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Review

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# Radiotherapy in Lung Cancer: Current and Future Role

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**Abstract**

Lung cancer is divided into two subgroups concerning its natural course and treatment strategies as follows: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). In this review, for NSCLC, the role of stereotactic body radiation therapy (SBRT) in early-stage, chemoradiation in the locally advanced stage, post-operative radiotherapy for patients with high risk after surgery and radiotherapy for metastatic disease will be discussed. Also, for SCLC, the role and timing of thoracic irradiation and prophylactic cranial irradiation (PCI) for the limited and extensive stages will be discussed.

**Keywords:** Lung Cancer; Non-small cell lung cancer (NSCLC); prophylactic cranial irradiation (PCI); Small cell lung cancer (SCLC); stereotactic body radiation therapy (SBRT).

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Lung cancer is known to be the most commonly diagnosed cancer with high mortality and morbidity. Lung cancer is divided into two groups as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). These two groups should be seen as two different diseases concerning their clinical course. 80-85% of newly diagnosed lung cancer patients are NSCLC, and 15-20% is SCLC. According to Turkey cancer statistics in 2017, lung cancer is the first in cancer rate in men (52.5/100.000) and the fifth most common type of cancer in women (8.7/100000).

## 1-The Role of Radiotherapy in Non-Small Cell Lung Cancer

Non-small cell lung cancer (NSCLC), which forms the majority of lung cancers, consists of squamous cell cancer, adenocarcinoma and large cell cancers. Although surgical resection is curative in the group without severe concomitant disease at the early-stage, radiosurgery has taken its place as the standard treatment approach in patients with comorbid disease. However, this group covers only 30% of the patients.[1, 2] Radiotherapy can be applied as definitive in the group with local and regional advanced disease with no surgical chance, as neoadjuvant in the group that has the potential to have surgery and can be applied as adjuvant considering some risk factors after surgery.

Radiotherapy in metastatic disease is often used for palliative purposes, but radiosurgery may be an option for metastases in oligometastatic disease.

## 1A-Early Stage (I-II)

### Stereotactic Body Radiotherapy or Lung Radiosurgery

Radiosurgery, which was introduced to our practice by Swedish brain surgeon Lars Leksell in 1950, was first used in the treatment of brain lesions. With the development

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of technology in time, radiosurgery applications have become available in linac-based devices in the 1980s, and high-dose radiotherapy was started to be used in regions other than the brain. SBRT began to be applied for early stage lung tumors. American Society of Therapeutic Radiation Oncology (ASTRO) accepted the treatment of 1 to 5 fractions. The European group accepted the treatment of 1 to 8 fraction ablative doses as Stereotactic Body Radiotherapy (SBRT).

SBRT is the non-invasive application that has been reproduced with three-dimensional tomography planning, prepared with precision to a limited target volume with high fraction doses (7.5-34 Gy) in single or several fractions (1-5 fractions (USA), 1-8 fractions (Europe)). The difference from the intensity-modulated radiotherapy treatment is that the number of fractions is low, the fraction dose is high, and the total treatment time is short. Immobilization of the patient, respiratory movements, control and follow-up of tumor movement, accurate determination of target and application of treatment with the same accuracy in each fraction are important for treatment efficacy and normal tissue toxicity.

SBRT is more effective because high ablative doses are administered, and it is also radiobiologically more effective due to the high fraction doses. Good local control and survival rates have been shown in studies using at least 100 Gy biologically effective doses, taking into account normal tissue dose limitations in early-stage NSCLC.[3–6] SBRT is most commonly used in tumors less than 5 cm in size and located in the periphery.

Firstly, phase 1toxicity data, in which 37 patients were examined, was published by Timmerman et al., a pioneer of radiosurgery, in 2003. Only two patients had grade 3 toxicity. Subsequently, RTOG 0236 was initiated. Radiation Therapy Oncology Group (RTOG) 0236 study was a multicenter prospective study of 55 patients with early-stage inoperable NSCLC, and very valuable for SBRT. The three-year disease-free and overall survival rates were 48.3% and 55.8%, respectively, and the three-year primary tumor control and local control rates were 97.6% and 90.6%, respectively.[7, 8] Grade 3-4 toxicity rate was 16.3%.

In the Japanese Clinical Oncology Group study (JCOG0403), 100 inoperable patients were examined, and the three-year local control and survival rates were 87.3% and 59.9%, respectively.[9]

SBRT has been shown in many studies to have better local control and survival rates in early-stage inoperable cases than conventional RT.[10–13] In the prospective phase II "Stereotactic Precision and Conventional Radiotherapy Evaluation (SPACE)" study comparing conventional RT and SBRT, three-year overall survival (54% and 59%), progression-free survival (42% and 42%) and local control rates (86.4% and 85.7%) showed no difference, and both toxicity and disease progression were lower, although there were worse prognostic factors in SBRT cases.[14] In the randomized phase III Trans-Tasman Radiation Oncology Group (TROG) 09.02 CHISEL study, both overall and progression-free survival were much better in SBRT-treated inoperable cases, compared with conventional RT.[15]

SBRT provides similar results with less morbidity, especially when compared to elderly patients who underwent surgery.[16] The most common failure in SBRT is distant metastasis (10-20%), and regional lymph node recurrence (10-15%) and local recurrences are seen in 5-10%.[17]

SBRT is seen as a standard treatment in patients with early-stage NSCLC who are not suitable for surgery due to comorbid diseases or who refuse surgery, with higher overall survival and local control rates equivalent to lobectomy and higher than 3D conformal RT applications. It can be presented as an alternative treatment option to patients with cancer-related survival and local control results equivalent to sublobar resection, and in patients with a high surgical risk that cannot tolerate lobectomy.[10, 11, 13, 18–23]

One of the most important discussion topics today is whether SBRT may be an alternative treatment to surgery in early-stage medically operable patients. We do not have yet completed phase 3 randomized trials until now. The retrospective comparison of the results of lobectomy and SBRT series is not feasible. Because patient selection criteria are different. Patients who were performed surgery are usually younger, with better performance. The results cannot be compared in a healthy way since the patients who underwent surgery were staged pathologically, and the patients who underwent SBRT radiologically.

Retrospective and prospective Phase II studies report that similar local recurrence and survival rates can be achieved by both SBRT and surgery for operable stage I patients. Onishi et al. reported five-year local control rates in T1 and T2 tumors as 92% and 73%, and 5-year overall survival rates as 72% and 62%, respectively, in 87 patients with SBRT.[18] Lagerwaard et al.[24] reported the 3-year overall survival, local control, regional and distant failure rates as 85%, 93%, 9.7% and 9.7%, respectively, in 177 patients who underwent SBRT. In the prospective phase 2 study of Nagata et al.,[9] 3-year local control and overall survival rates in 64 operable cases were 85.4% and 76.5%, respectively. In the Phase II RTOG 0618 study, in 26 operable cases who had SBRT, the 2-year local failure rate was 19.2%, the regional failure rate was 11.7%, the progression-free survival rate was 65.4%, and overall survival rate was 84.4%.[25] Grade 4-5

toxicity was not reported in the studies.

Three-phase III prospective studies comparing SBRT with surgery in early-stage operable NSCLC have been initiated (STARS-NCT00840749, ROSEL-NCT00687986 and ACOSOG Z4099-NCT01336894), and these studies were closed early due to slow and inadequate patient intake. The results of STARS and ROSEL studies were published in a joint analysis by Chang et al.:[26] SBRT (31 patients) and lobectomy (27 patients) were compared in operable patients. While the STARS study included histological verification of NSCLC, there was no such condition in the ROSEL study. STARS study identified 54 Gy/3 fx, 60 Gy/5 fx for peripheral and central tumors, respectively. The three-year overall survival rate was found as significantly higher in favor of SBRT. Only peripheral tumors were included in the ROSEL study, and the fractionation scheme was determined as 54 Gy/3 fx or 60 Gy/5 fx. Of course, early closure of these studies causes a fewer number of patients, decreases statistical power, and weakens the comparison of the two treatment arms concerning survival, efficacy and toxicity. However, it supports the thesis that SBRT is an alternative to surgery in operable cases. The three-year survival rate of 95% obtained in this study is high compared to retrospective series. Lagerwaard et al. reported the 3-year survival rate as 85%, and Hamaji et al. reported it as 60.2%. Onishi et al. reported the 5-year survival rate as 72% for stage Ia tumors and 62% for Ib tumors in 80 cases treated with SBRT.[18, 24, 27]

Long-term results of SBRT equivalent to surgery have not been demonstrated in operable patients. Late recurrences have been reported more than five years after SBRT. Thus, close monitoring is important.[28] In Phase 3 randomized trials that are currently conducted; randomized POSTILV (NCT01753414) conducted in China, SABR-tooth (NCT02629458) conducted in the UK, randomized VALOR (NCT02984761) and multicentre STABLE-MATES (NCT02468024) conducted in the United States, RAXSIA (NCT03431415) conducted in Canada, were designed to compare the results of surgery and SBRT.

## 1B- Local Advanced Stage (II-III):

**Chemoradiotherapy (CRT):** Non-metastatic local advanced stage NSCLC accounts for 35% of all NSCLC.[29] Radiotherapy alone has been used in inoperable non small cell lung cancers without metastasis for many years; with the advances in systemic treatment, radiotherapy and chemotherapy have been started to be combined.

In a meta-analysis published by the Non-small Cell Lung Cancer Collaborative Group in 1995 (1780 cases, which reviewed 11 randomized trials), the addition of CT to RT provided a survival advantage in this patient group.[30] Cochrane meta-analysis showed that the concurrent use of platinum-based chemotherapy and radiotherapy has a survival advantage over consecutive chemo-radiotherapy.[31] After these results, the current approach to most of stage III diseases is CRT. Since the prognosis is good in T3N1 patients without mediastinal involvement, surgery is also available in these patients. Surgery is also recommended for T4N0-1 patients who are suitable for resection.[32]

Although CRT is the standard treatment for stage IIIA and IIIB disease that is not suitable for surgery, RT alone can be used as definitive in patients with poor performance and who cannot tolerate combined treatment. Although the contribution of thoracic RT to survival alone is limited, it seems to be effective in tumor-related symptom control and tumor control. RT effectiveness is associated with tumor volume.[33]

The main emphasis of many randomized studies and meta-analyses on the efficacy of combined CRT in locally advanced NSCLC is that CT or RT alone is not sufficient for survival and local control. Combined therapies have high survival and local success rates.[30–32]

There are randomized studies investigating the timing of chemotherapy and RT. One of these is the RTOG (610 patients) study; this is a comparison of concurrent CRT with sequential CRT contributions. In this study, the group who had concurrent CRT was found to be statistically significantly better in both median survival and 4-year survival (17 vs. 14.6 months, 4-year survival 21% vs. 12%).[32] Japan Clinical Oncology Group study (320 cases) showed a significant increase in median and overall survival with concurrent CRT in patients with locally advanced NSCLC. The treatment response rate was significantly higher in the CRT group (84% vs. 66%).[33] Concurrent use of CRT in locally advanced NSCLC has been accepted as the standard treatment approach due to disease control and its contribution to survival, although there are some increases in toxicity.[32] Another opinion on this issue supports simultaneous CRT administration following induction CT. In the CALGB 9431 phase II study, good results were obtained with concurrent RT with the 3rd cycle after two cycles of induction CT.[34] However, in the locally advanced multi-modality protocol (LAMP) phase II study, concurrent, concurrent post-induction CT, post-concurrent consolidative CT were compared, and the concurrent CRT/consolidative CT arm was found to be better.[35] In the CALGB phase III study, it was stated that toxicity increased with induction CT and there was no survival advantage.[36] Currently, the recommended treatment for locally advanced NSCLC is concurrent CRT or concurrent CRT/consolidative CT.

Immunotherapy has been studied in NSCLC as in many tu-

mor groups in recent years. The PACIFIC study compared placebo with Durvalumab added to standard chemoradiotherapy in stage III NSCLC, and the 2-year survival rate was significant in favor of Durvalumab with 55.6% and 66.3%. Immunotherapy should now be a part of standard treatment after these findings.[37]

in the study conducted by RTOG in 1970 group on effective RT dose and fractionation, 60 Gy was found to be significantly better in disease control.[38] In the studies conducted in the following years, no significant contribution of a dose higher than 60Gy was shown.[38]

60-66 Gy (1.8-2 Gy/fr) applied in 6-8 weeks in locally advanced NSCLC RT is now accepted as the standard procedure.[33]

**Neoadjuvant Chemoradiotherapy in Non-Small Cell Lung Cancer:** Mediastinal involvement is an important problem in operable stage IIIA disease. In patients with mediastinal N2 disease, 5-year survival is 5-10% with surgery alone or RT alone.[39] Low survival rates make pre-operative and post-operative treatment approaches important in this patient group. On the other hand, the high rate of local failure seen in patients receiving definitive CRT has suggested that the addition of surgery may contribute tumor control of these patients.

Preoperative therapies are preferred over postoperative therapies because of their contribution to tumor resectability, control of micrometastases, better tolerability by patients and completion of therapies. There may be disadvantages, such as delayed surgery, low efficacy in large tumors and the development of serious post-operative complications.[39] In studies, RT has taken place in concurrent applications with CT in preoperative treatment. Phase II studies on this subject have shown that neoadjuvant CRT contributes to survival.[40–42] However, the Intergroup 0139 phase III randomized trial did not show any contribution to survival.[38] In this study, resectable stage IIIA cases were divided into neoadjuvant CRT-Surgery and CRT arms. Disease-free survival significantly increased in the neoadjuvant CRT-surgical arm, but the increase in overall survival was not statistically significant.[43] In this study, mortality significantly increased in patients who underwent pneumonectomy, and the addition of neoadjuvant CRT in patients undergoing lobectomy was reported to have a contribution. Preoperative CRT studies suggest a concurrent CT with a total of 45 Gy RT of 1.8-2 Gy fractions.

**Post-operative Radiotherapy in Non-small Cell Lung Cancer (PORT):** Local failure and distant metastasis rates after NSCLC have led to the adjuvant treatment approach in this patient group. As a result of the meta-analysis published in 1998, the negative contribution of RT to survival led to a decrease in the post-operative RT approach in many centers.[38] However, when subgroup analyses are considered, RT leads to deterioration in survival in stage I and II patients, while the situation is not clear in stage III patients. Another important deficit is that in the studies included in the meta-analysis, RT techniques are mostly conventional.[44]

When we look at Surveillance, Epidemiology, and End Results database (SEER) and ANITA studies, RT shows survival advantage, especially in N2 disease.[38] A retrospective study of 224 patients with poor-risk factors after surgery showed multiple mediastinal involvements and Post-operative contribution of RT to survival in T3, T4 disease.[40] In surgical margin positivity, the risk of local recurrence is expected to be high; thus, PORT is conventionally recommended.[45, 46] It is thought that the efficacy of the resection margin in stage III disease is unclear because distant metastases are leading in this patient group.[47]

In summary, PORT is recommended in patients with N2 disease and positive surgical margins. Radiotherapy is recommended to be administered after adjuvant CT as a total of 50-54 Gy of 1.8-2 Gy fractions. In patients with positive surgical margins and residual tumors, definitive doses and postoperative application are recommended.[48]

**The Approach in Metastatic Disease:** In metastatic lung cancer, palliative radiotherapy for bones and palliative and curative radiosurgery for brain metastases are usually performed for pain palliation and fracture risk. More curative high-dose ablative treatments may be introduced in some patient groups. This approach comes into prominence, as life expectancy is higher in oligometastatic (1-3 metastasis) disease or adenocarcinomas with known mutations. In the COMET study, the contribution of SBRT to oligometastatic disease in different primary tumors, including NSCLC, was examined, ablative dose administration especially for metastasis in NSCLC provided progression-free survival and survival advantage.[49, 50]

## 2- The Role of Radiotherapy in Small Cell Lung Cancer

Small Cell Lung Cancer (SCLC) has a different treatment algorithm than other histological types with its rapid metastatic spread and good chemotherapy response. Thus, SCLC is considered a different disease. Two third of the cases are in the metastatic stage at admission; a high incidence of brain metastases caused the need to treat the brain, even if no metastases were detected at the beginning. These tumors are staged as limited-stage and extensive disease. Chemotherapy is the main treatment modality due to its rapid systemic spread potential and being a

chemotherapy-sensitive tumor. In this section, timing and dose prescription of radiotherapy and identifying optimal candidates for rt will be discussed.

## 2A- Limited Stage SCLC

The efficacy of radiotherapy has been known for many years in thoracic limited disease. The timing of chemotherapy and radiotherapy, the dose of radiotherapy and prophylactic cranial irradiation in these patients have been evaluated by randomized studies, and the standard has been determined today.

**Timing of Chemotherapy Radiotherapy:** In phase III randomized study examining whether radiotherapy was effective when applied concurrently with chemotherapy or after chemotherapy was completed, 308 patients were randomized into two arms, as one group of patients having thoracic irradiation concurrent with the second cycle of chemotherapy and as the other group of patients having thoracic irradiation at the end of six cycles. Chemotherapy was administered as alternating cisplatin etoposide and cyclophosphamide doxorubicin and vincristine, and radiotherapy was administered at 40 Gy in 15 fractions; 25 Gy prophylactic cranial irradiation was applied at 25 Gy in 10 fractions after chemotherapy was completed in cases with no progression. Median survival was 21 months in the early RT arm and 16 months in the late RT arm. 5-year survival rates were 20% and 11%. The standard approach after this study was the initiation of thoracic radiotherapy concurrent with the second cycle of chemotherapy.[51]

Another topic discussed in radiotherapy was the dose to be administered. In a randomized study by Turrisi et al. involving 417 patients, patients were randomized to receive thoracic radiotherapy at 45 Gy in 25 fractions (5 weeks) (Standard) and at 45 Gy in 30 fractions (2 fractions per day for 3 weeks) (BID), concurrent to the second cycle of CT. Prophylactic cranial radiotherapy was applied to both arms at the end of chemotherapy. Median survival was 19 months in the standard RT group and 23 months in the accelerated arm. 5-year survival rates were calculated as 16% and 26%.[52] Although these results have made accelerated radiotherapy the standard treatment, most centers were unable to routinely perform 2-fraction treatment on a day and 60-66 Gy 30-33 fraction RT was preferred. In parallel, randomized trials were conducted to confirm the accuracy of this practical situation. In the British CONVERT study, 547 patients from eight countries were randomized to 45 Gy BID and 66 Gy standard fractionation arms, and a median survival of 30 months in the BID arm and 25 months in the Standard 66 Gy arm was found. 5-year survival rates were 34% and 31%. Although there was no statistically significant difference between survival rates, the researchers emphasized that 45 Gy BID RT should be accepted as the standard since the study design predicted that 66 Gy RT would be better.[53] The CALGB study designed the study by randomizing into 2 arms as 45 Gy BID 70 Gy standard and 61.2 Gy (Concomitant boost (CB) 1.8 Gy/fr 5 weeks), but the CB arm was closed. The study continues to receive patients (NCT 00632853). According to the results of these studies, 45 Gy BID radiotherapy should be preferred if resources are convenient; otherwise 66 Gy RT should be applied.

Prophylactic cranial irradiation (PCI) has come up with the loss of patients due to intracranial failure, despite frequent brain metastasis in SCLC and systemic control in many cases. In 1999, Auperin et al.[54] conducted a meta-analysis of seven randomized trials using 987 individual patients data, which showed that when PCI was applied to patients under remission, 3-year survival was found to be 5.4% (15.3% and 20.7%) higher in patients undergoing PCI. In the same study, the findings showed that different doses of RT did not affect survival, but the incidence of brain metastasis decreased with the usage of higher doses. Mostly 25 gray in 10 fraction is in use. Good staging and improvements in systemic therapies in SCLC have increased survival rates in limited-stage disease. Cognitive impairment due to prophylactic cranial irradiation is becoming more prominent in patients who live longer in disease-free stage.[55] Two paths were followed to reduce cognitive impairment in whole-brain radiotherapy (WBRT): hippocampal-sparing cranial irradiation, and radiotherapy with memantine. RTOG 0933 phase II study showed that memory could be preserved with hippocampal protection.[56] On the other hand, a double-blind phase III randomized trial comparing the addition of memantine and placebo to WBRT showed that addition of memantine was effective in preserving cognitive function.[57] Both methods were demonstrated to prevent a certain degree of memory impairment, and this led to the design of a phase III randomized trial comparing the combined use of both methods. The early results of this study were presented at the ASTRO meeting in 2018. Whether hippocampal protection was added to 30 Gy WBRT+memantine or not compared in 518 patients with brain metastasis. Its contribution to the preservation of cognitive functions has been demonstrated without affecting disease control and regardless of patient age. The study on hippocampus protection in patients undergoing PCI in SCLC continues to recruit patients. In the light of these findings, sparing the hippocampus should be performed if conditions allow when PCI decision is taken. It should be kept in mind that memantine is also effective in preserving cognitive function, and its side effects are no different from placebo.

## 2B- Extensive-Stage Small Cell Lung Cancer

Chemotherapy is the main treatment for extensive-stage SCLC without a doubt. However, a need arises for palliative RT for both lung and metastases during the treatment process. Although RT is successful in symptom control under these conditions, no effect on survival was observed.

Thoracic radiotherapy, radiotherapy for metastases and PCI in patients with good response to chemotherapy have been investigated in randomized trials. Slotman et al. showed that 30 Gy radiotherapy in 10 fractions directed to the thorax had a positive effect on survival in patients who responded to chemotherapy. There are two randomized trials that tested PCI for extensive-stage patients with chemotherapy response. The first study is the Japanese study that randomized 163 patients and found that PCI reduced brain metastasis, but had no effect on survival. In the EORTC study, 286 patients were randomized according to whether they received PCI or not. The probability of brain metastasis was reduced in one year, PCI showed to improve survival. This study has been criticized given that patients were not evaluated by routine cranial MRI unless they were symptomatic. The Japanese study has a more accurate design to evaluate patients after staging and chemotherapy, but the sample size is not sufficient to show the difference in survival. Although the results seem to be contradictory, both studies confirm that the probability of developing brain metastasis in one year with PCI is reduced. Considering the difference in survival in the EORTC study, PCI should be recommended in patients with a good response to chemotherapy.

One of the important advances in the treatment of extensive-stage SCLC is the positive results of the addition of immunotherapy to chemotherapy. The addition of Atezoluzimab to standard chemotherapy in extensive-stage disease provides a 2-month absolute increase in median survival, indicating that immunotherapy will also be part of the treatment. However, its integration with radiotherapy is not yet clear.

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## References

1. Ihde DC. Chemotherapy of lung cancer. N Engl J Med 1992;327:1434–41.
2. Uzel EK, Abacıoğlu U. Treatment of early stage non-small cell lung cancer: surgery or stereotactic ablative radiotherapy? Balkan Med J 2015;32:8–16.
3. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94–100.
4. Grills IS, Hope AJ, Guckenberger M, Kestin LL, Werner-Wasik M, Yan D, et al. A collaborative analysis of stereotactic lung radiotherapy outcomes for early-stage non-small-cell lung cancer using daily online cone-beam computed tomography image-guided radiotherapy. J Thorac Oncol 2012;7:1382–93.
5. Liu F, Tai A, Lee P, Biswas T, Ding GX, El Naqa I, et al. Tumor control probability modeling for stereotactic body radiation therapy of early-stage lung cancer using multiple bio-physical models. Radiother Oncol 2017;122:286–94.
6. Stephans KL, Woody NM, Reddy CA, Varley M, Magnelli A, Zhuang T, et al. Tumor Control and Toxicity for Common Stereotactic Body Radiation Therapy Dose-Fractionation Regimens in Stage I Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2018;100:462–9.
7. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070–6.
8. Timmerman RD, Hu C, Michalski J, Straube W, Galvin J, Johnstone D, et al. Long-term results of RTOG 0236: A phase II trial of stereotactic body radiation therapy (SBRT) in the treatment of patients with medically inoperable stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2014;90:S30.
9. Nagata Y, Hiraoka M, Shibata T, Onishi H, Kokubo M, Karasawa K, et al. Prospective Trial of Stereotactic Body Radiation Therapy for Both Operable and Inoperable T1N0M0 Non-Small Cell Lung Cancer: Japan Clinical Oncology Group Study JCOG0403. Int J Radiat Oncol Biol Phys 2015;93:989–96.
10. Baumann P, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 2009;27:3290–6.
11. Shirvani SM, Jiang J, Chang JY, Welsh JW, Gomez DR, Swisher S, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. Int J Radiat Oncol Biol Phys 2012;84:1060–70.
12. Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. J Clin Oncol 2010;28:5153–9.
13. Widder J, Postmus D, Ubbels JF, Wiegman EM, Langendijk JA. Survival and quality of life after stereotactic or 3D-conformal radiotherapy for inoperable early-stage lung cancer. Int J Radiat Oncol Biol Phys 2011;81:e291–7.

14. Nyman J, Hallqvist A, Lund JÅ, Brustugun OT, Bergman B, Bergström P, et al. SPACE - A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. Radiother Oncol 2016;121:1–8.
15. Siva S, Kron T, Bressel M, Haas M, Mai T, Vinod S, et al. A randomised phase II trial of Stereotactic Ablative Fractionated radiotherapy versus Radiosurgery for Oligometastatic Neoplasia to the lung (TROG 13.01 SAFRON II). BMC Cancer 2016;16:183.
16. Brooks ED, Sun B, Zhao L, Komaki R, Liao Z, Jeter M, et al. Stereotactic Ablative Radiation Therapy is Highly Safe and Effective for Elderly Patients With Early-stage Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2017;98:900–7.
17. Senthi S, Lagerwaard FJ, Haasbeek CJ, Slotman BJ, Senan S. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. Lancet Oncol 2012;13:802–9.
18. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys 2011;81:1352–8.
19. Iyengar P, Westover K, Timmerman RD. Stereotactic ablative radiotherapy (SABR) for non-small cell lung cancer. Semin Respir Crit Care Med 2013;34:845–54.
20. Ettinger DS, Wood DE, Akerley W, Bazhenova LA, Borghaei H, Camidge DR, et al. Non-small cell lung cancer, version 1.2015. J Natl Compr Canc Netw 2014;12:1738–61.
21. Boily G, Filion É, Rakovich G, Kopek N, Tremblay L, Samson B, et al. Stereotactic Ablative Radiation Therapy for the Treatment of Early-stage Non-Small-Cell Lung Cancer: CEPO Review and Recommendations. J Thorac Oncol 2015;10:872–82.
22. Videtic GMM, Donington J, Giuliani M, Heinzerling J, Karas TZ, Kelsey CR, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. Pract Radiat Oncol 2017;7:295–301.
23. Guckenberger M, Andratschke N, Dieckmann K, Hoogeman MS, Hoyer M, Hurkmans C, et al. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. Radiother Oncol 2017;124:11–7.
24. Lagerwaard FJ, Verstegen NE, Haasbeek CJ, Slotman BJ, Paul MA, Smit EF, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2012;83:348–53.
25. Timmerman RD, Paulus R, Pass HI, Gore EM, Edelman MJ, Galvin J, et al. Stereotactic Body Radiation Therapy for Operable Early-Stage Lung Cancer: Findings From the NRG Oncology RTOG 0618 Trial. JAMA Oncol 2018;4:1263–6.
26. Chang JY, Senan S, Paul MA, Mehran RJ, Louie AV, Balter P, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol 2015;16:630–7.
27. Hamaji M, Chen F, Matsuo Y, Kawaguchi A, Morita S, Ueki N, et al. Video-assisted thoracoscopic lobectomy versus stereotactic radiotherapy for stage I lung cancer. Ann Thorac Surg 2015;99:1122–9.
28. Matsuo Y, Shibuya K, Nagata Y, Norihisa Y, Narabayashi M, Sakanaka K, et al. Preliminary report of late recurrences, at 5 years or more, after stereotactic body radiation therapy for non-small cell lung cancer. J Thorac Oncol 2012;7:453–6.
29. Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E, et al. Cancer statistics, 2004. CA Cancer J Clin 2004;54:8–29.
30. 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;311:899–909.
31. O'Rourke N, Roqué I Figuls M, Farré Bernadó N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev 2010:CD002140.
32. Ohe Y. Chemoradiotherapy for lung cancer. Expert Opin Pharmacother 2005;6:2793–804.
33. Basaki K, Abe Y, Aoki M, Kondo H, Hatayama Y, Nakaji S. Prognostic factors for survival in stage III non-small-cell lung cancer treated with definitive radiation therapy: impact of tumor volume. Int J Radiat Oncol Biol Phys 2006;64:449–54.
34. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 1999;17:2692–9.
35. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 1999;17:2692–9.
36. Akerley W, Herndon JE Jr, Lyss AP, Choy H, Turrisi A, Graziano S, et al. Induction paclitaxel/carboplatin followed by concurrent chemoradiation therapy for unresectable stage III non-small-cell lung cancer: a limited-access study-CALGB 9534. Clin Lung Cancer 2005;7:47–53.
37. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med 2018;379:2342–50.
38. Vokes EE, Herndon JE 2nd, Kelley MJ, Cicchetti MG, Ramnath N, Neill H, 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 2007;25:1698–704.
39. Sause W, Kolesar P, Taylor S IV, Johnson D, Livingston R, Komaki R, 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;117:358–64.

40. Anderson CS, Curran WJ. Combined modality therapy for stage III non-small-cell lung cancer. Semin Radiat Oncol 2010;20:186–91.
41. Albain KS, Rusch VW, Crowley JJ, Rice TW, Turrisi AT 3rd, Weick JK, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. J Clin Oncol 1995;13:1880–92.
42. Reddy S, Lee MS, Bonomi P, Taylor SG 4th, Kaplan E, Gale M, et al. Combined modality therapy for stage III non-small cell lung carcinoma: results of treatment and patterns of failure. Int J Radiat Oncol Biol Phys 1992;24:17–23.
43. Weitberg AB, Liu L, Yashar J, Glicksman AS. Twelve-year follow-up of trimodality therapy for stage IIIA non-small cell lung cancer. J Exp Clin Cancer Res 2001;20:335–40.
44. Albain KS, Swann RS, Rusch VW, Turrisi AT 3rd, Shepherd FA, Smith C, 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 2009;374:379–86.
45. PORT Meta-analysis Trialists Group. Postoperative radiotherapy for non-small cell lung cancer. Cochrane Database Syst Rev 2005:CD002142.
46. Matsuguma H, Nakahara R, Ishikawa Y, Suzuki H, Inoue K, Katano S, et al. Postoperative radiotherapy for patients with completely resected pathological stage IIIA-N2 non-small cell lung cancer: focusing on an effect of the number of mediastinal lymph node stations involved. Interact Cardiovasc Thorac Surg 2008;7:573–7.
47. Krupitskaya Y, Loo BW Jr. Post-operative radiation therapy (PORT) in completely resected non-small-cell lung cancer. Curr Treat Options Oncol 2008;9:343–56.
48. Wind J, Smit EJ, Senan S, Eerenberg JP. Residual disease at the bronchial stump after curative resection for lung cancer. Eur J Cardiothorac Surg 2007;32:29–34.
49. Abel S, Hasan S, Horne ZD, Colonias A, Wegner RE. Stereotactic body radiation therapy in early-stage NSCLC: historical review, contemporary evidence and future implications. Lung Cancer Manag 2019;8:LMT09.
50. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet 2019;393:2051–8.
51. Murray N, Coy P, Pater JL, Hodson I, Arnold A, Zee BC, 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 1993;11:336–44.
52. Turrisi AT 3rd, Kim K, Blum R, Sause WT, Livingston RB, Komaki 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 1999;340:265–71.
53. Faivre-Finn C, Snee M, Ashcroft L, Appel W, Barlesi F, Bhatnagar A, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol 2017;18:1116–25.
54. Aupérin A, Arriagada R, Pignon JP, Le Péchoux C, Gregor A, Stephens RJ, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in completeremission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 1999;341:476–84.
55. Simó M, Vaquero L, Ripollés P, Gurtubay-Antolin A, Jové J, Navarro A, et al. Longitudinal Brain Changes Associated with Prophylactic Cranial Irradiation in Lung Cancer. J Thorac Oncol 2016;11:475–86.
56. Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multiinstitutional trial. J Clin Oncol 2014;32:3810–6.
57. Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, et al; Radiation Therapy Oncology Group (RTOG). Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro Oncol 2013;15:1429–37.