnostic and therapeutic management of neuroendocrine lung tumors: A clinical study of 44 cases. Lung Cancer 29:217–225, 2000.
206. Li L, Lally B, Egleston BL, et al: Significant increased survival in mesothelioma patients treated with radiation and surgery: An analysis of the SEER registry [abstract 2700]. Int J Radiat Oncol Biol Phys S496–S497, 2009.
210. Kristensen CA, Nøttrup TJ, Berthelsen AK, et al: Pulmonary toxicity following IMRT after extrapleural for malignant pleural mesothelioma. Radiat Oncol 92:96–99, 2009.

REFERENCES

1. Jemal A, Siegal R, Ward E, et al: Cancer statistics. CA Cancer J Clin 59:225–249, 2009.
2. Alberg AJ, Ford JG, Samet JM: Epidemiology of lung cancer: ACCP evidence based clinical practice guidelines (2nd edition). Chest 132:29S–55S, 2007.
3. Egleston BL, Meireles SI, Flieder DB, et al: Population-based trends in lung cancer incidence in women. Semin Oncol 36:506–515, 2009.
4. Neuberger JS, Gesell TF: Residential radon exposure and lung cancer: Risk in nonsmokers. Health Phys 83:1–18, 2002.
5. Samet JM, Avila-Tang E, Boffetta P, et al: Lung cancer in never smokers: Clinical epidemiology and environmental risk factors. Clin Cancer Res 15:5626–5645, 2009.
6. National Cancer Institute: Surveillance, Epidemiology, and End Results (SEER) Program, Available at: <http://seer.cancer.gov/csr/1975_2000/sections.html>.
7. Warde P, Payne D: Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. J Clin Oncol 10:890–895, 1992.
8. Siegel R, Naishadham D, Jemal A: Cancer statistics, 2013. CA Cancer J Clin 63:2013.
9. Kelsen D: Preoperative chemoradiotherapy for esophageal cancer. J Clin Oncol 19:283–285, 2001.
10. Engel LS, Chow WH, Vaughan TL, et al: Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst 95:1404–1413, 2003.
11. Engels EA, Pfeiffer RM: Malignant thymoma in the United States: Demographic patterns in incidence and associations with subsequent malignancies. Int J Cancer 105:546–551, 2003.
12. Batata MA, Martini N, Nuvos AG, et al: Thymomas: Clinicopathologic features, therapy, and prognosis. Cancer 34:389, 1974.
13. Kondo K, Monden Y: Therapy for thymic epithelial tumors: A clinical study of 1,320 patients from Japan. Ann Thorac Surg 76:878–884, 2003.
14. Hsu CP, Chen CY, Chen CL, et al: Thymic carcinoma: Ten years' experience in twenty patients. J Thorac Cardiovasc Surg 107:615–620, 1994.
15. Economopoulos GC, Lewis JW, Lee MW, et al: Carcinoid tumors of the thymus. Ann Thorac Surg 50:58–61, 1990.
16. Travis WD, Linnoila RI, Tsokos MG, et al: Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma: An ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. Am J Surg Pathol 15:529–553, 1991.
17. Mendonca C, Baptista C, Ramos M: Typical and atypical lung carcinoids: Clinical and morphological diagnosis. Microsc Res Tech 38:468–472, 1997.
18. Godwin JD, 2nd: Carcinoid tumors: An analysis of 2,837 cases. Cancer 36:560–569, 1975.
19. Connelly RR, Spirtas R, Myers MH, et al: Demographic patterns for mesothelioma in the United States. J Natl Cancer Inst 78:1053–1060, 1997.
20. Weill H, Hughes JM, Churg AM: Changing trends in US mesothelioma incidence. Occup Environ Med 61:438–441, 2004.
21. Robinson BW, Lak RA: Advances in malignant mesothelioma. N Engl J Med 353:1591–1603, 2005.
22. Mok TS, Wu YL, Thongprasert S, et al: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361:947–957, 2009.
23. Neal JW: Histology matters: Individualizing treatment in non–small cell lung cancer. Oncologist 15:3–5, 2010.
24. Koppert LB, Wijnhoven BP, van Dekken H, et al: The molecular biology of esophageal adenocarcinoma. J Surg Oncol 92:169–190, 2005.
25. Lin J, Beerm DG: Molecular biology of upper gastrointestinal malignancies. Semin Oncol 31:476–486, 2004.
26. Patton DP, Ribeiro RC, Jenkins JJ, et al: Thymic carcinoma with a defective Epstein-Barr virus encoding the BZLF1 transactivator. J Infect Dis 170:7–12, 1994.
27. Jensen MO, Antonenko D: Thyroid and thymic malignancy following childhood irradiation. J Surg Oncol 50:206–208, 1992.
28. Lee ACW, Kwong YL, Fu KH, et al: Disseminated mediastinal carcinoma with chromosomal translocation (15:19). Cancer 72:2273–2276, 1993.
29. Herens C, Radermecker M, Servais A, et al: Deletion (6:22,25) is a recurrent anomaly of thymoma: Report of a second case and review of the literature. Cancer Genet Cytogenet 146:66–69, 2003.
30. Hayashi Y, Ishii N, Obayashi C, et al: Thymoma: Tumour type related to expression of epidermal growth factor (EGF), EGF-receptor, p53, v-erb B and ras p21. Virchows Arch 426:43–50, 1995.
31. Jung KJ, Lee KS, Han J, et al: Malignant thymic epithelial tumors: CT-pathologic correlation. AJR Am J Roentgenol 176:433–439, 2001.
32. Fukai I, Masaoka A, Hashimoto T, et al: Cytokeratins in normal thymus and thymic epithelial tumors. Cancer 71:99–105, 1993.
33. Oyama T, Osaki T, Mitsudomi T, et al: P53 alteration, proliferating cell nuclear antigen, and nucleolar organizer regions in thymic epithelial tumors. Int J Mol Med 1:823–826, 1998.
34. Hishima T, Fukayama M, Hayashi Y, et al: CD70 expression in thymic carcinoma. Am J Surg Pathol 24:742–746, 2000.
35. Fukai I, Masaoka A, Hashimoto T, et al: The distribution of epithelial membrane antigen in thymic epithelial neoplasms. Cancer 70:2077–2081, 1992.
36. Mendonca C, Baptista C, Ramos M: Typical and atypical lung carcinoids: Clinical and morphological diagnosis. Microsc Res Tech 38:468–472, 1997.
37. Feldman JM, O'Dorisio TM: Role of neuropeptides and serotonin in the diagnosis of carcinoid tumors. Am J Med 81:41–48, 1986.
38. Kaplan B, Stevens CW, Allen P, et al: Outcomes and patterns of failure in bronchial carcinoid tumors. Int J Radiat Oncol Biol Phys 55:125–131, 2003.
39. Thomas CF, Jr, Tazelaar HD, Jett JR: Typical and atypical pulmonary carcinoids: Outcome in patients presenting with regional lymph node involvement. Chest 119:1143–1150, 2001.
40. Debelenko LV, Brambilla E, Agarwal SK, et al: Identification of MEN1 gene mutations in sporadic carcinoid tumors of the lung. Hum Mol Genet 6:2285–2290, 1997.
41. Sugio K, Osaki T, Oyama T, et al: Genetic alteration in carcinoid tumors of the lung. Ann Thorac Cardiovasc Surg 9:149–154, 2003.
42. Onuki N, Wistuba II, Travis WD, et al: Genetic changes in the spectrum of neuroendocrine lung tumors. Cancer 85:600–607, 1999.
43. Fischer B, Lassen U, Mortensen J, et al: Preoperative staging of lung cancer with combined PET-CT. N Engl J Med 361:32–39, 2009.
44. Spratt DE, Diaz R, McElmurray J, et al: Impact of FDG PET/CT on delineation of the gross tumor volume for radiation planning in non–small-cell lung cancer. Clin Nucl Med 35:237–243, 2010.
45. Bradley JD, Dehdashti F, Mintun MA, et al: Positron emission tomography in limited-stage small-cell lung cancer: A prospective study. J Clin Oncol 22:3248–3254, 2004.
46. Rami-Porta R, Ball D, Crowley J, et al: The IASLC lung cancer staging project: Proposal for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for the lung cancer. J Thorac Oncol 2:593–602, 2007.
47. Stahel RA, Ginsberg R, Havermann K, et al: Staging and prognostic factors in small cell lung cancer: A consensus. Lung Cancer 5:119–126, 1989.
48. Cerfolio RJ, Bryant AS, Ojha B, et al: Improving the inaccuracies of clinical staging of patients with NSCLC: A prospective trial. Ann Thorac Surg 80:1207–1213, 2005.
49. Meyers BF, Haddad F, Siegel BA, et al: Cost-effectiveness of routine mediastinoscopy in computed tomography- and positron emission tomography-screened patients with stage I lung cancer. J Thorac Cardiovasc Surg 131:822–829, 2006.
50. Gress FG, Savides TJ, Sandler A, et al: Endoscopic ultrasonography, fine-needle aspiration biopsy guided by endoscopic ultrasonography, and computed tomography in the preoperative staging of non–small cell lung cancer: A comparison study. Ann Intern Med 127:604–612, 1997.
51. Flamen P, Lerut A, Van Cutsem E, et al: Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. J Clin Oncol 18:3202–3210, 2000.
52. Van Westreenan HL, Westerterp M, Bossuyt PM, et al: Systematic review of the staging performances of 18F-fluorodeoxyglucose positron emission tomography in esophageal carcinoma. J Clin Oncol 18:3805–3812, 2004.
53. Flamen P, Lerut T, Haustermans K, et al: Position of positron emission tomography and other imaging diagnostic modalities in esophageal cancer. Q J Nucl Med Mol Imaging 48:96–108, 2004.
54. Meyers BF, Downey RJ, Decker PA, et al: Surgeons Oncology Group Z0060 trial carcinoma of the thoracic esophagus: Results of the American College of the utility of positron emission tomography in staging of potentially operable. J Thorac Cardiovasc Surg 133:738–745, 2007.
55. Morgenthaler TI, Brown LR, Colby TV, et al: Thymoma. Mayo Clin Proc 68:1110–1123, 1993.
56. Hoffman OA, Gillespie DJ, Aughenbaugh GL, et al: Primary mediastinal neoplasms (other than thymoma). Mayo Clin Proc 68:880–891, 1993.
57. Wick MR, Rosai J: Neuroendocrine neoplasms of the mediastinum. Semin Diagn Pathol 8:35–51, 1991.
58. Detterbeck FC, Parsons AM: Thymic tumors. Ann Thorac Surg 77:1860–1869, 2004.
59. Baron RL, Lee JK, Sagel SS, et al: Computed tomography of the abnormal thymus. Radiology 142:127–134, 1982.
60. Casamassima F, Villari N, Fargnoli R, et al: Magnetic resonance imaging and high-resolution computed tomography in tumors of the lung and the mediastinum. Radiother Oncol 11:21–29, 1988.
61. Eng TY, Fuller CD, Jagirdar J, et al: Thymic carcinoma: State of the art review. Int J Radiat Oncol Biol Phys 59:654–664, 2004.
62. Masaoka A, Monden Y, Nakahara K, et al: Follow-up study of thymomas with special reference to their clinical stages. Cancer 48:2485–2492, 1981.
63. Lee JD, Choe KO, Kim SJ, et al: CT findings in primary thymic carcinoma. J Comput Assist Tomogr 15:429–433, 1991.
64. Modlin IM, Sandor A: An analysis of 8305 cases of carcinoid tumors. Cancer 79:813–829, 1997.
65. Kaltsas G, Korbonits M, Heintz E, et al: Comparison of somatostatin analog and meta-iodobenzylguanidine radionuclides in the diagnosis and localization of advanced neuroendocrine tumors. J Clin Endocrinol Metab 86:895–902, 2001.
66. Anderson CJ, Dehdashti F, Cutler PD, et al: 64Cu-TETA-octreotide as a PET imaging agent for patients with neuroendocrine tumors. J Nucl Med 42:213–221, 2001.
67. Prasad V, Ambrosini V, Hommann M, et al: Detection of unknown primary neuroendocrine tumours (CUP-NET) using (68)Ga-DOTA-NOC receptor PET/CT. Eur J Nucl Med Mol Imaging 37:67–77, 2010.

68. Renshaw AA, Dean BR, Antman KH, et al: The role of cytologic evaluation of pleural fluid in the diagnosis of malignant mesothelioma. Chest 111:106–109, 1997.
69. Bueno R, Reblando J, Glickman J, et al: Pleural biopsy: A reliable method for determining the diagnosis but not subtype in mesothelioma. Ann Thorac Surg 78:1774–1776, 2004.
70. Edge SB, Byrd DR, Compton CC, et al: AJCC Cancer staging manual, ed 7, New York, 2010, Springer.
71. Marks LB: The impact of organ structure on radiation response. Int J Radiat Oncol Biol Phys 4:1165–1171, 1996.
72. Chi A, Liao Z, Nguyen NP, et al: Systemic review of the patterns of failure following stereotactic body radiation therapy in early-stage non–small-cell lung cancer: Clinical implications. Radiother Oncol 94:1–11, 2010.
73. Timmerman R, McGarry R, Yiannoutsos C, et al: Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 24:4833–4839, 2006.
74. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al: Stereotactic body radiation therapy for early-stage non–small-cell lung carcinoma: Four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 75:677–682, 2009.
75. Timmerman R, Paulus R, Galvin J, et al: Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 303:1070–1076, 2010.
76. Forquer JA, Fakiris AJ, Timmerman RD, et al: Brachial plexopathy from stereotactic body radiotherapy in early-stage NSCLC: Dose-limiting toxicity in apical tumor sites. Radiother Oncol 93:408–413, 2009.
77. Pettersson N, Nyman J, Johansson KA: Radiation-induced rib fractures after hypofractionated stereotactic body radiation therapy of non–small cell lung cancer: A dose- and volume-response analysis. Radiother Oncol 91:360–368, 2009.
78. Dunlap NE, Cai J, Biedermann GE, et al: Chest wall volume receiving >30 Gy predicts risks of severe pain and/or rib fracture after lung stereotactic. Int J Radiat Oncol Biol Phys 76:796–801, 2010.
79. Marks LB, Bentzen SM, Deasy JO, et al: Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys 76(Suppl):S70–S76, 2010.
80. Graham MV, Purdy JA, Emami B, et al: Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non–small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 45:323–329, 1999.
81. Kwa SL, Lebesque JV, Theuws JC, et al: Radiation pneumonitis as a function of mean lung dose: An analysis of pooled data of 540 patients. Int J Radiat Oncol Biol Phys 42:1–9, 1998.
82. Hernando ML, Marks LB, Bentel GC, et al: Radiation-induced pulmonary toxicity: A dose-volume histogram analysis in 201 patients with lung cancer. Int J Radiat Oncol Biol Phys 51:650–659, 2001.
83. Hope AJ, Lindsay PE, El Naqa I, et al: Modeling radiation pneumonitis risk with clinical, dosimetric, and spatial parameters. Int J Radiat Oncol Biol Phys 65:112–124, 2006.
84. Anscher MS, Kong FM, Andrews K, et al: Plasma transforming growth factor beta1 as a predictor of radiation pneumonitis. Int J Radiat Oncol Biol Phys 41:1029–1035, 1998.
85. Belani CP, Choy H, Bonomi P, et al: Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non–small-cell lung cancer: A randomized phase II locally advanced multi-modality protocol. J Clin Oncol 23:5883–5891, 2005.
86. Kristensen CA, Nottrup TJ, Berthelsen AK, et al: Pulmonary toxicity following IMRT after extrapleural pneumonectomy for malignant pleural mesothelioma. Radiother Oncol 92:96–99, 2009.
87. Singh AK, Lockett MA, Bradley JD: Predictors of radiation-induced esophageal toxicity in patients with non–small cell lung cancer treated with three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys 55:337–341, 2003.
88. Werner-Wasik M, Pequignot E, Leeper D, et al: Predictors of severe esophagitis include use of concurrent chemotherapy, but not the length of irradiated esophagus: A multivariate analysis of patients with lung cancer treated with non-operative therapy. Int J Radiat Oncol Biol Phys 48:689–696, 2000.
89. Rose J, Rodrigues G, Yaremko B, et al: Systematic review of dose-volume parameters in the prediction of esophagitis in thoracic radiotherapy. Radiother Oncol 91:282–287, 2009.
90. Liao Z, Cox JD, Komaki R: Radiochemotherapy of esophageal cancer. J Thorac Oncol 2:553–568, 2007.
91. Movsas B, Scott C, Langer C, et al: Randomized trial of amifostine in locally advanced non- small-cell lung cancer patients receiving chemotherapy and hyperfractionated radiation: Radiation Therapy Oncology Group trial 98-01. J Clin Oncol 23:2145–2154, 2005.
92. Bradley JD, Paulus R, Komaki R, et al: A randomized phase III comparison of standard-dose (60GY) versus high-dose (74Gy) conformal chemoradiotherapy with or without cetuximab for stage III non–small lung cancer: Results on radiation dose in RTOG. J Clin Oncol 31(7501):2013.
93. Aleman BM, Belt-Dusebout AW, Klokman WJ, et al: Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol 21:3431–3439, 2003.
94. Early Breast Cancer Trialists' Collaborative Group: Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomized trials. Lancet 366:2087–2106, 2005.
95. Borger JH, Hooning MJ, Boersma LJ, et al: Cardiotoxic effects of tangential breast irradiation in early breast cancer patients: The role of irradiated heart volume. Int J Radiat Oncol Biol Phys 69:1131–1138, 2007.
96. Ginsberg RJ, Rubinstein LV: Randomized trial of lobectomy versus limited resection for T1 N0 non–small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 60:615–622, 1995.
97. Watanabe T, Okada A, Imakiire T, et al: Intentional limited resection for small peripheral lung cancer based on intraoperative pathologic exploration. Jpn J Thorac Cardiovasc Surg 53:29–35, 2005.
98. National Cancer Institute (NCI): Phase III randomized study of lobectomy versus sublobar resection in patients with small peripheral stage IA non–small cell lung cancer. Available at: <http://www.cancer.gov/clinicaltrials/CALGB-140503>.
99. National Cancer Institute (NCI): Trial of either surgery or stereotactic radiotherapy for early stage (IA) lung cancer. Available at: <http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=597713&version=HealthProfessional&protocolsearchid=7611352>.
100. National Cancer Institute (NCI): Phase II study of stereotactic body radiotherapy in patients with resectable stage I or II non–small cell lung cancer. Available at: <http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=571744&version=HealthProfessional&protocolsearchid=7611352>.
101. Hiraoka M, Ishikura S: A Japan clinical oncology group trial for stereotactic body radiation therapy of non–small cell lung cancer. J Thorac Oncol 2(7 Suppl 3):S115–S117, 2007.
102. Haasbeek CJ, Senan S, Smit EF, et al: Non–small cell lung cancer: A critical review of nonsurgical treatment options for stage I. Oncologist 13:309–319, 2008.
103. Powell JW, Dexter E, Scalzetti EM, et al: Treatment advances for medically inoperable non–small-cell lung cancer: Emphasis on prospective trials. Lancet Oncol 10:885–894, 2009.
104. Bogart JA, Hodgson L, Seagren SL, et al: Phase I study of accelerated conformal radiotherapy for stage I non–small-cell lung cancer in patients with pulmonary dysfunction: CALGB 39904. J Clin Oncol 28:202–206, 2010.
105. Phase II study of accelerated hypofractionated 3-dimensional conformal radiotherapy in patients with inoperable stage I or II non–small cell lung cancer. Available at: <http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=486919&version=HealthProfessional&protocolsearchid=5691106>. Accessed June 1, 2014.
106. Chen M, Hayman JA, Ten Haken RK, et al: Long-term results of high-dose conformal radiotherapy for patients with medically inoperable T1-3N0 non–small-cell lung cancer: Is low incidence of regional failure due to incidental nodal irradiation. Int J Radiat Oncol Biol Phys 64:120–126, 2006.
107. Rosenzweig KE, Fox JL, Leibel SA, et al: Results of a phase I dose-escalation study using three-dimensional conformal radiotherapy in the treatment of inoperable non small cell lung carcinoma. Cancer 103:2118–2127, 2005.
108. Bradley J, Graham MV, Winter K, et al: Toxicity and outcome results of RTOG9311: A phase I-II dose escalation study using three-dimensional conformal radiotherapy in patients with inoperable non–small-cell lung cancer. Int J Radiat Oncol Biol Phys 61:318–328, 2005.
109. Fernando HC, Landreneau RJ, Mandrekar SJ, et al: Impact of brachytherapy on local recurrence after sublobar resection: Results from ACOSOG Z40322 (Alliance), a phase III randomized trial for high-risk operable non–small cell lung cancer (NSCLC). J Clin Oncol 31(7502):2013.
110. Arriagada R, Dunant A, Pignon JP, et al: Long-term results of the international adjuvant lung cancer trial evaluating adjuvant cisplatin-based chemotherapy in resected lung cancer. J Clin Oncol 28:35–42, 2010.
111. Strauss GM, Herndon JE, Maddaus MA, et al: Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non–small-cell lung cancer: CALGB 9633 with Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 31:5043–5051, 2008.
112. Albain KS, Swann RS, Rusch VW, et al: Radiotherapy plus chemotherapy with or without surgical resection for stage III non–small-cell lung cancer: A phase III randomised controlled trial. Lancet 374:379–386, 2009.
113. Curran WJ, Scott C, Langer CJ, et al: Long-term benefits is observed in a phase III comparison of sequential vs. concurrent chemo-radiation for patients with unresectable stage III NSCLC: RTOG 9410 [abstract 2499]. Proc Am Soc Clin Oncol 22:621, 2003.
114. Belani CP, Choy H, Bonomi P, et al: Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non–small cell lung cancer: A randomized phase II locally advanced multi-modality protocol. J Clin Oncol 23:5883–5891, 2005.
115. Blackstock AW, Govindan R: Definitive chemoradiation for the treatment of locally advanced non–small-cell lung cancer. J Clin Oncol 25:4146–4152, 2007.
116. Vokes EE, Herndon JEII, Kelley MJ, et al: Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non–small-cell lung cancer: Cancer and Leukemia Group B. J Clin Oncol 25:1698–1704, 2007.
117. Hanna N, Neubauer M, Ansari R, et al: Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (D) in patients (pts) with inoperable stage III non–small cell lung cancer (NSCLC) HOG LUN01-24/USO-023. Proc Am Soc Clin Oncol 25:2007.

118. Coate LE, Shepherd FA: Maintenance therapy in advanced non–small cell lung cancer. J Thorac Oncol 26:4849–4850, 2008.
119. Perez CA, Stanley K, Rubin P, et al: A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung: Preliminary report by the Radiation Therapy Oncology Group. Cancer 45:2744–2753, 1980.
120. Rosenman JG, Halle JS, Socinski MA, et al: High-dose conformal radiotherapy for treatment of stage IIIA/IIIB non–small-cell lung cancer: Technical issues and results of a phase I/II trial. Int J Radiat Oncol Biol Phys 54:348–356, 2002.
121. Socinski MA, Blackstock AW, Bogart JA, et al: Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non–small-cell lung cancer: CALGB 30105. J Clin Oncol 2026:2457–2463, 2008.
122. Saunders M, Dische S, Barrett A, et al: Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non–small-cell lung cancer: A randomised multicentre trial. Chart Steering Committee. Lancet 350:161–165, 1997.
123. Belani CP, Wang W, Johnson DH, et al: Phase III study of the Eastern Cooperative Oncology Group (ECOG 2597): Induction chemotherapy followed by either standard thoracic radiotherapy or hyperfractionated accelerated radiotherapy for patients with unresectable stage IIIA and B non–small-cell lung cancer. Eastern Cooperative Oncology Group. J Clin Oncol 23:3760–3767, 2005.
124. Sause W, Kolesar P, Taylor S, IV, et al: Final results of phase III trial in regionally advanced unresectable non–small cell lung cancer. Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Chest 117:358–364, 2000.
125. Bonner JA, McGinnis WL, Stella PJ, et al: The possible advantage of hyperfractionated thoracic radiotherapy in the treatment of locally advanced non small cell lung carcinoma: Results of a North Central Cancer Treatment Group Phase III Study. Cancer 82:1037–1048, 1998.
126. Schild SE, Bonner JA, Shanahan TG, et al: Long-term results of a phase III trial comparing once-daily radiotherapy with twice-daily radiotherapy in limited stage small-cell lung cancer. Int J Radiat Oncol Biol Phys 59:943–951, 2004.
127. Radiation Therapy Oncology Group: Comparing photon therapy to proton therapy treat patients with lung cancer. Available at: <http://clinicaltrials.gov/show/NCT019938101>.
128. Kepka L, Bujko K, Zolciak-Siwinska A: Risk of isolated nodal failure for non–small cell lung cancer (NSCLC) treated with the elective nodal irradiation (ENI) using 3D-conformal radiotherapy (3D-CRT) techniques—a retrospective analysis. Acta Oncol 47:95–103, 2008.
129. Emami B, Mirkovic N, Scott C, et al: The impact of regional nodal radiotherapy (dose/volume) on regional progression and survival in unresectable non–small cell lung cancer: An analysis of RTOG data. Lung Cancer 41:207–214, 2003.
130. Yuan SP, Sun XMD, Li MP, et al: A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III non small cell lung cancer. Am J Clin Oncol 30:239–244, 2007.
131. Kelly K, Chansky K, Gaspar LE, et al: Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non–small-cell lung cancer: SWOG S0023. J Clin Oncol 26:2450–2456, 2008.
132. Ready N, Janne P, Herndon J, et al: Chemoradiotherapy (CRT) and gefitinib (G) in stage III non–small cell lung cancer (NSCLC): A CALGB stratified phase II trial [abstract]. J Clin Oncol 24:7046, 2006.
133. Cancer and Leukemia Group B: Carboplatin and paclitaxel albumin-stabilized nanoparticle formulation followed by radiation therapy and erlotinib in treating patients with stage III non–small cell lung cancer that cannot be removed by surgery, Available at: <www.clinicaltrials.gov/ct2/show/NCT00553462>.
134. Blumenschein G, Moughan J, Jr, Curran W, et al: A phase II study of cetuximab (C225) in combination with chemoradiation (CRT) in patients (pts) with stage III A/B non–small cell lung cancer (NSCLC): An interim report of the RTOG 0324 trial. 2007 ASCO Annual Meeting Proceedings Part I. J Clin Oncol 25:7531, 2007.
135. Govindan R, Bogart J, Wang X, et al: Chemotherapy in stage III non–small cell lung cancer [abstract]. J Clin Oncol 27(Suppl):15s, 2009.
136. Sandler A, Gray R, Perry MC, et al: Paclitaxel-carboplatin alone or with bevacizumab for non–small-cell lung cancer. N Engl J Med 355:2542–2550, 2006.
137. Spigel DR, Hainsworth JD, Yardley DA, et al: Tracheoesophageal fistula formation in patients with lung cancer treated with chemoradiation and bevacizumab. J Clin Oncol 1:43–48, 2010.
138. Mira JG, Miller TP, Crowley JJ: Chest irradiation (RT) vs. chest RT + chemotherapy + prophylactic brain RT in localized non small cell lung cancer: A Southwest Oncology Group randomized study [abstract]. Am Soc Ther Radiol Oncol 43(19):145, 1990.
139. Cox JD, Stanley K, Petrovich Z, et al: Cranial irradiation in cancer of the lung of all cell types. JAMA 245:469–472, 1981.
140. Russell AH, Pajak TE, Selim HM, et al: Prophylactic cranial irradiation for lung cancer patients at high risk for development of cerebral metastasis: Results of a prospective randomized trial conducted by the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 21:637–643, 1991.
141. Umsawasdi T, Valdivieso M, Chen TT, et al: Role of elective brain irradiation during combined chemoradiotherapy for limited disease non–small cell lung cancer. J Neuro-oncol 2:253–259, 1991.
142. Radiation Therapy Oncology Group: Cisplatin and docetaxel with or without radiation therapy in treating patients who are undergoing surgery for newly diagnosed stage III non–small cell lung cancer, Available at: <http://clinicaltrials.gov/ct2/show/NCT00113386>.
143. PORT Meta-analysis Trialists Group: Postoperative radiotherapy in non–small-cell lung cancer: Systematic review and meta-analysis of individual patient data from nine randomized controlled trials. Lancet 352:257–263, 1998.
144. Lally BE, Zelterman D, Colasanto JM, et al: Postoperative radiotherapy for stage II or III non small cell lung cancer using the surveillance, epidemiology and end results database. J Clin Oncol 24:2998–3006, 2006.
145. Phase III study comparing post-operative conformal radiotherapy to no post-operative radiotherapy in patients with completely resected non–small cell lung cancer and mediastinal N2 involvement (EORTC 22055-08053). Available at: <http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=5686>.
146. Turrisi AT, 3rd, Kim K, Blum R, et al: Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 340:265–271, 1999.
147. Movsas B, Moughan J, Komaki R, et al: Radiotherapy patterns of care study in lung carcinoma. J Clin Oncol 21:4553–4559, 2003.
148. Choi NC, Herndon JE, 2nd, Rosenman J, et al: Phase I study to determine the maximum-tolerated dose of radiation in standard daily and hyperfractionated-accelerated twice-daily radiation schedules with concurrent chemotherapy for limited-stage small-cell lung cancer. J Clin Oncol 16:3528–3536, 1998.
149. Bogart JA, Herndon JE, 2nd, Lyss AP, et al: 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: Analysis of Cancer and Leukemia Group B study 39808. Int J Radiat Oncol Biol Phys 59:460–468, 2004.
150. Radiation Therapy Oncology Group: Phase II study of cisplatin and etoposide combined with accelerated high-dose thoracic radiotherapy in patients with limited stage small cell lung cancer. Protocol IDs: RTOG 0239, Available at: <http://www.nci.nih.gov/clinicaltrials>.
151. Alliance for Clinical Trials in Oncology (Cancer and Leukemia Group B): Phase III randomized study of three different thoracic radiotherapy regimens in patients with limited-stage small cell lung cancer receiving cisplatin and etoposide, Available at:: <http://www.clinicaltrials.gov/ct/show/NCT00632853>.
152. Sally Falk: Concurrent once daily versus twice daily radiotherapy for limited stage small cell lung cancer (CONVERT), Available at: <http://clinicaltrials.gov/ct2/show/NCT00433563>.
153. Perry MC, Herndon JE, 3rd, Eaton WL, et al: Thoracic radiation therapy added to chemotherapy for small-cell lung cancer: An update of Cancer and Leukemia Group B Study 8083. J Clin Oncol 16:2466–2467, 1998.
154. Murray N, Coy P, Pater JL, et al: Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 11:336–344, 1993.
155. De Ruysscher D, Pijls-Johannesma M, Vansteenkiste J, et al: Systematic review and meta-analysis of randomised, controlled trials of the timing of chest radiotherapy in patients with limited-stage, small-cell lung cancer. Ann Oncol 17:543–552, 2006.
156. Huncharek M, McGarry R: A meta-analysis of the timing of chest irradiation in the combined modality treatment of limited stage small cell lung cancer. Oncologist 9:665–672, 2004.
157. Kies MS, Mira JG, Crowley JJ, et al: Multimodal therapy for limited small cell lung cancer: A randomized study of induction combination chemotherapy with or without thoracic radiation in complete responders, and with wide-field versus reduced-field radiation in partial responders. A Southwest Oncology Group study. J Clin Oncol 5:592–600, 1987.
158. Bonner JA, Sloan JA, Shanahan TG, et al: Phase III comparison of twice-daily split-course irradiation versus once-daily irradiation for patients with limited stage small-cell lung carcinoma. J Clin Oncol 17:2681–2691, 1999.
159. Schild SE, Bonner JA, Shanahan TG, et al: Long-term results of a phase III trial comparing once-daily radiotherapy with twice-daily radiotherapy in limited-stage small-cell lung cancer. Int J Radiat Oncol Biol Phys 59:943–951, 2004.
160. Aupérin A, Arriagada R, Pignon JP, et al: Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 341:476–484, 1999.
161. Baas P, Belderbos JS, Senan S, et al: Concurrent chemotherapy (carboplatin, paclitaxel, etoposide) and involved-field radiotherapy in limited stage small cell lung cancer: A Dutch multicenter phase II study. Br J Cancer 94:625–630, 2006.
162. Le Pechoux C, Dunant A, Senan S, et al: Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): A randomised clinical trial. Lancet Oncol 10:467–474, 2009.

163. Niell HB, Herndon JE, 2nd, Miller AA, et al: Randomized phase III intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B Trial 9732. J Clin Oncol 23:3752–3759, 2005.
164. Ettinger DS, Berkey BA, Abrams RA, et al: Study of paclitaxel, etoposide, and cisplatin chemotherapy combined with twice-daily thoracic radiotherapy for patients with limited-stage small-cell lung cancer: A Radiation Therapy Oncology Group 9609 phase II study. J Clin Oncol 23:4991–4998, 2005.
165. Lyss AP, Herndon J, Lynch T, et al: Novel doublets in extensive stage small cell lung cancer: A randomized phase II study of topotecan plus cisplatin or paclitaxel (CALGB 9430). Clin Lung Cancer 3:205–210, 2001.
166. Noda K, Nishiwaki Y, Kawahara M, et al: Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 346:85–91, 2002.
167. Hanna N, Bunn PA, Jr, Langer C, et al: Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 24:2038–2043, 2006.
168. Lara PN, Jr, Natale R, Crowley J, et al: Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: Clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol 15:2530–2535, 2009.
169. Ell C, May A, Gossner L, et al: Endoscopic resection of early cancer and high-grade dysplasia in Barrett's esophagus. Gastroenterology 118:670–677, 2000.
170. Herskovic A, Martz K, al-Sarraf M, et al: Combined chemotherapy and radiotherapy compared with radiotherapy alone. N Engl J Med 26:1593–1598, 1992.
171. Tepper J, Krasna MJ, Niedziecki D, et al: Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 26:1086–1092, 2008.
172. van Hagen P, Hulshof MC, van Lanschot JJ, et al: Peroperative chemoradiotherapy for esophageal or Junctional cancer. N Engl J Med 366:2074–2084, 2012.
173. Gebski V, Burmeister B, Smithers BM, et al: Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: A meta-analysis. Lancet Oncol 8:226–234, 2007.
174. Allum WA, Stenning SP, Bancewicz J, et al: Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol 27:5062–5067, 2009.
175. Bedenne L, Michel P, Bouche O, et al: Randomized phase III trial in locally advanced esophageal cancer: Radiochemotherapy followed by surgery versus radiochemotherapy alone (FFCD 9102) [abstract]. Proc Am Soc Clin Oncol 21:130a, 2002.
176. Stahl M, Stuschke M, Lehmann N, et al: Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 23:2310–2317, 2005.
177. Oppedijk V, van derGaast A, van Lanschot JJ, et al: Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. J Clin Oncol 32:385–391, 2014.
178. Minsky BD, Pajak TF, Ginsberg RJ, et al: INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: High-dose versus standard-dose radiation therapy. J Clin Oncol 20:1167–1174, 2002.
179. Cancer and Leukemia Group B: Randomized phase II trial of PET scan–directed combined modality therapy in esophageal cancer, Available at: <http://clinicaltrials.gov/ct/show/NCT01333033>.
180. Siewart JR, Stein HJ: Carcinoma of the cardia: Carcinoma of the gastroesophageal junction-classification, pathology, and extent of resection. Dis Esoph 9:173–182, 1996.
181. Hurt CN, Nixon LS, Griffiths GO, et al: SCOPE1: A randomized phase II/III multicentre clinical trial of definitive chemoradiation, with or without cetuximab, in carcinoma of the oesophagus. BMC Cancer 11(466):2001.
182. National Cancer Institute (NCI): Radiation therapy, paclitaxel, and carboplatin with or without trastuzumab in treating patients with esophageal cancer, Available at: <http://www.cancer.gov/clinicaltrials/search/view?cdrid=683717&version=healthprofessional>.
183. Macdonald JS, Smalley SR, Benedetti J, et al: Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 345:725–730, 2001.
184. National Cancer Institute (NCI): Phase II study of neoadjuvant panitumumab, docetaxel, cisplatin, and radiotherapy followed by surgery in patients with newly diagnosed, locally advanced adenocarcinoma of the distal esophagus or gastroesophageal junction, Available at: <http://www.cancer.gov/search/ResultsClinicalTrials.aspx?protocolsearchid=7611806>.
185. Phase II randomized study of extended neoadjuvant therapy comprising docetaxel, oxaliplatin, capecitabine, fluorouracil, and radiotherapy in patients with potentially resectable, locally advanced adenocarcinoma of the esophagus, gastroesophageal junction, or gastric cardia. Available at: <http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=646724&version=HealthProfessional&protocolsearchid=7611806>.
186. Yagi K, Hirata T, Fukuse T, et al: Surgical treatment for invasive thymoma, especially when the superior vena cava is involved. Ann Thorac Surg 61:521–524, 1996.
187. Curran WJ, Jr, Kornstein MJ, Brooks JJ, et al: Invasive thymoma: The role of mediastinal irradiation following complete or incomplete surgical resection. J Clin Oncol 6:1722–1727, 1988.
188. Urgesi A, Monetti U, Rossi G, et al: Role of radiation therapy in locally advanced thymoma. Radiother Oncol 19:273–280, 1990.
189. Haniuda M, Miyazawa M, Yoshida K, et al: Is postoperative radiotherapy for thymoma effective? Ann Surg 224:219–224, 1996.
190. Forquer JA, Rong N, Fakiris AJ, et al: Postoperative radiotherapy after surgical resection of thymoma: Differing roles in localized and regional disease. Int J Radiat Oncol Biol Phys 76:440–445, 2010.
191. Thomas CR, Wright CD, Loehrer PJ: Thymoma: State of the art. J Clin Oncol 17:2280–2289, 1999.
192. Urgesi A, Monetti U, Rossi G, et al: Aggressive treatment of intrathoracic recurrences of thymoma. Radiother Oncol 24:221–225, 1992.
193. Eng TY, Fuller CD, Jagirdar J, et al: Thymic carcinoma: State of the art review. Int J Radiat Oncol Biol Phys 59:654–664, 2004.
194. Hsu CP, Chen CY, Chen CL, et al: Thymic carcinoma: Ten years' experience in twenty patients. J Thorac Cardiovasc Surg 107:615–620, 1994.
195. Hsu HC, Huang EY, Wang CJ, et al: Postoperative radiotherapy in thymic carcinoma: Treatment results and prognostic factors. Int J Radiat Oncol Biol Phys 52:801–805, 2002.
196. Filosso PL, Rena O, Donati G, et al: Bronchial carcinoid tumors: Surgical management and long-term outcome. J Thorac Cardiovasc Surg 123:303–309, 2002.
197. Kubota A, Yamada Y, Kagimoto S, et al: Identification of somatostatin receptor subtypes and an implication for the efficacy of somatostatin analogue SMS 201-995 in treatment of human endocrine tumors. J Clin Invest 93:1321–1325, 1994.
198. Beasley MB, Thunnissen FB, Brambilla E, et al: Pulmonary atypical carcinoid: Predictors of survival in 106 cases. Hum Pathol 31:1255–1265, 2000.
199. Carretta A, Ceresoli GL, Arrigoni G, et al: Diagnostic and therapeutic management of neuroendocrine lung tumors: A clinical study of 44 cases. Lung Cancer 29:217–225, 2000.
200. Granberg D, Eriksson B, Wilander E, et al: Experience in treatment of metastatic pulmonary carcinoid tumors. Ann Oncol 12:1383–1391, 2001.
201. Oberg K, Astrup L, Eriksson B, et al: Guidelines for the management of gastroenteropancreatic neuroendocrine tumours (including bronchopulmonary and thymic neoplasms). Acta Oncol 43:617–625, 2004.
202. Oberg K, Eriksson B: The role of interferons in the management of carcinoid tumours. Br J Haematol 79:74–77, 1991.
203. Schupak KD, Wallner KE: The role of radiation therapy in the treatment of locally unresectable or metastatic carcinoid tumors. Int J Radiat Oncol Biol Phys 20:489–495, 1991.
204. Treasure T, Sedrakyan A: Pleural mesothelioma: Little evidence, still time to do trials. Lancet 364:1183–1185, 2004.
205. Ung YC, Yu E, Falkson C, et al: The role of radiation therapy in malignant pleural mesothelioma: A systematic review. Radiat Oncol 80:13–18, 2006.
206. Li L, Lally B, Egleston BL, et al: Significant increased survival in mesothelioma patients treated with radiation and surgery: An analysis of the SEER registry [abstract 2700]. Int J Radiat Oncol Biol Phys S496–S497, 2009.
207. Santaro A, O'Brien ME, Stahel RA, et al: Pemetrexed plus cisplatin or pemetrexed plus cardioplatin for chemonaive patients with malignant pleural mesothelioma: Results of the International Expanded Access Program. J Thorac Oncol 3:756–763, 2008.
208. Flores RM, Krug LM, Rosenzweig KE, et al: Induction chemotherapy, extrapleural pneumonectomy, and postoperative high-dose radiotherapy for locally advanced malignant pleural mesothelioma: A phase II trial. J Thorac Oncol 1:289–295, 2006.
209. Allen AM, Den R, Wong JS, et al: Influence of radiotherapy technique and dose on patterns of failure for mesothelioma patients after extrapleural pneumectomy. Int J Radiat Oncol Biol Phys 68:1366–1374, 2007.
210. Kristensen CA, Nøttrup TJ, Berthelsen AK, et al: Pulmonary toxicity following IMRT after extrapleural for malignant pleural mesothelioma. Radiat Oncol 92:96–99, 2009.