Title

Surveillance imaging following definitive radiotherapy for non–small cell lung cancer: What is the clinical impact?

Journal

Seminars in Oncology, 44(5)

ISSN

0093-7754

Authors

Dyer, Brandon A

Daly, Megan E

Publication Date

2017-10-01

DOI

10.1053/j.seminoncol.2018.01.007

Peer reviewed

HHS Public Access

Author manuscript

Semin Oncol. Author manuscript; available in PMC 2019 February 09.

Published in final edited form as:

Semin Oncol. 2017 October ; 44(5): 303–309. doi:10.1053/j.seminoncol.2018.01.007.

Surveillance Imaging Following Definitive Radiotherapy for Non-Small Cell Lung Cancer: What is the Clinical Impact?

Brandon A. Dyer, MD[1] and **Megan E. Daly, MD**[1]

[1]University of California Davis Comprehensive Cancer Center, Department of Radiation Oncology, Sacramento, CA

Abstract

Lung cancer is the leading cause of cancer death worldwide. Recurrence rates at all stages are high, but evidence-based post-treatment surveillance imaging strategies to detect recurrence are poorly defined, and salvage options are frequently limited. A number of national and international oncology guidelines address post-treatment imaging, but are largely based on low-level, retrospective evidence due to a paucity of high quality data, particularly in regard to cost-effectiveness and quality-of-life endpoints. Given the lack of randomized data addressing appropriate surveillance imaging modality and interval following definitive treatment of lung cancer, there remains an unmet clinical need. Meaningful surveillance endpoints should include the financial impact, patient quality of life outcomes, and access-to-care issues associated with intensive follow up to ensure that guidelines reflect quality and sustainability. A need for prospective randomized data on the subject of imaging surveillance after definitive local therapy remains an unmet need, and an opportunity for collaboration and further research.

Keywords

Lung cancer; surveillance imaging; radiotherapy

Introduction

Worldwide, with an estimated 1.6 million deaths in 2012, lung cancer is the leading cause of cancer death in men and the second leading cause in women [1], and is the leading cause of cancer death in the United States for both men and women [2]. Non-small cell lung cancers (NSCLC) represent the vast majority of lung cancer cases, accounting for 85% of new lung cancer diagnoses [3]. Surgery is the preferred definitive treatment approach for medically fit,

Corresponding Author: Megan E. Daly MD, Department of Radiation Oncology, University of California, Davis, 4501 X Street, Sacramento, CA 95817, Phone: (916) 734-5428, Fax: (916) 703-5069, medaly@ucdavis.edu.

Disclosures/Conflicts of Interest:

B. Dyer: None

M. Daly: Research Funding, EMD Serono,

No other conflicts of interest to declare

early stage NSCLC patients, and for select locally advanced patients with low-volume disease and good performance status. Definitive radiation or chemoradiation is employed for medically inoperable, early stage NSCLC and for locally advanced disease not amenable to resection. At all stages of disease, recurrence rates are high, with a predominantly distant pattern of failure (Figure 1). Limited data address the optimal post-treatment surveillance approach, and most existing studies address post-operative, rather than post-radiation follow up.

Surveillance imaging with computed tomography (CT) following thoracic radiation is often a challenge to interpret, as high doses of radiation often cause extensive local fibrosis that may obscure or mimic local tumor recurrence [4], potentially resulting in additional – potentially unnecessary, or dangerous – medical procedures. Positron emission tomography (PET) can clarify equivocal CT findings for some patients [5], but post-radiation inflammation can cause increased FDG avidity, particularly in the first 6 months post-treatment [6], and the appropriate integration of PET into surveillance algorithms is poorly defined. Salvage options for recurrence lung cancer are often limited, as the predominant failure pattern for NSCLC remains distant [7–9] (Figure 1). However, rates of second primary lung cancers may be as high as 1-2% per year [10], and may be amenable to stereotactic radiation (SBRT) or other local therapies. Herein we review the available data pertaining to surveillance imaging after definitive treatment of NSCLC, with a focus on the post-radiation setting, and discuss the clinical impact on survival, subsequent interventions, cost, and quality-of-life.

Current Status of Surveillance Imaging Guidelines

Despite a paucity of high-level evidence, several national and international oncology societies and the National Comprehensive Cancer Network (NCCN) have generated guideline statements that include recommendations for post-treatment surveillance imaging, largely based on expert opinion [11–15]. Current NCCN guidelines recommend computed tomography (CT) of the chest every 6-12 months following definitive-intent treatment of lung cancer for 2 years, followed by annual low-dose non-contrast CT for patients who remain without evidence of disease [16]. Guidelines from the American Academy of Chest Physicians (AACP) suggest either chest x-ray or CT in combination with clinical examination every 6 months for 2 years post-treatment, while acknowledging the limited data supporting this recommendation [17]. Several other societies have also generated guidelines, as outlined in Table 1. Notably, no guidelines currently recommend the integration of positron emission tomography (PET) into the surveillance algorithm in the absence of suspicious CT or clinical findings.

Several patterns-of-care studies suggest broad variability in surveillance approaches in clinical practice. A study of 38 European cancer centers found marked variation in post-treatment initiation, frequency, and type of imaging used for locally advanced NSCLC (LA-NSCLC) patients treated with definitive intent [23]. A patterns-of-care survey from US-based radiation oncologists showed that, following SBRT for early stage NSCLC, almost a third of respondents obtain the first surveillance imaging within 6 weeks of treatment, while 45% wait 11 weeks or more, and 58% incorporate PET/CT [24]. Furthermore, many

cooperative group clinical trials within the United States in both the early and locally advanced settings specify post-treatment CT imaging on an every 3 month basis [25–27].

Post-Operative Surveillance

Most of the limited surveillance imaging data addressing disease control and survival impact has focused on the post-operative, rather than post-radiation setting (Table 2). Plain chest radiograph was often the predominant modality for post-treatment surveillance in early studies and yielded minimal benefit in asymptomatic patients. Walsh *et al* [28] reviewed the records of 358 patients (stage I – IIIB) with completely resected lung cancer from 1987-1991. Patients were evaluated for tumor recurrence or the development of a second primary tumor using plain chest radiograph. Recurrence ultimately developed in 135 patients (37%) with the predominant mode of failure distant (25.1%). Local-only failure occurred in 8.9%, and synchronous local and distant failure occurred in 3.6%. Of patients with recurrence, 76% presented with symptoms, and of the patients who were asymptomatic, chest radiograph diagnosed recurrence in 26 of 33 patients (79%). Of patients with asymptomatic recurrences detected radiographically, only 10 (2.8% of the total study population) were treated with curative intent. The authors conclude that monitoring surgical patients regularly is expensive and appears not to be cost-effective, thus radiographic follow-up of asymptomatic patients following pulmonary resections may be medically unnecessary.

Studies incorporating CT as part of post-treatment surveillance have shown conflicting results. Gourcerol *et al* retrospectively analyzed 162 post-operative lung cancer patients followed with chest radiograph every 3 months and CT of the chest and head, bronchoscopy, abdominal ultrasound, and bone scan every 6 months for three years [34]. The authors found that curative intent salvage therapy was attempted more frequently in patients with asymptomatic recurrence (41% versus 10%), and OS from time of recurrence was improved among asymptomatic versus symptomatic patients, 15.5 versus 7.2 months (p=0.001), respectively. Similarly, a French single-center prospective cohort study performed by Westeel *et al* [29] enrolled 192 patients with completely resected NSCLC from 1980-1993. Patients were followed with chest radiograph every 3 months and CT chest with bronchoscopy every 6 months for 3 years, followed by chest radiograph every 6 months and CT chest with bronchoscopy annually for an additional 4 years. 136 recurrences were identified with 63% detected on scheduled surveillance, and 37% identified clinically from symptoms. Recurrence was detected by CT in 30 patients (22%). Three-year OS was improved among asymptomatic versus symptomatic recurrences (31% versus 13%; p<0.001), and five patients remained candidates for definitive-intent salvage therapy for isolated locoregional disease. Detection of a second primary tumor was made in 22 patients (11%) during the follow up interval. However, in both the Westeel and Gourcerol studies, lead-time bias was not accounted for as a potential source of the noted survival advantage among asymptomatic recurrences.

To overcome this limitation, the French investigators subsequently initiated a randomized phase III trial through the Intergroupe Francophone de Cancerologie Thoracique (IFCT) evaluating the survival impact, quality of life, and cost-effectiveness of intensive surveillance imaging following surgery for stage I- IIIA NSCLC. Patients were randomized into 2

groups; group 1 received clinical examination and chest radiograph every 6 months for 2 years, then annually for 3 years, whereas group 2 received CT chest, abdomen and bronchoscopy every 6 months for 2 years, then annually for 3 years. Results for this study have not yet been presented.

In contrast, other studies suggest no survival impact from routine surveillance imaging in the post-operative setting. Lamont *et al* [30] retrospectively evaluated 124 patients with completely resected NSCLC followed with chest radiograph every 4 months for 2 years, then every 6 months thereafter, and diagnostic chest CT annually. The authors identified second primary lung cancers (SPLC) in 19 patients (15.3%) at a rate of 2.1% per year, and identified locoregional recurrences in nine patients (7.3%), only one of whom (0.8%) was treated with curative intent. The authors conclude that routine radiographic follow up allows for detection of early-stage SPLC which are potentially amenable to resection, but that locally recurrent lung cancers are infrequently amenable to curative-intent therapy. Furthermore, a population-based study by Backhas *et al* did not suggest a survival benefit from surveillance imaging [35]. The authors analyzed the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database to identify surveillance studies performed during a designated surveillance window of 4-8 months following surgery, and did not identify any difference in overall or lung cancer-specific survival between patients who underwent imaging during the window and those who did not. A systematic review by Srikantharajah *et al* published in 2012 identified a total of 5 available studies addressing the survival impact of CT surveillance following lobectomy for lung cancer [15]; three studies identified a survival benefit, while two did not. The authors concluded that the available evidence is “limited and contradictory”, and that “there is a need for a randomized controlled trial to assess the survival outcomes of patients followed up with a CT screening protocol versus a symptom-based follow-up.” Studies addressing surveillance imaging in the post-operative setting are summarized in Table 2.

Post-Radiotherapy Surveillance

Far fewer studies have specifically addressed the clinical impact of surveillance imaging following definitive radiation for NSCLC (Table 3). Radiation is typically used as a curative-intent treatment modality for both for early stage, medically inoperable NSCLC patients. Early stage, medically inoperable NSCLC patients are frequently treated with SBRT, an approach that employs 1-5 fractions of ablative-dose, conformal RT to the tumor. Following SBRT, in-field tumor control consistently exceeds 80% at 5 years [2] with predominantly regional and distant patterns of failure [36–38]. Patients with locally advanced, unresectable NSCLC are commonly treated with concurrent chemoradiation using conventional fractionation, with high rates of both locoregional and distant recurrence, and median survival of 16 to 29 months [39–43].

Unique to post-radiation surveillance, radiation-induced fibrosis markedly complicates detection of locoregional recurrence. Distinguishing recurrent tumor from treatment-related fibrotic lung changes on chest CT is difficult as the temporal course of recurrent disease and radiation-induced pulmonary fibrosis are similar, evolving over months to the first 2 years following treatment [37, 49]. In contrast with the linear pulmonary fibrosis seen in patients

treated with standard fractionation external beam lung radiation (1.8-2.0 Gy per treatment) the pattern of fibrosis following SBRT tends to be spherical due to the conformity of the radiotherapy treatment plans which, unfortunately, can mimic the appearance of disease recurrence (Figure 2) [49–51]. A body of literature has evaluated high-risk radiographic features indicative of recurrence as opposed to fibrosis following SBRT, including bulging margin [52, 53], craniocaudal growth [53], and opacity enlargement after 12 months [54]. However, very limited data have specifically evaluated the clinical and survival impact from the modality, timing, or frequency of radiographic surveillance following definitive radiation.

In the post-SBRT setting, Daly *et al* performed a single-institution retrospective analysis to evaluate the clinical impact of early, defined as within 6 months post-treatment, CT following SBRT for early stage NSCLC. The authors found that such early scans resulted in a curative-intent intervention in ~3% of patients, and conclude that initiating surveillance at 6 months may be sufficient [44]. Benamore *et al* retrospectively evaluated the survival impact of surveillance imaging frequency following radiation for locally advanced NSCLC. The authors identified a cohort of locally advanced NSCLC patients treated with radiation or chemoradiation enrolled on clinical trials and a matched cohort of 35 patients. The trial cohort underwent significantly more cross-sectional body imaging (average of 2.9 versus 2.0 scans per year) and CNS-directed imaging (1.1 versus 0.4 scans per year) for the first two years post-treatment. Despite more frequent imaging there was no significant difference in survival between the trial and non-trial cohort; however, more asymptomatic cancers were identified among trial patients, and these patients were more frequently offered curative-intent salvage therapies [45]. Ho *et al* evaluated the clinical impact of “frequent” cross-sectional imaging (defined as at least every 4 month) in a single institution retrospective cohort study of 63 patients treated with chemoradiation for locally advanced NSCLC. The authors found that frequent imaging detected asymptomatic recurrences in 60% of patients, but only 2 (3.2%) were candidates for definitive-intent treatment [46]. Van Loon *et al* performed a prospective cohort study designed to evaluate the clinical impact of the integration of PET/CT into post-radiation surveillance for locally advanced NSCLC. They enrolled 100 patients who underwent PET/CT at 3 months post-treatment. Eight cases of asymptomatic progression were identified by PET, none of which were visible by CT alone, and 3 were amenable to curative-intent salvage treatment [48].

Integration of PET/CT

As previously described, existing national and society guidelines do not recommend routine incorporation of PET/CT into surveillance algorithms, and limited data evaluate the ability of PET to improve salvage rates and survival following treatment of NSCLC. Among the limited data on this topic, in a single-center prospective cohort study from Korea by Choi *et al* [31], 358 patients with completely resected NSCLC tumors from 2005-2008 were evaluated for tumor recurrence and method of recurrence detection. Patients were evaluated clinically at 3 month intervals for 2 years, then at 6 month intervals for 3 years. CT chest with contrast was performed every 6 months for 2 years, followed by low-dose chest CT (LDCT) every 6 months thereafter, with PET/CT annually for 5 years. 111 patients (31%) recurred. Of the patients with recurrence, 25 cases were detected based on clinical suspicion

(23%), 35 cases were detected with LDCT (32%), and 51 cases were detected with integrated simultaneous PET/CT *and* LDCT (46%). Median survival following radiographically detected as compared to clinically detected recurrence was longer (3.6 versus 2.1 years; p = 0.002). For recurrences detected with simultaneous PET/CT *and* LDCT versus clinical suspicion *or* LDCT median survival was 3.8 versus 2.9 years (p=0.012), but there was no statistically significant survival difference identified between chest CT alone or PET/CT and chest CT. Overall, their data suggest that PET/CT may detect recurrence earlier, but do not clearly demonstrate a survival benefit to PET/CT.

Cost Considerations

Medical imaging spending comprises a substantial component of the United States healthcare budget, accounting for an estimated $10 billion USD 2012 [55]. Although further growth in imaging utilization has been curtailed over the past several years, emphasis is increasingly placed on establishing evidence-based guidelines that improve clinical outcomes to support use of costly diagnostic studies, such as the Choosing Wisely initiative from the American Board of Internal Medicine [56], or the American Society for Radiation Oncology clinical practice statements [57].

Among the limited studies to address the clinical impact of surveillance imaging, far fewer incorporate cost-effectiveness metrics. In the previously discussed Westeel study, the cost per year of life gained due to thoracic CT imaging (and bronchoscopy) was over $13,000 franc (FF) in 2000. However, it should be noted that the cost of this surveillance schedule in the United States is significantly more expensive than in France. For example, the authors quote a total procedural cost of $20 FF for a chest radiograph, $143-163 FF for a thoracic CT including the liver and adrenals, and $229 FF for bronchoscopy. On an annual basis for the proposed surveillance schedule the cost amounts to around $840 FF. To contrast this with 2017 Centers for Medicare and Medicaid Services a chest radiograph reimbursement (not billed cost) is $29 USD, CT chest is $247 USD, CT abdomen (to cover the liver and adrenals) is $249 USD, and bronchoscopy (depending on procedure location) is $246-1270 USD [58]. Calculated on an annual basis for the proposed surveillance schedule the US cost amounts to $1600-3650 – or 2 to 4 times greater than in France, bringing into question the economic feasibility and benefit of rigorous screening practices. In the more contemporary study by Gourcerol *et al* [34] from 2013, intensive imaging follow up including chest CT every 3 months, and CT brain and bone every 6 months for 3 years showed no difference in disease-free survival between symptomatic and asymptomatic recurrences; however, median overall survival was 7.2 versus 15.5 months (p=0.01) for the two groups, respectively, with a detailed cost analysis of €22,397 per life year gained ($29,745 USD over the same period). However, as previously noted the authors failed to account for lead-time bias as a source of the survival benefit identified with intensive surveillance.

Quality of Life Outcomes

There are no studies evaluating quality of life outcomes in the post-treatment (surgery or radiotherapy) setting as it pertains to surveillance imaging or aggressive post-treatment surveillance. It is important to note that psychologic distress in lung cancer patients is often

higher than in other types of malignancies and lung cancer patients may feel relatively increased disease stigmata, and subjective distress which can negatively impact help-seeking behavior and disease outcomes [59]. In a French phase III randomized trial by Denis *et al* [60] 121 patients with LA-NSCLC and without evidence of disease progression after initial treatment were randomized to web-based (internet) follow up with weekly self-scored symptoms, and with chest CT imaging scheduled every three to six months stratified by disease stage versus standardized clinical follow up and CT chest imaging at least every 3 months. If the patient-reported symptom score met a predefined criterion the oncologist was notified and further follow up/workup ensued. The primary outcome was OS. After a median follow up of 13 months the median OS was 19 months in the web-based group versus 12 months in the clinical control group (p=0.001). Interestingly, the authors note that imaging surveillance was performed less frequently in the web-based follow up versus the clinical follow up cohort. Additionally, the six-month mean change from baseline in the quality of life Functional Assessment of Cancer Therapy (FACT) scores demonstrated stable or improved scores in the web-based cohort with less intense surveillance imaging versus the clinical follow up cohort (80.6% versus 58.5%, p=0.04), respectively, and less deterioration in quality of life in the web-based cohort versus the clinical follow up cohort (19.4% versus 41.4%, p=0.04), respectively. This data raises the question whether quality of life was improved in the web-based cohort due to less frequent imaging surveillance. Overall, there is a dearth of high quality research in this area, presenting an opportunity for further research and discovery.

Conclusions

In aggregate, there remains a paucity of high-quality data assessing the optimal imaging modality, interval and duration of surveillance following definitive treatment of lung cancer, particularly in the post-radiation setting. A single prospective randomized control trial comparing conservative versus intensive surveillance imaging following surgical resection with or without neoadjuvant or adjuvant chemotherapy and/or radiation has not yet been published. The available retrospective cohort data regarding surveillance imaging are equivocal, and the financial impact and effects on patient quality of life are not well established. Additionally, the available surveillance schedules are largely based on weak, low- or very-low quality evidence, or moderate evidence for efficacy, but with limited clinical benefit. Furthermore, patients with early-stage NSCLC who are treated with definitive intent radiation remain at persistent risk of developing a SPLC at 3-6% per person years, suggesting the need for continued long-term screening for new malignancies [14].

The need for prospective randomized data addressing surveillance imaging after definitive local therapy remains an unmet need, and an opportunity for collaboration and further research. Important components of surveillance imaging analysis include the financial impact, patient quality of life outcomes, and access to care issues associated with intensive follow up – particularly as health care consumers, advocates, professional societies, and payers seek to bend the cost curve in cancer care while maintaining a high quality of care.

Acknowledgments

Dr. Daly is supported in part by the National Cancer Institute of the National Institutes of Health under Award Number K12CA138464. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Health.

References

1. American Cancer Society. Global Cancer Facts & Figures. 3rd. Atlanta: American Cancer Society; 2015.
2. DeSantis CE, et al. Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin. 2014; 64(4):252–71. [PubMed: 24890451]
3. Molina JR, et al. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc. 2008; 83(5):584–94. [PubMed: 18452692]
4. Dunlap NE, et al. Computed tomography-based anatomic assessment overestimates local tumor recurrence in patients with mass-like consolidation after stereotactic body radiotherapy for early-stage non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2012; 84(5):1071–7. [PubMed: 22898383]
5. Fischer B, et al. Preoperative staging of lung cancer with combined PET-CT. N Engl J Med. 2009; 361(1):32–9. [PubMed: 19571281]
6. McCurdy MR, et al. [18F]-FDG uptake dose-response correlates with radiation pneumonitis in lung cancer patients. Radiother Oncol. 2012; 104(1):52–7. [PubMed: 22578806]
7. Robinson CG, et al. Patterns of failure after stereotactic body radiation therapy or lobar resection for clinical stage I non-small-cell lung cancer. J Thorac Oncol. 2013; 8(2):192–201. [PubMed: 23287852]
8. Fournel P, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Francais de Pneumo-Cancerologie NPC 95-01 Study. J Clin Oncol. 2005; 23(25):5910–7. [PubMed: 16087956]
9. Kim TY, et al. A phase III randomized trial of combined chemoradiotherapy versus radiotherapy alone in locally advanced non-small-cell lung cancer. Am J Clin Oncol. 2002; 25(3):238–43. [PubMed: 12040280]
10. Johnson BE. Second lung cancers in patients after treatment for an initial lung cancer. J Natl Cancer Inst. 1998; 90(18):1335–45. [PubMed: 9747865]
11. Crabtree TD, et al. Does the method of radiologic surveillance affect survival after resection of stage I non-small cell lung cancer? J Thorac Cardiovasc Surg. 2015; 149(1):45–52. 53 e1–3. [PubMed: 25218540]
12. Erb CT, et al. Surveillance Practice Patterns after Curative Intent Therapy for Stage I Non-Small-Cell Lung Cancer in the Medicare Population. Lung Cancer. 2016; 99:200–7. [PubMed: 27565940]
13. Colt HG, et al. Follow-up and surveillance of the patient with lung cancer after curative-intent therapy: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013; 143(5 Suppl):e437S–e454S. [PubMed: 23649451]
14. Lou F, et al. Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. J Thorac Cardiovasc Surg. 2013; 145(1):75–81. discussion 81–2. [PubMed: 23127371]
15. Srikantharajah D, et al. Is computed tomography follow-up of patients after lobectomy for non-small cell lung cancer of benefit in terms of survival? Interact Cardiovasc Thorac Surg. 2012; 15(5):893–8. [PubMed: 22859511]
16. NCCN Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer Version 4.2016. 2016 [cited 2016 June 14].

17. Rubins J, et al. Follow-up and surveillance of the lung cancer patient following curative intent therapy: ACCP evidence-based clinical practice guideline (2nd edition). Chest. 2007; 132(3 Suppl):355S–367S. [PubMed: 17873180]
18. American Society of Clinical, O. et al. American Society of Clinical Oncology clinical practice guideline for the use of larynx-preservation strategies in the treatment of laryngeal cancer. J Clin Oncol. 2006; 24(22):3693–704. [PubMed: 16832122]
19. Jaklitsch MT, et al. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. J Thorac Cardiovasc Surg. 2012; 144(1):33–8. [PubMed: 22710039]
20. Vansteenkiste J, et al. 2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. Ann Oncol. 2014; 25(8):1462–74. [PubMed: 24562446]
21. National Institutes of Health: National Cancer Institute: Non-Small Cell Lung Cancer Treatment, version 3.2017. https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq#link/_48572_toc
22. National Comprehensive Cancer Network: NCCN Clinical Practice Guildelines in Oncology: Non-small cell lung cancer version 7.2017. http://www.nccn.com
23. Yumuk PF, et al. How do lung cancer specialists follow their patients with stage III non-small cell lung cancer (NSCLC) after definitive treatment? A short report. Eur J Cancer. 2012; 48(14):2163–5. [PubMed: 22633748]
24. Daly ME, Perks JR, Chen AM. Patterns-of-care for thoracic stereotactic body radiotherapy among practicing radiation oncologists in the United States. J Thorac Oncol. 2013; 8(2):202–7. [PubMed: 23222368]
25. NRG-LU002: Maintenance Systemic Therapy Versus Consolidative Stereotactic Body Radiation Therapy (SBRT) Plus Maintenance Systemic Therapy For Limited Metastatic Non-Small Cell Lung Cancer (NSCLC): A Randomized Phase II/III Trial. Available from: https://www.nrgoncology.org/Clinical-Trials/Protocol-Table
26. RTOG-1306: A Randomized Phase II Study of Individualized Combined Modality Therapy for Stage III Non-Small Cell Lung Cancer (NSCLC). Available from: https://www.nrgoncology.org/Clinical-Trials/Protocol-Table#
27. RTOG-1308: A Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-IIIB NSCLC. Available from: https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1308
28. Walsh GL, et al. Is follow-up of lung cancer patients after resection medically indicated and cost-effective? Ann Thorac Surg. 1995; 60(6):1563–70. discussion 1570–2. [PubMed: 8787445]
29. Westeel V, et al. Relevance of an intensive postoperative follow-up after surgery for non-small cell lung cancer. Ann Thorac Surg. 2000; 70(4):1185–90. [PubMed: 11081867]
30. Lamont JP, et al. Systematic postoperative radiologic follow-up in patients with non-small cell lung cancer for detecting second primary lung cancer in stage IA. Arch Surg. 2002; 137(8):935–8. discussion 938–40. [PubMed: 12146993]
31. Choi SH, et al. Positron emission tomography-computed tomography for postoperative surveillance in non-small cell lung cancer. Ann Thorac Surg. 2011; 92(5):1826–32. discussion 1832. [PubMed: 22051278]
32. Koike T, et al. Characteristics and timing of recurrence during postoperative surveillance after curative resection for lung adenocarcinoma. Surg Today. 2017
33. Karzijn R, et al. Post-treatment Surveillance for Stage I and II Non-small Cell Lung Cancer: Impact on Clinical Outcome. Anticancer Res. 2016; 36(10):5413–5418. [PubMed: 27798908]
34. Gourcerol D, et al. Relevance of an extensive follow-up after surgery for nonsmall cell lung cancer. Eur Respir J. 2013; 42(5):1357–64. [PubMed: 23520312]
35. Backhus LM, et al. Imaging surveillance and survival for surgically resected non-small-cell lung cancer. J Surg Res. 2016; 200(1):171–6. [PubMed: 26231974]
36. Chi A, 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. 2010; 94(1):1–11. [PubMed: 20074823]

37. Senthi S, et al. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. Lancet Oncol. 2012; 13(8):802–9. [PubMed: 22727222]
38. Timmerman R, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA. 2010; 303(11):1070–6. [PubMed: 20233825]
39. Schaake-Koning C, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. N Engl J Med. 1992; 326(8):524–30. [PubMed: 1310160]
40. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. BMJ. 1995; 311(7010):899–909. [PubMed: 7580546]
41. Dillman RO, et al. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. J Natl Cancer Inst. 1996; 88(17):1210–5. [PubMed: 8780630]
42. Pritchard RS, Anthony SP. Chemotherapy plus radiotherapy compared with radiotherapy alone in the treatment of locally advanced, unresectable, non-small-cell lung cancer. A meta-analysis. Ann Intern Med. 1996; 125(9):723–9. [PubMed: 8929005]
43. Sause W, 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. 2000; 117(2):358–64. [PubMed: 10669675]
44. Daly ME, Beckett LA, Chen AM. Does early posttreatment surveillance imaging affect subsequent management following stereotactic body radiation therapy for early-stage non-small cell lung cancer? Pract Radiat Oncol. 2014; 4(4):240–6. [PubMed: 25012832]
45. Benamore R, et al. Does intensive follow-up alter outcome in patients with advanced lung cancer? J Thorac Oncol. 2007; 2(4):273–81. [PubMed: 17409797]
46. Ho QA, Harandi NK, Daly ME. Clinical Impact of Frequent Surveillance Imaging in the First Year Following Chemoradiation for Locally Advanced Non-small-cell Lung Cancer. Clin Lung Cancer. 2017; 18(4):410–414. [PubMed: 28007410]
47. Ebright MI, et al. Positron emission tomography combined with diagnostic chest computed tomography enhances detection of regional recurrence after stereotactic body radiation therapy for early stage non-small cell lung cancer. J Thorac Cardiovasc Surg. 2013; 145(3):709–15. [PubMed: 23317944]
48. van Loon J, et al. Follow-up with 18FDG-PET-CT after radical radiotherapy with or without chemotherapy allows the detection of potentially curable progressive disease in non-small cell lung cancer patients: a prospective study. Eur J Cancer. 2009; 45(4):588–95. [PubMed: 19046631]
49. Dahele M, et al. Radiological changes after stereotactic radiotherapy for stage I lung cancer. J Thorac Oncol. 2011; 6(7):1221–8. [PubMed: 21623237]
50. Takeda A, et al. Possible misinterpretation of demarcated solid patterns of radiation fibrosis on CT scans as tumor recurrence in patients receiving hypofractionated stereotactic radiotherapy for lung cancer. Int J Radiat Oncol Biol Phys. 2008; 70(4):1057–65. [PubMed: 17905527]
51. Matsuo Y, et al. Evaluation of mass-like consolidation after stereotactic body radiation therapy for lung tumors. Int J Clin Oncol. 2007; 12(5):356–62. [PubMed: 17929117]
52. Halpenny D, et al. Computed tomographic features predictive of local recurrence in patients with early stage lung cancer treated with stereotactic body radiation therapy. Clin Imaging. 2015; 39(2): 254–8. [PubMed: 25571791]
53. Peulen H, et al. Validation of High-Risk Computed Tomography Features for Detection of Local Recurrence After Stereotactic Body Radiation Therapy for Early-Stage Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2016; 96(1):134–41. [PubMed: 27325481]
54. Huang K, et al. High-risk CT features for detection of local recurrence after stereotactic ablative radiotherapy for lung cancer. Radiother Oncol. 2013; 109(1):51–7. [PubMed: 23953413]
55. Commission, M.P.A. A Data Book: Health Care Spending and The Medicare Program. Jun.2014 [cited 2015 May 31].
56. Medicine, A.B.o.I. http://www.choosingwisely.org/. [cited 2015 June 2]
57. American Society for Radiation Oncology. https://www.astro.org/Clinical-Practice-Statements.aspx. [cited 2017 June 29]

58. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/PFS-Federal-Regulation-Notices-Items/CMS-1654-F.html. [cited 2017 June 30].

59. Chambers SK, et al. A systematic review of the impact of stigma and nihilism on lung cancer outcomes. BMC Cancer. 2012; 12:184. [PubMed: 22607085]

60. Denis F, et al. Randomized Trial Comparing a Web-Mediated Follow-up With Routine Surveillance in Lung Cancer Patients. J Natl Cancer Inst. 2017; 109(9)

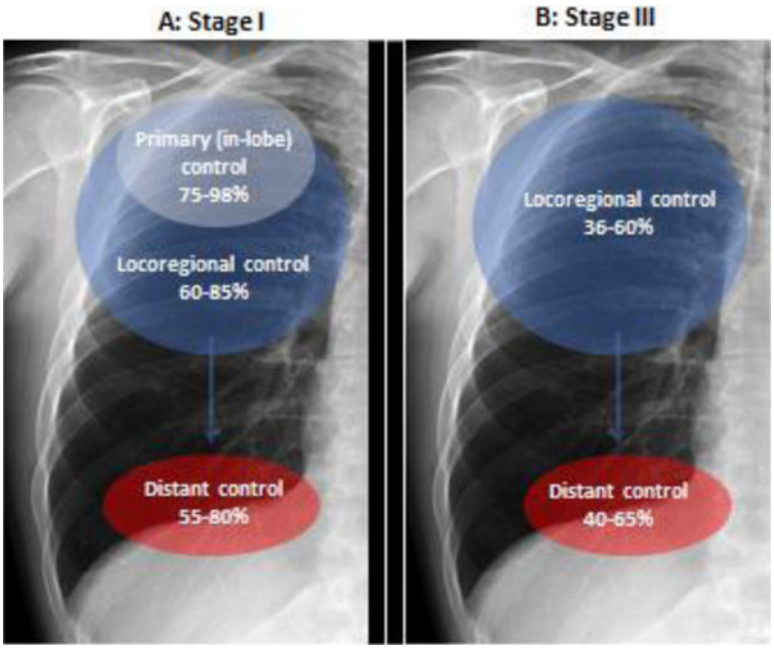

Figure 1.

Approximate 3-year patterns-of-failure for a) stage I and b) locally advanced nonsmall cell lung cancer

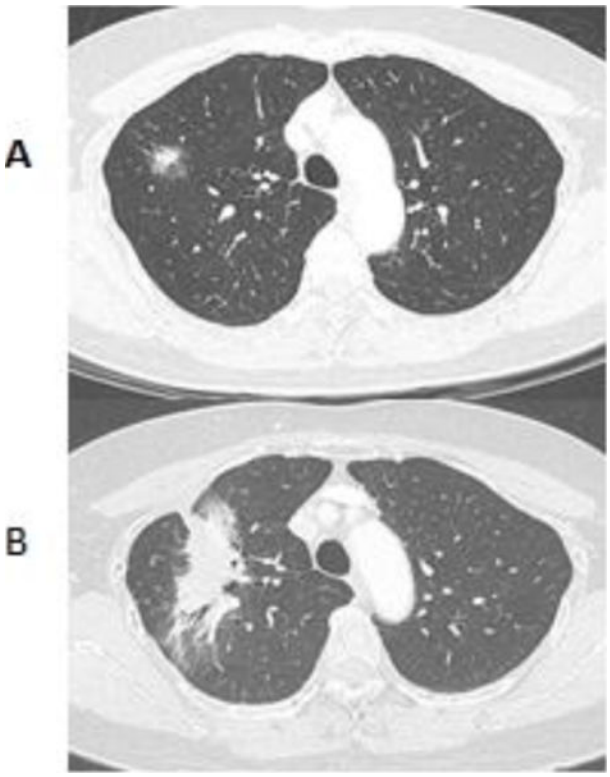

Figure 2.
Post-radiation consolidation and fibrosis often obscure treated tumors and may mimic recurrence. In panel A, aT1a NSCLC is shown. The tumor was treated to 54 Gy over 3 fractions. A 12 month post-treatment CT scan with extensive post-radiation consolidation is shown in panel B.

Table 1

Medical Society	Year	CT Screening Recommendation	Strength of Recommendation	PET Screening Recommendation	Strength of Recommendation
American Society of Clinical Oncology [18]	2003	None unless patient is symptomatic	–	Not recommended	–
American Association for Thoracic Surgery [19]	2012	q6m for 2-3 years, then annually through year 4, then lifelong annually	Moderate evidence of net benefit	–	–
American College of Chest Physicians [13]	2013	q6m for 2 years, then annually	Weak, low- or very-low quality evidence (Grade 2C)	Not recommended	Strong, low- or very-low-quality evidence
European Society of Medical Oncology [20]	2014	q6m for 2-3 years, then annually	Strong or moderate evidence for efficacy, but with a limited clinical benefit	Not recommended	Moderate evidence against efficacy or for adverse outcome, generally not recommended
National Institutes of Health [21]	2017	–	–	Not recommended	Strong, low- or very-low-quality evidence
National Comprehensive Cancer Network [22]	2017	q3-6m for 3 years, then q6m for 2 years, then annually	Low level evidence	Not recommended	Low level evidence

Table 2

Study	Year	Design	Patients (n)	Disease Setting	Surveillance Regimen	Impact of Surveillance
Walsh *et al* [28]	1995	Retrospective, single institution	358	Stage I-IIIB, surgically resected	CXR, variable schedule	2.8% asymptomatic recurrences treated with curative intent
Westeel *et al* [29]	2000	Prospective cohort, single institution	192	Stage I-IV, surgically resected	CXR q3m, CCT q6m, bronch q6m	3.7% recurrences treated with curative intent
Lamont *et al* [30]	2002	Retrospective, single institution	124	Stage I-III, surgically resected	CXR q4m × 2yr then q6m, CCT q12m, PET/CT if indicated	2.1% per year SPLC 0.8% recurrences treated with curative intent
Choi *et al* [31]	2011	Prospective cohort, single institution	358	Stage I-IIIA, surgically resected	CXR q3m × 2yr then q6m CCT q6m × 2yr then LDCCT q6m, PET/CT q1yr × 5	Improved MS if recurrence radiographically detected (3.6 vs 2.1 yrs)
Crabtree *et al* [11]	2015	Retrospective, single institution	554	Stage I, surgically resected	CXR or CCT q6m × 2-3yr then q12m	No difference in survival by imaging modality, or intent of treatment for subsequent intervention
Koike *et al* [32]	2017	Retrospective, single institution	485	Stage I-III, surgically resected	CCT q6-12m	No difference in survival based on imaging
Karzijn *et al* [33]	2016	Retrospective, single institution	73	Stage I-II	CXR or CCT	No difference in OS or PFS based on imaging
Gourcerol *et al* [34]	2013	Retrospective, single institution	162	Stage I-IV, surgically resected	CXR q3m, and CCT + bronch + AUS + BCT + bone scan q6m × 3yr, then annually	Improved survival with asymptomatic detection, 15.5 versus 7.2 months
Srikantharajah *et al* [15]	2012	Systematic literature review	–	Stage I-IV, surgically resected	Various	No OS difference based on imaging
Backhas *et al* [35]	2016	Retrospective SEER database review	18,406	Stage I-II, surgically resected	q4-8m × 2 years	No OS difference based on imaging

Abbreviations: AUS – abdominal ultrasound, BCT – brain computed tomography, bronch – bronchoscopy, CCT – chest computed tomography, combined failure – combination of synchronous local or locoregional or regional or distant recurrence, CXR – chest x-ray, DF – distant failure, LDCCT – low dose chest computed tomography, LRR – locoregional recurrence, MS – median survival, NS – not specified, NTF – no treatment failure, OS – overall survival, PET/CT – positron emission tomography/computed tomography, PFS – progression free survival, SEER – Surveillance, Epidemiology, and End Results, SPLC – second primary lung cancer, TF – treatment failure.

Table 3

Study	Year	Design	Patients (n)	Disease Setting	Surveillance	Impact of Surveillance
Daly *et al* [44]	2014	Retrospective, single institution	62	Early stage SBRT	CCT or PET/CT < 6 months after surgery	6.5% had treatment altered by early surveillance; 3.2% of those with recurrent disease treated with curative intent
Benamore *et al* [45]	2007	Retrospective, SWOG cancer trial database	75	Locally advanced CRT	Various CXR q3m CCT q6m × 3yr	No difference in time to relapse or SPLC based on imaging; 33% of subsequent cancers treated with curative intent
Ho *et al* [46]	2017	Retrospective, single institution	63	Locally advanced CRT	CCT < q4m	3.2% of recurrent disease treated with curative intent
Ebright *et al* [47]	2013	Retrospective, single institution	35	Early stage SBRT	PET/CT or CCT q3m × 2yrs	PET/CT improves sensitivity in detection of regional relapse with uncertain effect on survival
Van Loon *et al* [48]	2009	Prospective cohort, single institution	100	Stages I-IV, RT or CRT	PET/CT 3 months after the start of RT	3% of progressive disease amenable to treatment with curative intent

Abbreviations: CCT – chest computed tomography, CRT – chemoradiotherapy, PET/CT – positron emission tomography/computed tomography, RT – radiotherapy, SPLC – second primary lung cancer, SWOG – Southwest Oncology Group.