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NONSURGICAL TREATMENT FOR NON-SMALL-CELL LUNG CANCER: POOR PERFORMANCE STATUS OR PALLIATIVE INTENT

Expert Panel on Radiation Oncology–Lung: Kenneth E. Rosenzweig, MD[1]; Joe Yujiao Chang, MD, PhD[2]; Indrin J. Chetty, PhD[3]; Roy H. Decker, MD, PhD[4]; Mark E. Ginsburg, MD[5]; Larry L. Kestin, MD[6]; Feng-Ming (Spring) Kong, MD, PhD, MPH[7]; Brian E. Lally, MD[8]; Corey J. Langer, MD[9]; Benjamin Movsas, MD[10]; Gregory M. M. Videtic, MD, CM[11]; Henning Willers, MD.[12]

Summary of Literature Review

Approximately 40% of patients with newly diagnosed non-small-cell lung cancer (NSCLC) present with local regional disease that is not amenable to surgical treatment [1]. An additional 40% present with disseminated disease (stage IV) [1]. Radiation therapy has played a major role in the treatment of these patients for potential cure or long-term survival and palliation. Radiation therapy is the standard therapy for patients with inoperable NSCLC. Essentially, radiation therapy replaces surgery as the definitive treatment. This summary addresses definitive radiation therapy with or without other modalities in inoperable patients. Patients may be deemed inoperable because of stage or comorbid medical diseases. Stage IIIA and B patients have traditionally been considered unresectable because of the local-regional extent of disease. Patients with stage IV disease should be considered for palliative radiation therapy for the relief of specific symptoms either to the site of metastatic disease or to the primary tumor. In certain cases, such as solitary brain metastases or other oligometastatic disease, patients can be considered for more aggressive therapy such as surgical resection or stereotactic body radiation therapy.

In choosing a nonaggressive, nonsurgical treatment, the therapy decision may be based on patient characteristics other than stage, including age, performance status, and the presence or absence of weight loss. Typically, a standardized scale, such as the Eastern Cooperative Oncology Group (ECOG) ≥2 is used to assess performance status. When assessing trials of radiation therapy for NSCLC it is essential to evaluate the patient population in the trial and to identify the prognostic variables that may have a significant impact on the results. In general, patients included in this section are either those who would not be expected to withstand very aggressive therapy or those whose outlook for survival is so poor that efforts to reduce the time and toxicity of treatment would be desirable. This paper discusses nonsurgical treatment for NSCLC with a focus on radiation therapy. If radiation therapy is combined with other agents, including chemotherapy, the intent is to be relatively nontoxic and less aggressive.

In general, the nonsurgical treatment of NSCLC can be divided into broad categories:

- Radiation therapy alone: this is used primarily for early-stage (stage I and II) patients. For patients with locally advanced disease (stage IIIA and IIIB) it is used for the rare patients who cannot tolerate any chemotherapy due to comorbid conditions or poor performance status.
- Sequential chemotherapy followed by radiation therapy: this approach is reserved for patients with locally advanced disease who are unable to tolerate concurrent chemotherapy and radiation therapy.
- Concurrent chemotherapy and radiation therapy: this is the standard of care for fit patients with locally advanced disease. This approach is not discussed in this document.
- Endobronchial brachytherapy for patients with obstructing endobronchial lesions.
- Palliative radiation therapy for patients with metastatic disease.

[1]Principal Author and Panel Chair, Mount Sinai School of Medicine, New York, New York. [2]Panel Vice-chair, MD Anderson Cancer Center, Houston, Texas. [3]Henry Ford Health System, Detroit, Michigan. [4]Yale University School of Medicine, New Haven, Connecticut. [5]Columbia University, New York, New York, Society of Thoracic Surgeons. [6]William Beaumont Hospital, Royal Oak, Milwaukee. [7]VA Health Center and University of Michigan, Ann Arbor, Michigan. [8]University of Miami, Miami, Florida. [9]Fox Chase Cancer Center, Philadelphia, Pennsylvania, American Society of Clinical Oncology. [10]Henry Ford Health System, Detroit, Michigan. [11]Cleveland Clinic Foundation, Cleveland, Ohio. [12]Massachusetts General Hospital, Boston, Massachusetts.

Reprint requests to: Department of Quality & Safety, American College of Radiology, 1891 Preston White Drive, Reston, VA 20191-4397.

Results of Curative Intent Radiation Therapy Alone

External Beam Alone

The radiation therapy standard of care for the past decade was established by a randomized prospective trial by the Radiation Therapy Oncology Group® (RTOG®) published in 1982. This study randomized 378 patients to 40 Gy continuous-course versus 40 Gy split-course versus 50 or 60 Gy continuous-course treatments. The 60 Gy arm was superior to the other doses for intrathoracic control and overall survival (OS). This was particularly evident at the 1- and 3-year evaluations where 60 Gy resulted in the 1- and 3-year survival rates of 42% and 15%, respectively. However, there was no significant difference by 5 years [2].

Medically inoperable stage I and II NSCLC patients may be treated definitively with radiation therapy alone. These patients primarily have cardiovascular or chronic pulmonary disease that makes surgical resection too risky. Multiple studies have evaluated treating patients with standard-fraction radiation therapy [3-10]. Results vary slightly, but in general, patients who have poor pulmonary or cardiac reserve and are often elderly have respectable results with radiation therapy alone. Reported 3-year survival rates range from 17%-55% [8,9].

Currently extracranial stereotactic body radiotherapy (SBRT) is being examined as an alternative to conventionally fractionated radiotherapy in patients with inoperable stage I disease. In a study by McGarry et al [11] assessing toxicity and local control rates in 47 patients with stage I inoperable NSCLC who were treated with SBRT, the crude local control rate was found to be 79% (37/47 patients), with local failures occurring between 3 and 31 months after treatment. Maximum tolerated dose (MTD) was not reached for patients with stage IA disease (maximum dose delivered was 60 Gy in 3 fractions) and was found to be 72 Gy for stage IB disease for tumors >5 cm, with dose-limiting toxicities including bronchitis, pericardial effusion, hypoxia, and pneumonitis [11]. In a study by Onishi et al [12] 257 patients with both operable and inoperable, early-stage disease and more peripheral tumors were treated using SBRT to total doses ranging from 18 Gy to 75 Gy in 1-22 fractions. An overall local control rate of 85.5% and a pulmonary complication rate of 2.4% were observed. A follow-up study from the same group reported a 71% 5-year survival rate if the biological effective dose (BED) was >100 Gy compared to 30% if the BED was <100 Gy, suggesting a dose response for SBRT [13].

RTOG® 0236 was a phase II multicenter trial of SBRT in patients with T1-2N0M0 NSCLC [14]. Patients were treated with 18 Gy per fraction for 3 fractions (54 Gy total). Fifty-nine patients were accrued, and the 3-year local control was 97.6%. Only one patient had local failure, three had recurrence within the lobe outside the field, and two patients experienced regional failure. Grade 3 adverse events occurred in 12.7% of patients and grade 4 adverse events in 3.6%.

In an effort to increase tumoricidal effect and maintain acceptable normal tissue toxicity, several trials have been carried out using hyperfractionation regimens. The RTOG® conducted a large randomized phase I/II trial with hyperfractionated radiotherapy with total doses of 60 Gy to 79.2 Gy. A statistically significant improvement in survival was seen with the 69.6 Gy dose for patients having favorable characteristics, including good performance status and absence of weight loss. This was tested against conventional external beam radiation therapy (EBRT) (60 Gy in 6 weeks), versus chemotherapy and radiation therapy (2 cycles of neoadjuvant cisplatin velban followed by conventional radiotherapy) by the RTOG® [15]. The hyperfractionated arm to 69.6 Gy without chemotherapy resulted in improved median survival and 3-year survival rates over the conventional fractionated radiotherapy, but the difference was not statistically significant.

In a follow-up three-armed phase III trial, two arms compared hyperfractionated radiation therapy to 69.6 Gy with daily radiation to 60 Gy and reported no significant difference with median survival of 12.3 months and 11.4 months respectively [15].

Another three-armed phase III trial, RTOG 9410, compared the use of hyperfractionated radiation therapy to a dose of 69.6 Gy with concurrent chemotherapy with two daily radiation regimens of sequential and concurrent chemoradiation and reported no significant improvement in outcome [16]. Based on these trials and the inherently difficulties in delivering twice daily radiation therapy, it is not routinely used.

Pigott and Saunders [17] reported their phase I/II results with the continuous hyperfractionated accelerated radiation treatment (CHART) regimen of 50.4 to 54 Gy in 1.4 to 1.5 Gy fractions given three times daily over 12 elapsed days. The median survival time (MST) was 12.8 months, and the 1-year survival rate was 52%. One-third of the patients died of local regional failure. It should be noted that many of the patients treated in this manner

were otherwise fit and could have tolerated combined-modality therapy. Due to the intensity and toxicity of treatment, hyperfractionation might not be suitable for patients with poor performance status.

In a retrospective study of 31 operable stage I patients, Slotman et al [18] reported an OS rate of 42% at 3 years with a regional recurrence rate of 6% (two patients). This study showed that noninvolved lymph nodes do not need to be included in the planning target volume and that primary radiotherapy is an effective option compared to surgery for early-stage NSCLC. Another retrospective review of 524 patients treated with primary radiation therapy for various stages of NSCLC demonstrated a failure rate of 9% at 2 years in elective nodal regions [1,19]. A randomized phase III trial from China comparing elective nodal irradiation (60-64 Gy) with involved-field irradiation (68-74 Gy) reported an improved response rate and local control rate in patients who received involved-field [20].

Conformal therapy using 3-dimensional (3D) radiation therapy also may be used to improve the therapeutic ratio (ie, reduce toxicity and give tumoricidal radiation doses). Several reports have now been published supporting the concept that 3D conformal therapy and dose volume histogram analysis is useful to predict pneumonitis [21-23]. Early reports also suggest a benefit to higher doses [24,25] and that mean tumor doses of ≥74-75 Gy may result in better outcomes [24,26]. One fundamental difference between traditional radiation portals and most 3D trials has been the omission of elective nodal radiation. This has allowed significant dose escalation while maintaining acceptable tolerance. As demonstrated by Armstrong et al [27], 3D conformal radiation therapy (3D-CRT) has been shown to provide an adequate dose to the tumor volume while minimizing the total volume of both ipsilateral and contralateral lung that is irradiated. This dose distribution allows for both an improved local tumor control and a better side effect profile. Local failure is a leading cause of death in inoperable NSCLC, and therefore techniques for improving local control such as the use of 3D-CRT may lead to improved outcomes. (See Variant 1.)

Hayman et al [28] conducted a prospective study in which 104 patients were separated into bins based on tumor volume, and dose escalation was attempted using 3D-CRT. The MTD was reached for the largest bin and was found to be 65.1 Gy. In the smallest bin (by volume), dose was safely escalated to 102.9 Gy without reaching MTD. For stage I/II patients, the 2-year OS rate was 49% with a MST of 20 months. In patients with stage III recurrent disease the 2-year OS rate was 36% with a MST of 16 months.

RTOG® 9311, a multi-institutional phase I-II dose-escalation study that evaluated acute and late toxicities in 177 patients with stage I-IIIB inoperable NSCLC, reported 2-year local control rates ranging from 50%-78% and OS rates were between 20%-50%. Doses were safely escalated to 83.8 Gy for patients with V_{20} values of <25% and 77.4 Gy for patients with V_{20} between 25%-36% [29]. At the Memorial Sloan-Kettering Cancer Center a phase I dose-escalation study established a MTD of 84 Gy, and improved OS was seen among patients who received at least 80 Gy [30].

More modern treatment planning techniques have also been incorporated for these patients. There has been some evidence that intensity-modulated radiation therapy (IMRT) can limit radiation-related toxicity as compared to 3D-CRT [31]. Additionally, proton beam radiation therapy, a type of particle treatment, has been investigated as a method to further reduce the toxicity of treatment in this patient population. A phase I/II clinical study at MD Anderson Cancer Center showed that proton therapy can deliver ablative dose to target while minimizing dose exposure to surrounding critical structures and achieved excellent local control and acceptable toxicity in this patient population [32].

Another phase II study reported tolerable side effects and promising OS when 74 Gy of proton therapy was given concurrently with chemotherapy in stage III NSCLC [33]. As compared with their historical data using 63 Gy photon therapy, it appears to be associated with reduced side effects [34].

Curative Intent Radiation Therapy Combined with Sequential Chemotherapy

Curative intent radiation therapy combined with chemotherapy has been developed with the goal of addressing the significant problem of distant metastasis. The addition of chemotherapy has added toxicity to the regimens, however, and the discussion to follow is aimed at the relatively nontoxic or better tolerated regimens. This is certainly open to interpretation. When one begins to add chemotherapy to a radiation therapy regimen, the definition of "nonaggressive" becomes ambiguous. However, there may be some sequences and some agents in the combination of chemotherapy and radiation therapy that may result in relatively nontoxic and thus less aggressive therapy.

There have been numerous randomized controlled prospective trials comparing radiation therapy alone versus chemotherapy and radiation therapy [15,35-39]. The results are similar, with radiation therapy alone resulting in a 9-10-month MST compared to chemotherapy and radiation therapy resulting in a 12-14-month MST. Additionally the 2-year survival rates usually doubled from around 12%-15% to 21%-26% [15,35,36,39]. While increased toxicities have been reported for concurrent chemotherapy and radiation therapy, primarily involving myelosuppression, nausea, vomiting, and esophagitis, a sequential strategy, with radiation following chemotherapy will frequently mitigate toxicity while preserving some survival improvement over radiation therapy alone. Many of these trials, however, have had limited enrollment of patients with good performance status and absence of weight loss. Thus, these results may not be automatically applicable to patients outside the performance or functional categories of those enrolled.

The Cancer and Leukemia Group B (CALGB) 8433 study compared sequential chemoradiation therapy to radiotherapy in 155 patients with locally advanced NSCLC. Patients enrolled in the study had good performance status upon entry. Patients in the induction chemotherapy arm received a combination of cisplatin (100 mg/m^2 on days 1 and 29) and vinblastine (5mg/m^2 once weekly for 5 cycles). The dose of radiation was 60 Gy in 30 fractions in both arms and started on day 50 in the sequential chemoradiation arm. Initially, results showed that induction chemotherapy improved MST from 9.7 months to 13.8 months (P=0.0066). Three-year survival was found to be 23% in the sequential chemoradiation arm versus 11% in the radiation-alone arm. Upon 7-year follow-up the original results were confirmed, with the MST in the induction chemotherapy arm being 13.7 months versus 9.6 months in the radiation-alone arm (P=0.012) [35,40]. (See Variant 2.) Recently, a phase III randomized study showed that concurrent radiotherapy and low dose carboplatin improved OS as compared with radiotherapy alone (22.4 months vs 16.9 months, P=0.0179) in patients older than 70 years with stage III NSCLC [41].

Recently the CALGB reported the results of trial 30106. In this trial, patients were stratified by their performance status, and poor-risk patients (≥5% weight loss or ECOG ≥2) received 6600 cGy with concurrent gefitinib (250 mg). They had a very promising median survival time of 19 months [42]. A similar outcome with median OS of 15 to 19.5 months was reported by the NEAR trial [43] and Mayo Clinic [44] when radiotherapy (60-66 Gy) was given concurrently with cetuximab (250 to 400 mg/m^2) in this patient population. Another trial, RTOG® 0213, used concurrent thoracic radiation therapy to 6600 cGy with concurrent celecoxib. The treatment was well tolerated, and the median OS time was 10 months [45]. These trials suggest that there may be good results with the use of biologic agents instead of cytotoxic chemotherapy.

RTOG® 0617 was a four-arm phase III randomized trial that evaluated 60 Gy versus 74 Gy concurrently delivered with carboplatin and paclitaxel chemotherapy (with or without cetuximab). In a planned interim survival analysis, it was determined that the 74 Gy dose arm would not be able to show improved survival compared to the 60 Gy dose arm, and that portion of the trial was closed. The portion of the trial evaluating the use of cetuximab completed accrual and is awaiting analysis [46].

In summary, in selected patients who are thought to be able to withstand the potential increased toxicity of adding chemotherapy or molecular target therapy to radiotherapy, this combination appears to be superior to radiation therapy alone.

Importantly, we cannot discount the vital role radiation therapy plays in this setting. Kubota et al [47] reported on a prospective randomized trial comparing chemotherapy alone to chemotherapy and radiation therapy. The 2-year survival rate was 36% with chemotherapy and radiation therapy compared to only 9% with chemotherapy alone.

Palliative Intent Therapy

EBRT has played a major role in the palliative therapy of NSCLC [48]. The primary symptoms evaluated have included dyspnea, cough, hemoptysis, postobstructive pneumonia, collapse or atelectasis, and pain. Simpson et al [49] reported on 409 patients treated in a randomized prospective trial for the palliation of their symptoms. The comparison was between 40 Gy split course versus 30 Gy conventional, and 30 Gy in 10 fractions versus 40 Gy in 20 fractions. MST was 6 months, and there was no significant difference between the three groups. Approximately 60% of patients had their symptoms relieved.

In a series by the Medical Research Council (MRC), Macbeth et al [50] randomized 509 patients and compared outcomes of 17 Gy in 2 fractions versus 39 Gy in 13 fractions for palliative treatment. Results showed that 17 Gy in 2 fractions provided a more rapid palliation of symptoms, but the 39 Gy in 13 fractions yielded a longer MST

(9 months vs 7 months). A Canadian trial conducted by Bezjak et al [51] randomized 231 NSCLC patients to 20 Gy in 5 fractions or 10 Gy in a single fraction. Similar palliation was observed in the two arms, but the 20 Gy in the 5-fractions arm was observed to result in a longer MST (6 months vs 4.2 months). (See Variant 3.)

To reduce the time spent in radiation therapy departments, hypofractionated regimens have been evaluated for palliation. Pirtoli et al [52] reported regimens of 42 to 44 Gy in 5.5 to 8.8 Gy fraction weekly doses. They reported objective remission in 49% of patients and an improvement in performance status in 42%, with an additional 42% having stable performance status. They reported increased side effects, however, in regimens using 8.8 Gy fractions. The MRC reported on a randomized trial comparing 17 Gy in 8.5 Gy fractions in one fraction per week versus 30 Gy in 10 fractions over 2 weeks [53]. There was no difference in survival or palliation of symptoms. In general, hemoptysis was palliated the best, with 81%-86% having relief of this symptom. Cough was relieved in 56%-65%, and chest pain was relieved in over half of the patients. Collins et al [54] reported on 18 Gy in 5 fractions versus 48 Gy with a split course and a 1-month break. Symptom responses were about 60%, and the average duration was 6 months. They found no difference in their two regimens. Teo et al [55] compared 45 Gy in 18 fractions over 4.5 weeks versus 31.2 Gy in 4 fractions over 4 weeks. The MST was 20 weeks for both arms; however, the more protracted course of 45 Gy in 4.5 weeks had a 71% palliation rate versus 54% in the other arm ($P \leq .02$). Carroll et al [56] reported on the immediate or delayed use of radiation therapy for the palliation of symptoms. They found no significant difference. However, 64% required immediate radiation therapy, and an additional 19% required it later.

A systematic review of 13 randomized controlled trials involving 3,473 patients compared lower-dose and higher-dose radiation therapy. Higher-dose radiation did not improve specific symptoms (hemoptysis, cough, or chest pain), but there was a significant improvement in overall symptoms. There was also a significant improvement in OS at 1 year with higher-dose radiation. Higher-dose radiation was defined as a biologic equivalent dose of 35 Gy_{10} which is approximately 30 Gy in 10 fractions [57].

Endobronchial brachytherapy has been used for palliation of intraluminal tumor symptoms, including hemoptysis, obstruction with resultant postobstructive pneumonia, atelectasis, dyspnea, and cough. All of these studies suffer from being nonrandomized, primarily retrospective reviews. Zajac et al [58] reported the use of remote afterloading high-dose-rate brachytherapy for airway obstruction. Eighty-two percent of the patients had improvement in their obstructive score, and the symptoms were palliated until death in 76% of the patients. (See Variant 4.)

Chemotherapy has been compared to best supportive care (BSC) in many meta-analyses [59-62]. These meta-analyses have favored chemotherapy for palliation, and some have shown that it increases median survival time. Souquet et al [62] reported a decreased mortality at 6 months, as did Grilli et al [60]. However, Grilli et al reported that the extension of life was only 6 weeks. The British Collaborative Group showed a 27% reduction in the risk of death and a 10% improvement in survival in 1 year [59]. Cullen et al [63] compared platinum-based chemotherapy with mitomycin, ifosfamide, and cisplatin (MIP) and BSC versus BSC alone in a randomized trial of 351 patients with stage IV NSCLC. Results from this study showed that the MIP arm yielded a statistically significant increase in MST (6.7 months vs 4.8 months) compared to the BSC arm ($P=0.03$). As reviewed by Sociniski et al [64], improvement in symptoms and quality of life (QoL) is seen with most platinum-based chemotherapeutic regimens in stage IV NSCLC. In a phase III prospective trial in treatment-naïve patients with advanced NSCLC, a combination of paclitaxel and carboplatin proved superior to single-agent paclitaxel with a doubling of median survival time (4.8 vs 2.4 months) in a PS 2 subset [65]. These data and other similar trials support the notion that systemic therapy can lead to improved outcome as well as QoL in advanced NSCLC patients with compromised PS. This benefit is likely to be greatest in those who are symptomatic from their cancer rather than from a comorbid condition. (See Variant 5.)

As demonstrated by Lilenbaum et al [65], results appear a bit more promising in the context of third-generation cytotoxics. In a prospective trial, Roszkowski et al [66] randomized 207 patients to BSC versus docetaxel. Using The European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30), they reported a significant improvement in pain, dyspnea, and emotional functioning in the chemotherapy arm. Ranson et al [67] randomized 157 patients to paclitaxel versus BSC and found an improved MST in the paclitaxel arm (6.8 months vs 4.8 months, $P=0.037$). A trial by ECOG showed that combining platinum-based chemotherapy with newer agents such as paclitaxel improves survival over the older regimens [68]. And work from the UK showed that a modern regimen consisting of gemcitabine and carboplatin offers longer survival time than MIP [69].

Second-line chemotherapy has also been shown to improve survival time when compared to BSC in those patients whose tumors have progressed after first-line therapy. Shepherd et al [70] randomized 103 patients with stage IIIB/IV disease whose disease had progressed either during or after platinum-based chemotherapy to either docetaxel or BSC and demonstrated a significant survival benefit in the docetaxel arm, with a MST of 7.5 months versus 4.6 months in the BSC arm (P=0.010). The 1-year survival rate was 37% in the docetaxel arm versus 11% in the BSC arm (P=0.003). Fosella et al [71] reported an advantage for docetaxel over vinorelbine/ifosfamide as second-line treatment for patients previously treated with platinum-based chemotherapy, especially in controlling symptoms of fatigue and total symptomatic distress. Tumor response was correlated to improved QoL regardless of the dose of docetaxel [71].

Targeted agents such as Tarceva (erlotinib), Iressa (gefitinib), and Avastin (bevacizumab) have been implemented in patients with advanced NSCLC [72-74]. Erlotinib demonstrated a survival benefit compared to placebo controls in the second- and third-line setting in unselected patients with advanced NSCLC, many of whom were PS 2 or 3; it also yielded a delay in symptomatic deterioration [75]. Bevacizumab in combination with standard chemotherapy (carboplatin and paclitaxel) proved superior to chemotherapy alone with a modest but statistically significant survival benefit in nonsquamous NSCLC and acceptable toxicity in good PS patients [76]. Finally, both erlotinib and pemetrexed have yielded survival benefits compared to placebo controls in the maintenance setting in patients who have responded or stabilized after 4 cycles of standard frontline platinum-based chemotherapy [77-79].

Aggressive palliative care also has an important role in the care of patients with metastatic disease. A randomized trial demonstrated that patients who received early palliative care in addition to standard oncologic care had improved QoL, less depression and anxiety, and improved survival, even though these patients tended to have less aggressive end-of-life care [80]. In short, chemotherapy and proactive, goal-directed noncytotoxic palliation such as focal radiation can each lead to prolonged survival and enhanced symptomatic control.

Summary

The treatment of patients with NSCLC with a poor-performance status remains a clinical challenge. The ACR Appropriateness Criteria Panel recommends:

- For early-stage disease, since surgical resection will be unlikely in this patient population, radiation therapy alone, preferably with modern techniques, such as SBRT, should be used.
- For patients with locally advanced stage disease (stage IIIA and IIIB) who are unable to tolerate surgery, concurrent chemoradiation therapy is the standard of care. If patients are unable to tolerate this treatment, either sequential chemoradiation or radiation therapy alone can be used.
- The dose of radiation therapy should be approximately 60 Gy for locally advanced disease.
- For patients with metastatic (Stage IV) disease, chemotherapy is the standard of care limited with palliative radiation therapy to a dose of approximately 30 Gy limited to symptomatic sites.
- Endobronchial brachytherapy is useful for patients with symptomatic endobronchial tumors.

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Evidence Table

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Clinical Condition: **Nonsurgical Treatment for Non-Small-Cell Lung Cancer: Poor Performance Status or Palliative Intent**

Variant 1: **66-year-old man with stage IIIB squamous cell carcinoma. Bulky mediastinal and supraclavicular disease. Twenty-five-pound weight loss and KPS 50.**

Treatment	Rating	Comments
EBRT alone	8	
Targeted/biologic therapy (ie, erlotinib) alone	4	
Chemotherapy alone	3	
Chemotherapy + RT	2	
Best supportive care alone	2	
Endobronchial brachytherapy alone	1	
External beam + brachytherapy	1	
Timing of Chemotherapy Relative to RT-if given		
Concurrent chemo/RT	1	
Concurrent chemo/RT followed by chemo	1	
Chemo followed by concurrent chemo/RT	1	
Chemo followed by RT	4	
Chemo followed by RT, followed by more chemo	3	
RT followed by chemo	7	Assume performance status improves.
Local Regional Radiation Therapy (RT alone)		
17 Gy/8.5 Gy fractions/1x week	2	
20-24 Gy/3-5 fractions	2	
30 Gy/10 fractions	5	
40 Gy/20 fractions	5	
45-50 Gy/25 fractions	5	
60-70 Gy/6-7½ weeks or biological equivalent	9	
74 Gy/7½ -8 weeks	3	
Treatment Planning Technique		
3D conformal RT	9	
2D radiation (AP/PA and/or off-cord obliques)	5	
SBRT	1	
Proton therapy	1	
IMRT	1	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Nonsurgical Treatment for Non-Small-Cell Lung Cancer: Poor Performance Status or Palliative Intent**

Variant 2: **76-year-old man with stage IIIB squamous cell carcinoma. Bulky mediastinal and supraclavicular disease. No weight loss and KPS 80. He received induction chemotherapy consisting of carboplatin and paclitaxel. Reimaging shows mediastinal tumor has increased in size 30% and supraclavicular node is stable.**

Treatment	Rating	Comments
Chemotherapy + RT	7	
EBRT alone	5	
Chemotherapy alone	2	
Endobronchial brachytherapy alone	1	
External beam + brachytherapy	1	
Best supportive care alone	1	
Timing of Chemotherapy Relative to RT-if given (following induction chemo)		
Concurrent chemo/RT	8	
Concurrent chemo/RT followed by chemo	5	
RT alone	2	
RT followed by chemo	2	
Local Regional Radiation Therapy (concurrent chemo/RT)		
17 Gy/8.5 Gy fractions/1x week	1	
20-24 Gy/3-5 fractions	1	
30 Gy/10 fractions	1	
40 Gy/20 fractions	1	
45-50 Gy/25 fractions	1	
60-70 Gy/6-7½ weeks or biological equivalent	9	
74 Gy/7½ -8 weeks	3	
Local Regional Radiation Therapy (RT alone)		
17 Gy/8.5 Gy fractions/1x week	1	
20-24 Gy/3-5 fractions	1	
30 Gy/10 fractions	1	
40 Gy/20 fractions	1	
40 Gy/10 fractions split course	1	
45-50 Gy/25 fractions	1	
54 Gy/1.5 Gy TID/12 days	5	
60-70 Gy/6-7½ weeks or biological equivalent	9	
74 Gy/7½ -8 weeks	5	
Treatment Planning Technique		
3D conformal RT	9	
2D radiation (AP/PA and/or off-cord obliques)	2	
SBRT	1	
Proton therapy	No Consensus	Promising strategy requiring more clinical studies.
IMRT	5	Tumor motion strategy required in addition to strict dosimetric criteria.

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Nonsurgical Treatment for Non-Small-Cell Lung Cancer: Poor Performance Status or Palliative Intent**

Variant 3: **55-year-old man with stage IV NSCLC, metastasis to bone and soft tissue. Dyspnea with symptomatic postobstructive pneumonia, fever, and central obstructing lesion (primarily extrinsic compression, 4-5 cm by CT). KPS 80.**

Treatment	Rating	Comments
Chemotherapy + RT	8	
EBRT alone	1	
Endobronchial brachytherapy alone	1	
External beam + brachytherapy	1	
Chemotherapy alone	3	
Best supportive care alone	1	
Timing of Chemotherapy Relative to RT-if given		
Concurrent chemo/RT	1	
Concurrent chemo/RT followed by chemo	1	
Chemo followed by concurrent chemo/RT	1	
Chemo followed by RT	3	
Chemo followed by RT, followed by more chemo	4	
RT followed by chemo	8	
Local Regional Radiation Therapy (RT alone)		
17 Gy/8.5 Gy fractions/1x week	4	
20-24 Gy/3-5 fractions	4	
30 Gy/10 fractions	8	
40 Gy/20 fractions	3	
45-50 Gy/25 fractions	1	
60-70 Gy/6-7½ weeks or biological equivalent	1	
74 Gy/7½ -8 weeks	1	
Treatment Planning Technique		
3D conformal RT	7	
2D radiation (AP/PA and/or off-cord obliques)	8	
SBRT	1	
Proton therapy	1	
IMRT	1	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Nonsurgical Treatment for Non-Small-Cell Lung Cancer: Poor Performance Status or Palliative Intent**

Variant 4: **68-year-old man with recurrent mediastinal and primary NSCLC after definitive radiation therapy 8 months ago (66 Gy/33 fractions). Now with hemoptysis, dyspnea and cough, and endobronchial tumor in LUL.**

Treatment	Rating	Comments
Endobronchial brachytherapy alone	8	
Chemotherapy + RT	5	
EBRT alone	4	
External beam + brachytherapy	4	Limited field.
Chemotherapy alone	1	
Best supportive care alone	1	
Timing of Chemotherapy Relative to RT-if given		
Concurrent chemo/RT	1	
Concurrent chemo/RT followed by chemo	1	
Chemo followed by concurrent chemo/RT	1	
Chemo followed by RT	1	
Chemo followed by RT, followed by more chemo	1	
RT followed by chemo	8	
Local Regional Radiation Therapy (External Beam RT alone)		
17 Gy/8.5 Gy fractions/1x week	1	
20-24 Gy/3-5 fractions	1	
30 Gy/10 fractions	3	
40 Gy/20 fractions	4	
45-50 Gy/25 fractions	1	
60-70 Gy/6-7½ weeks or biological equivalent	1	
74 Gy/7½ -8 weeks	1	
Treatment Planning Technique		
3D conformal RT	8	
2D radiation (AP/PA and/or off-cord obliques)	1	
SBRT	4	With more conventional fractionation.
Proton therapy	No Consensus	Promising strategy requiring more clinical studies.
IMRT	5	Tumor motion strategy required in addition to strict dosimetric criteria.

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Nonsurgical Treatment for Non-Small-Cell Lung Cancer: Poor Performance Status or Palliative Intent**

Variant 5: **62-year-old woman with widely spread stage IV NSCLC, KPS 80. No painful metastasis. No obstructive symptoms.**

Treatment	Rating	Comments
Chemotherapy alone	9	
Chemotherapy + RT	1	
EBRT alone	1	
Endobronchial brachytherapy alone	1	
External beam + brachytherapy	1	
Proton therapy	1	
Best supportive care alone	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		