ORIGINAL RESEARCH

DOI: 10.37047/jos.2023-95681

Impact of Adjuvant Chemotherapy in Patients with Medically Inoperable Non-Small Cell Lung Cancer Treated with Stereotactic Body Radiation Therapy

Ayşe KÖTEK SEDEF[a], Tanju BERBER[b], Özge KANDEMİR GÜRSEL[b], Necla GÜRDAL[b], Berna AKKUŞ YILDIRIM[b]

[a]Clinic of Radiation Oncology, Dr. Ersin Arslan Training and Research Hospital, Gaziantep, Türkiye
[b]Clinic of Radiation Oncology, Okmeydanı Training and Research Hospital, İstanbul, Türkiye

ABSTRACT Objective: To assess the treatment outcomes and impact of adjuvant chemotherapy on patients with early-stage medically inoperable lung cancer treated with stereotactic ablative radiosurgery (SABR). **Material and Methods:** The characteristics of 51 medically inoperable patients with lung cancer (T1–4 N0) who were treated with SABR and their response characteristics to the treatment were evaluated between June 2013 and June 2018. **Results:** The median patient age was 71 (range 48-86) years. Forty-three (84.3%) patients were men. Most patients had low-performance status (the Karnofsky Performance Scale 50-70), and 31 (60.8%) patients were aged above 65 years. The median tumor diameter was calculated as 32 (10-85) mm, and 29 (56.9%) patients had tumor diameters greater than 30 mm. The most common histology was squamous cell carcinoma (n=23, 45.1%). All patients received SABR treatment, and 12 (23.5%) patients received adjuvant chemotherapy. Disease-free survival could not be attained and overall survival (OS) was found at 32 (95% confidence interval, 21.2 to 42.8) months. Local recurrence was observed in only two (3.9%) patients. After SABR treatment, complete and partial responses were obtained in 35 (68.6%) and 15 (29.4%) patients, respectively. Significantly worse OS was observed in patients who received adjuvant chemotherapy compared to those who did not (16 and 40 months, respectively; and p=0.04). **Conclusion:** SABR treatment without chemotherapy could control the disease in individuals with low-performance status without any harmful side effects.

Keywords: Adjuvant chemotherapy; lung cancer; stereotactic body radiation therapy

The prognosis of lung cancer can be enhanced through numerous advancements that have been made in its treatment. One of the treatment modalities is stereotactic ablative radiosurgery (SABR), which is a standard of care for patients with early-stage lung cancer who are elderly or medically unable to undergo surgery.[1,2] Several studies have indicated that patients with non-metastatic lung cancer treated with SABR had a good rate of primary tumor control and overall survival (OS), little toxicity, and extremely cost-effective treatment that is higher than that of conventionally fractionated radiotherapy.[3-5] SABR is not superior to lobectomy in patients with operable early-stage non-small cell lung cancer (NSCLC); however, some prospective series have revealed comparable cancer-specific survival and OS.[6-9] Two randomized trials, STARS and ROSEL, compared SABR to surgery. In early-stage NSCLC patients, 3-year OS was reported to be in favor of SABR, which was 95% and 79%, respectively (p=0.037).[10] Thus, SABR is a reasonable alternative treatment modality to surgery; moreover, the NSCLC algorithm recommends it for patients with medically inoperable T1-3, N0, and M0 stage NSCLC.[11-14]

Based on the present randomized data, no clear consensus exists in the literature regarding the advantages of adjuvant therapy for patients with stage IB NSCLC. Most trials do not support its role in chemotherapy. The large studies that focused specifically on patients with early-stage IB NSCLC were JBR10 and CALGB 9633. Unlike late results, the standard modality for patients with stage IB, when earlier reported, was postoperative adjuvant chemotherapy.

Correspondence: Ayşe KÖTEK SEDEF
Clinic of Radiation Oncology, Dr. Ersin Arslan Training and Research Hospital, Gaziantep, Türkiye
E-mail: aysektk@hotmail.com

Peer review under responsibility of Journal of Oncological Sciences.

Received: 24 Jan 2023 ***Received in revised form:*** 23 Feb 2023 ***Accepted:*** 24 Feb 2023 ***Available online:*** 03 Mar 2023

In patients with early-stage NSCLC, SABR is one of the standard and effective modalities in node-negative T1-T3 tumors. However, studies depicting the patient groups that would benefit more from the addition of chemotherapy treatment to SABR according to specific tumor size in medically unfit or elderly populations are lacking. In our study, we investigated the relationship between tumor size and treatment outcomes in patients with lung cancer patients treated with SABR and adjuvant chemotherapy.

MATERIAL AND METHODS

This retrospective observational study aimed to determine the prognostic role of tumor diameter on survival parameters and chemotherapy decisions in patients with early-stage lung cancer treated with SABR. A total of 51 patients were included in the study from the Radiation Oncology and Medical Oncology Departments of our clinics between 2013 and 2022. The patients could not be surgery candidates and were staged as $T_{1-4}N0MO$. Tomography and positron emission tomography-computed tomography (CT) was used for staging. The patients with metastasis were excluded from the study. The patient electronic files were utilized for recording demographic features and treatment modalities. The tumor was histologically defined in 80% of patients, while only 20% had no tumor histology owing to poor Karnofsky Performance Scale (KPS), and even needle biopsy could not be performed. Twelve out of 51 patients received platinum-based chemotherapy after the radiotherapy period.

RADIATION THERAPY SPECIFICATIONS

Either a CyberKnife® (Accuracy Inc., Sunnyvale, CA, USA) radiosurgery system with 6-MV X-rays under respiratory gating or a Varian Trilogy linear accelerator platform with four-dimensional CT gating was utilized. In Cyberknife® patients, images from the inspirium and exprium were used to calculate gross tumor and internal target volumes for the x-site spine. Following the creation of kilovoltage orthogonal images, patients treated with x-site lung were monitored in real-time. The clinical target volume margin of 0.6 and 0.8 mm was used for squamous histologies and adenocarcinomas, respectively. Treatment was prescribed; therefore, 100% of the prescribed dose was received by 95% of the planning target volume (PTV). Approximately 90% of the dose was prescribed for 99% of PTV.

STATISTICAL DESIGN

OS was defined by the time from the date of death and the last control minus the first day of SABR and was analyzed using the Kaplan-Meier method. The significance level was set at $p<0.05$, and all significance levels were two-sided. The statistical analysis of this study was analyzed using IBM SPSS Statistics (version 22.0 IBM Corp., Armonk, NY), version 22 program.

ETHICAL APPROVAL

The Ethics committee was obtained from Okmeydanı Training and Research Hospital (approval number: 48670701-514.10) on May 08, 2018. All procedures performed were in accordance with the ethical standards of the 1964 Helsinki Declaration.

RESULTS

STUDY PATIENTS AND TREATMENTS

The median age of the patients was 71 (range 48-86) years. Forty-three (84.3%) patients were men, and eight (15.7%) were women. A total of 31 (60.8%) patients were aged above 65 years. Eleven (21.6%), 38 (74.5%), and 2 (3.9%) patients recorded KPS≤80, 50-70, and <40. All of our patients except four were heavy smokers with comorbid diseases. The median tumor diameter was 32 (10-85) mm, and 29 (56.9%) patients had a greater than 30 mm tumor diameter. Most patients were in T1 and T2 stages (n=20, 39.2%; and n=22, 43.1%, respectively). The most common histology was squamous cell carcinoma (n=23, 45.1%). Patient and tumor characteristics are demonstrated in Table 1. All patients received the SABR treatment, and 12 (23.5%) patients received adjuvant chemotherapy.

Chemotherapy was initiated for patients receiving chemotherapy 4-6 weeks after stereotactic body radiation therapy (SBRT). As a chemotherapeutic agent, carboplatin (area under the curve 6) and paclitaxel (175 mg/m^2) were often administered intra-

TABLE 1: Patient and tumor characteristics.

Characteristics	n (%)
Median age	71 (48-86) years old
Gender	
Men	43 (84.3)
Women	8 (15.7)
Age disturbition	
≤65	20 (39.2)
>65	31 (60.8)
Karnofsky performance status	
80-100	11 (21.6)
50-70	38 (74.5)
<40	2 (3.9)
Tumor diameter groups	
≤30 mm	22 (43.1)
>30 mm	29 (56.9)
T stages	
T1 tumor	20 (39.2)
T2 tumor	22 (43.1)
T3 tumor	3 (5.9)
T4 tumor	6 (11.8)
Tumor histology	
SCC	23 (45.1)
Adenocarcinoma	10 (19.6)
NSCLC	7 (13.7)
SCLC	1 (2)
Unknown	10 (19.6)
Imaging methods	
CT only	6 (11.8)
PET-CT only	14 (27.5)
Thorax MR	1 (2)
CT+PET-CT	30 (58.8)

SCC: Squamous cell carcinoma; NSCLC: Non-small cell lung cancer; CT: Computed tomography; PET: Positron emission tomography; MR: Magnetic resonance.

venously in four cycles every 21 days. However, less frequently, Etoposide 120 mg/m^2 for 1-3 days (max: 200 mg) one, two, and third days; cisplatin 80 mg/m^2 was administered for four cycles every 3 weeks only on the first day. On the eighth day after chemotherapy, neutrophil and platelet counts were measured, and non-hematological side effect controls were performed. If the patient could not tolerate chemotherapy after the first course or during chemotherapy, he was excluded from the chemotherapy group.

RADIOTHERAPY INFORMATION

Doses were 56 Gy in eight fractions in those with ultra central tumors, while they varied between 54 and 60 Gy in three fractions in peripheral tumors. All our BED_{10} doses were between 60 (1 fx 20 Gy-3 fx 30 Gy) and 180 Gy (60 Gy/3frx). BED_3 value was between 130 and 480 Gy. Seventeen (35.4%) patients were with BED_{10} 100 and below. Our patients were examined for local control, survival rates, and the detailed causes of death in ex-patients that might have affected survival.

TREATMENT OUTCOMES

Twenty-nine patients (56.9%) died during the median follow-up period of 22 months. Disease-free survival (DFS) was not attained, and OS was 32 (95% confidence interval, 21.2 to 42.8) months for the whole group (Figure 1, Figure 2). The 30th-and 90th-day

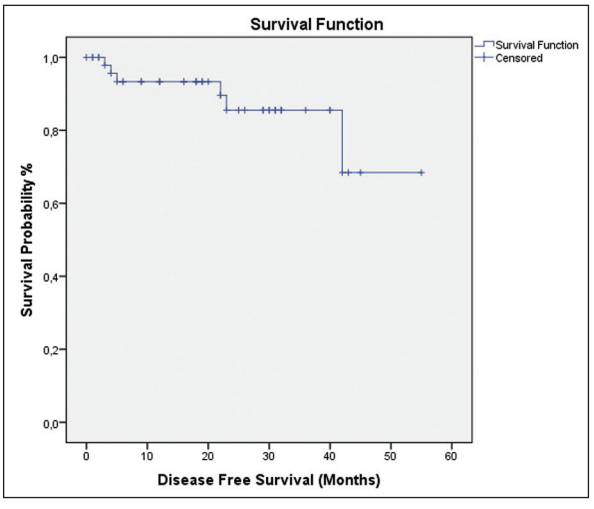

FIGURE 1: Kaplan-Meier estimates of disease free survival (DFS) of the whole patient cohort.

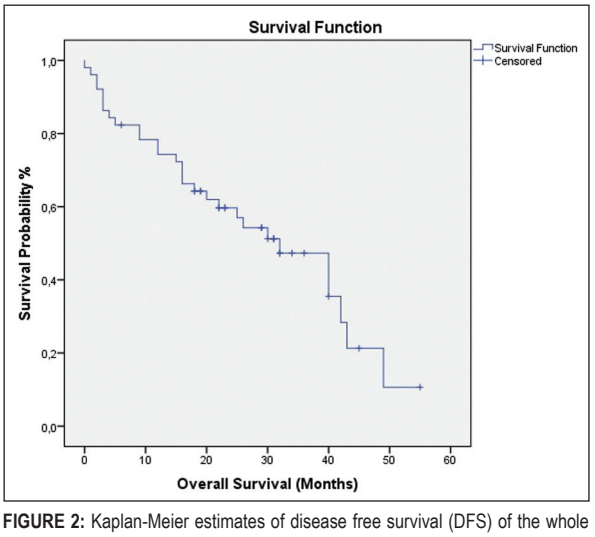

FIGURE 2: Kaplan-Meier estimates of disease free survival (DFS) of the whole patient cohort.

mortality was 4.1% and 12.5%, respectively. However, mortality associated with the disease was 4.1% in the third month. Another 8.4% of patients died owing to the comorbidities that caused them to be inoperable. After SABR treatment, complete, partial, and no responses were obtained in 35 (68.6%) patients, 15 (29.4%) patients, and 1 (2%) patient, respectively. Local recurrence was observed in only 2 (3.9%) patients, and distant metastases developed in 6 (11.8%) patients during follow-up. Intrapulmonary, brain and bone, and liver metastases were observed in 4 (2.7%), 1 (0.7%), and 1 (0.7%) patient, respectively. Treatment and outcomes are shown in Table 2.

In terms of median DFS, no significant difference was observed between patients with tumor diameters below and above 3 cm (NA vs. NA, respectively, and p=0.86). The median DFS and radiation BED_{10} values did not differ in a significant manner (NA and 42 months, respectively, and p=0.71). In terms of DFS, no significant difference was observed between the age groups (p=0.47). There was no discernible difference in DFS between individuals who received chemotherapy and those who did not (22 months and NA, respectively, and p=0.13). Relationships with DFS are shown in Table 3.

There was a difference in OS between patients with a tumor diameter of less than and above 3 cm; however, it was not statistically significant (42 and 26 months, respectively, and p=0.28) (Figure 3). No significant difference in median DFS and radiotherapy BED_{10} values was observed (32 and 30 months, respectively, and p=0.79). There was a difference in OS between age groups; however, it was not significant (16 and 32 months, respectively, and p=0.47). In patients who received adjuvant chemotherapy, the OS results were significantly worse compared to those who did not (16 and 40 months, respectively, and p=0.04) (Figure 4). Survival outcomes were worse for patients who received chemotherapy in those with tumors larger than 3 cm than for those who did not (16 and 40 months, respectively, p=0.04) (Figure 5).

ADVERSE EVENTS

In general, the SABR was well tolerated by our patients; however, those with peripheral localization tumors who received 60 Gy radiotherapy in three fractions had painful rib fractures and peripheral sensory neuropathies (12.5% in six patients) (Grade 2-3).

TABLE 2: Treatment and outcomes.

Characteristics	n (%)
Radiotherapy dose, Gy	60 (20-60)
BED_{10}, Gy	180 (60-180)
BED_3, Gy	460 (130-460)
BED_{10} groups	
≤100	18 (35.3)
>100	33 (64.7)
First response of SABR	
Complete response	35 (68.6)
Partial response	15 (29.4)
No response	1 (2)
Adjuvant chemotherapy	
Yes	12 (23.5)
No	39 (76.5)
Locally recurrence	
Yes	2 (3.9)
No	49 (96.1)
Distant metastasis	
Yes	6 (11.8)
No	45 (88.2)
Final status	
Died	29 (56.9)
Alive	22 (43.1)

SABR: Stereotactic ablative radiosurgery.

TABLE 3: Relationship between treatment and clinical features with survival parameters.

	Median OS		Median DFS	
Variables	Months	p value	Months	p value
Age		0.46		0.47
≤65	16		NA	
>65	32		NA	
Tumor diameter		0.28		0.86
≤30 mm	42		NA	
>30 mm	26		NA	
BED_{10} groups		0.79		0.71
≤100	32		NA	
>100	30		42	
Chemotherapy		**0.04**[a]		0.13
Yes	16		22	
No	40		NA	
First response		0.14		
Complete response	40			
Partial response	22			

[a]Statistically significant; OS Overall survival; DFS: Disease free survival.

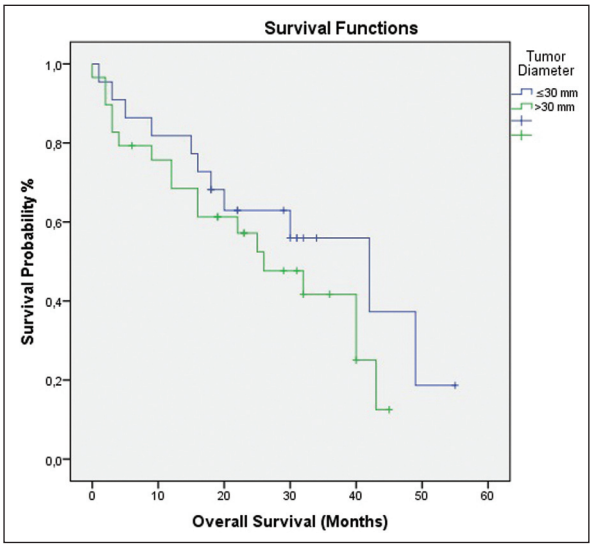

FIGURE 3: Comparison of the OS according to tumor diameter.

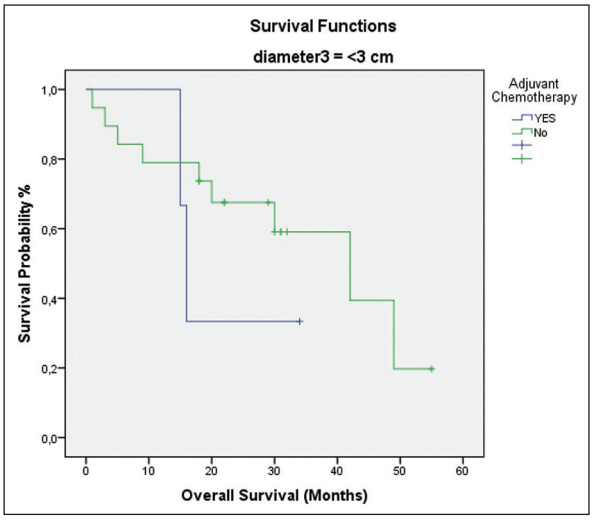

FIGURE 5: Comparison of the OS according to receiving CT whose tumor diameter <3 cm.

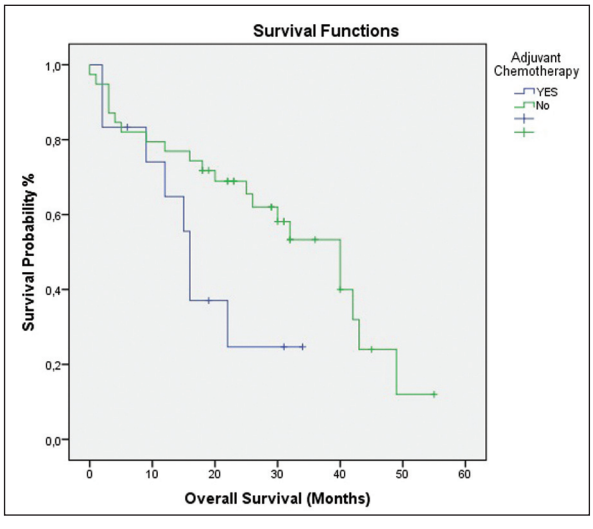

FIGURE 4: Comparison of the OS according to receiving Chemotherapy.

Additionally, radiologically asymptomatic Grade 1 radiation pneumonia was observed in 15 (31%) patients. No toxicity of Grade 4 and above was observed in our patients. No late toxicity associated with BED_3 values developed.

DISCUSSION

In our study, the patients with tumors larger than 3 cm and treated with adjuvant chemotherapy had worse OS rates than those who did not receive chemotherapy. Additionally, no significant relationship was detected between DFS and age, tumor diameter, BED_{10} values, and chemotherapy administration in our cohort. Patients with tumors less than 3 cm had better survival than those with larger diameter tumors; however, it was not statistically significant. There was found no significant relationship between OS and age or BED_{10} values.

In the early stages of medically inoperable patients, radiosurgery applications are considered standard treatment modalities.[15] Two randomized trials, "STARS and ROSEL," compared lobectomy with SABR, and 3-year OS was reported to be in favor of SABR at 95% and 79%, respectively (p=0.037).[10] SABR has outperformed routinely fractionated RT in terms of primary tumor control rates and OS rates regardless of tumor size.[5] In the Phase 3 TROG 09.02 CHISEL trial, in patients with stage 1 (T1-T2A) (<3 cm tumor) NSCLCs, when SABR was compared to conventional radiation, the former produced greater local management of the primary disease without increasing severe toxicity.[16] In our study, the survival results of Stage 1 (<3 cm tumor) patients were better, and local control rates were consistent with the literature. Moreover, there was no difference in DFS in tumors larger than 3 cm.

In a retrospective review of more than 5,000 patients with resected early-stage NSCLCs, Eguchi et al. detected a higher rate of non-cancer mortality, especially in those aged above 75 years.[17] This was stated as the leading cause of death for the first year after treatment. The most frequent reason for death

was found to be a cardiopulmonary disease in the first 90 days after the surgery. In our study, the median age of the patients was 71, and mortality associated with the disease was 4.1% in the third month. Another 8.4% of patients died owing to the comorbidities that caused them to be inoperable.

Uncertainties regarding adjuvant chemotherapy treatment after SBRT are observed in early-stage lung cancers. Several studies have detected that patients with early-stage NSCLCs who received surgery or SBRT had similar and long OS and cancer-specific survival.[6-9] In our study, the median follow-up time was 22 months, and OS was 32 months in accordance with the literature. Ernani et al. found that SBRT followed by adjuvant chemotherapy was associated with a better OS than SBRT alone in patients with tumors 4 cm or larger.[18] However, the survival advantage could not be demonstrated in our study, in patients who received chemotherapy and had tumors larger than 3 cm. The ANITA study demonstrated a relationship between tumor diameter and the need for adjuvant chemotherapy.[19] The use of adjuvant chemotherapy for patients with stage IB disease was supported by the JBR10 and CALGB 9633 studies, unlike the late-stage results in their first report in those with early-stage. There is no comprehensive randomized study with patients who need adjuvant therapy in the post-SABR period. However, none of these studies included patients receiving SABR. In our study, the OS rates of the patients who received chemotherapy were found to be significantly lower than those who did not receive chemotherapy. The result depicts that chemotherapy can be avoided in patients with low clinical performance status, even if they have locally advanced diseases. Additionally, SABR has a very low side effect profile, and the treatment safety profile was also good in our study.

There are several limitations to this study. First, it was a retrospective study with a diverse patient population. Second, the sample size was small, and factors that were significantly associated with outcomes here might be important in a larger population. In our study, the median follow-up time for patients treated with SBRT was 22 months, which might have been insufficient to detect some complications.

CONCLUSION

The SABR treatment without the addition of chemotherapy offers excellent local control in early-stage lung cancer patients with a low side effect profile.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ayşe Kötek Sedef, Berna Akkuş Yıldırım;* ***Design:*** *Ayşe Kötek Sedef, Necla Gürdal;* ***Control/Supervision:*** *Berna Akkuş Yıldırım;* ***Data Collection and/or Processing:*** *Ayşe Kötek Sedef, Necla Gürdal, Tanju Berber;* ***Analysis and/or Interpretation:*** *Ayşe Köstek Sedef, Özge Kandemir Gürsel;* ***Literature Review:*** *Özge Kandemir Gürsel, Tanju Berber;* ***Writing the Article:*** *Ayşe Kötek Sedef, Berna Akkuş Yıldırım;* ***Critical Review:*** *Berna Akkuş Yıldırım, Tanju Berber;* ***References and Fundings:*** *Ayşe Kötek Sedef, Necla Gürdal;* ***Materials:*** *Necla Gürdal, Özge Kandemir Gürsel.*

REFERENCES

1. Timmerman R, Paulus R, Galvin J,et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA.2010;303(11):1070-1076. [Crossref] [PubMed] [PMC]
2. NCCN Clinical Practice Guidelines in Oncology. NonSmall Cell Lung Cancer(NSCLC) Version 2.2021-December 15-2020. [Link]
3. Louie AV, Rodrigues GB, Palma DA,Senan S. Measuring the population impact of introducing stereotactic ablative radiotherapyfor stage I non-small cell lung cancer in Canada. Oncologist. 2014;19(8):880-885. [Crossref] [PubMed] [PMC]
4. Chang JY, Liu H, Balter P, et al.Clinical outcome and predictors of survival and pneumonitis after stereotactic ablativeradiotherapy for stage I non-small cell lung cancer. Radiat Oncol. 2012;7:152. [Crossref] [PubMed] [PMC]
5. BD Smith, Jiang J, Chang JY. etal. Cost-effectiveness of stereotactic radiation, sublobar resection, and lobectomy forearly non-small cell lung cancers in older adults. J Geriatr Oncol. 2015;6(4):324-31. [Crossref] [PubMed] [PMC]
6. Gjyshi O, Xu T, Elhammali A, etal. Toxicity and survival after intensity-modulated proton therapy versus passive scatteringproton therapy for NSCLC. J Thorac Oncol. 2021;16(2):269-277. [Crossref] [PubMed] [PMC]
7. Guckenberger M, Andratschke N,Alheit H, et al; Deutschen Gesellschaft für Radioonkologie (DEGRO). Definition ofstereotactic body radiotherapy: principles and practice for the treatment of stage Inon-small cell lung cancer. Strahlenther Onkol. 2014;190(1):26-33. [Crossref] [PubMed] [PMC]
8. Baumann P, Nyman J, Hoyer M, etal. Outcome in a prospective phase II trial of medically inoperable stage I non-small-celllung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol.2009;27(20):3290-3296. [Crossref] [PubMed]
9. Shultz DB, Filippi AR, Thariat J,et al. Stereotactic ablative radiotherapy for pulmonary oligometastases and oligometastaticlung cancer. J Thorac Oncol. 2014;9(10):1426-1433. [Crossref] [PubMed]
10. Chang JY, Senan S, Paul MA, etal. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-celllung cancer: a pooled analysis of two randomised trials. Lancet Oncol. 2015;16(6):630-637.Erratum in: Lancet Oncol. 2015;16(9):e427. [Crossref] [PubMed] [PMC]
11. Handforth C, Clegg A, Young C, etal. The prevalence and outcomes of frailty in older cancer patients: a systematic review.Ann Oncol. 2015;26(6):1091-1101. [Crossref] [PubMed]
12. Nagata Y, Hiraoka M, Shibata T,et al. Stereotactic body radiation therapy for T1N0M0 non-small cell lung cancer: firstreport for inoperable population of a phase II trial by Japan Clinical Oncology Group (JCOG0403). International Journal of Radiation Oncology*Biology*Physics 2012;84(3):S46. [Crossref]
13. Widder J, Postmus D, Ubbels JF,Wiegman EM, Langendijk JA. Survival and quality of life after stereotactic or 3D-conformalradiotherapy for inoperable early-stage lung cancer. Int J Radiat Oncol Biol Phys.2011;81(4):e291-297. [Crossref] [PubMed]
14. Rusthoven CG, Kavanagh BD, Karam SD. Improved survival with stereotacticablative radiotherapy (SABR) over lobectomy for early stage non-small cell lung cancer(NSCLC): addressing the fallout of disruptive randomized data. Ann Transl Med.2015;3(11):149. [PubMed] [PMC]
15. Palma D, Senan S. Stereotacticradiation therapy: changing treatment paradigms for stage I nonsmall cell lung cancer. CurrOpin Oncol. 2011;23(2):133-139. [Crossref] [PubMed]
16. Ball D, Mai GT, Vinod S, et al;TROG 09.02 CHISEL investigators. Stereotactic ablative radiotherapy versus standardradiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3,open-label, randomised controlled trial. Lancet Oncol. 2019;20(4):494-503. [Crossref] [PubMed]
17. Eguchi T, Bains S, Lee MC, et al.Impact of increasing age on cause-specific mortality and morbidity in patients with stage inon-small-cell lung cancer: a competing risks analysis. J Clin Oncol. 2017;35(3):281-290. [Crossref] [PubMed] [PMC]
18. Ernani V, Appiah AK, Marr A, etal. Adjuvant systemic therapy in patients with early-stage NSCLC treated with stereotacticbody radiation therapy. J Thorac Oncol. 2019;14(3):475-481. [Crossref] [PubMed]
19. Douillard JY, Rosell R, De LenaM, et al; Adjuvant Navelbine International Trialist Association. Impact of postoperativeradiation therapy on survival in patients with complete resection and stage I, II, or IIIAnon-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant NavelbineInternational Trialist Association (ANITA) Randomized Trial. Int J Radiat Oncol Biol Phys.2008;72(3):695-701. [Crossref] [PubMed]