REVIEW ARTICLE

Stereotactic Body Radiotherapy for Early-Stage Lung Cancer: A Review and Update

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ABSTRACT

The prevalence of lung cancer as of the elderly has been increasing parallel to the increase of age average in general population. In addition, widespread use of tomography has been elevating the prevalence of the early stage lung cancer. Surgical intervention cannot be performed in these cases due to co-morbidities.

The achievement performed by means of the administration of a classical dose of radiotherapy (RT), concerning the early stage, non-small cell lung cancer (NSCLC), has still been insufficient. "Stereotactic Body Radiotherapy" (SBRT) delivered in the extracranial area increases the local control rate to 80%. The purpose of this method is to deliver high doses with minimal damage to normal tissues. The success of the technique depends on the achieved stabilization of the patient together with the fact that the tumor remains within the RT portal area during the treatment. Considering SBRT administration, the biological equivalent tumour dose should be ≥100 Gy. Since the treatment period is limited to a few days, it facilitates the practicability of this treatment and provides a number of radiobiological advantages.

The aim of the study is to answer questions such as "Which patients can be delivered SBRT? What are the success and toxicity rates of the treatment?"

Keywords: Lung cancer; Stereotactic Body Radiotherapy; Non-small cell; Stage I; Radiation Pneumonitis, Elderly Patient, Adjuvant Treatment, Follow-up, Cost Effective

1. Introduction: The standard treatment in early stage of non-small cell lung cancer (NSCLC) (T1-2, N0) is still performing a surgery. More than 2/3 of these cases are observed in patients over 65 years of age. These patients suffer co-morbid conditions such as chronic obstructive pulmonary disease, hypertension, ischemic cardiovascular disease and diabetes, which constitute an impediment for a surgery. A 3-year local recurrence rates are found to be 19-70% regarding classical radiotherapy (RT) methods applied to these cases whereas overall survival rates vary between 16-57%[1].

On the other hand, it was reported that 92% of patients aged ≥70 years suffering from early stage, inoperable NSCLC did not receive any treatment and only 8% of them received "Stereotactic Body Radiation Therapy" (SBRT) [2] between 2003 and 2006 in an analysis published by the National Cancer Database.

The SBRT method which has been recently used significantly reduces local recurrence rates. The administration of SBRT is based on 3 basic principles: (1) Exact location of the tumor; (2) (Daily) Re-imaging of the tumor and normal tissues before each treatment; (3) Completion of all treatment at 1 to 5 fractions[3].

Recently SBRT can be delivered through SBRT-capable linear accelerators, Cyberknife/tomotherapy and performed in place of conventional RT for non-operable lung patients. In order to achieve acceptable local control values, the biological equivalent dose (BED_{10}) should be greater than 100 Gy[4]. This dose level cannot be achieved by conventional RT techniques. Although the optimal RT dose is still unknown, regarding the meta-analysis by Zhang et al., BED giving the best recovery rate is known to be between 106 Gy and 146 Gy[5]. It is believed that sphingomyelinase-dependent tumor endothelial apoptosis, vascular damage, and increased anti-tumor immune response in addition to high dose administration could be the reason [6-8].

Today, SBRT administration for lung cancer has been increasing significantly all over the world. The following questions will be addressed in the study; which patients should be treated with SBRT, what are the difficulties to be encountered in diagnosis, what are the local control/recovery/toxicity values to be encountered following SBRT administration and treatment? Is adjuvant therapy necessary after SBRT? Considering the cost-effectiveness, does SBRT require high costs compared to other therapies?

2. Discussion:

For which patients should Stereotactic Body Radiotherapy (SBRT) be considered?

Patients in 50-70% of the cases suffer chronic obstructive pulmonary disease (COPD) at the time of diagnosis[9]. Co-morbid cardiovascular diseases also constitute an impediment for curative surgery. Surgical intervention is the primary therapy for early stage NSCLC. However, there are additional medical problems preventing surgical option of extensive resections with a safe margin. In addition, postoperative mortality risk is significantly

higher regarding this age group[10]. It is known that SBRT provides a more appropriate, less invasive result and ends up with less morbidity considering such patients. In order to determine which treatment is optimal regarding the patient, factors such as oncologic outcomes (local control, overall survival) and toxicity of the treatment/quality of life should be kept in balance. However, individual preferences of a patient should also be considered. Formerly, in cases where FEV_1 (Force Expiratory Volume) was found to be <30-40%, postoperative complications were expected to be significantly high. DLCO (Carbon dioxide Diffusion Measurement <30-40%) and VO_2 (Oxygen Used in maximum Level of Exercise) values have recently become significantly important. Provided that the VO_2 level is <10mL/kg/min, non-surgical options should be considered for those cases[11].

Considering the early-stage non-operated patients, 3-year survival rates of patients with SBRT is found to be between 50-70%. This value is even worse for patients with that of surgical results. This is due to the poorer performance of the patients referred to RT with concomitant diseases, rather than the failure of SBRT[12].

With respect to a retrospective, multicenter Japanese study, 87 medically operable patients with early stage (T1-2N0) cases (due to patients' consent on not to accept surgery), SBRT (45-72.5 Gy/3-10 fraction) were administered. The median BED was found to be 116 Gy (Range 100-141 Gy). The overall 5 year survival rate was found out to be 69.5% (95% CI, 58.8-80.1%). Only 1 patient had local recurrence and 1 patient suffered grade 3 pulmonary complications. It has been reported that SBRT can be performed safely and the results are equivalent to a surgery[13].

In addition, a recent report comparing SBRT and surgical intervention has reported there was no difference between two methods in terms of local control, distant metastasis and overall survival[14]. In two randomized trials (STARS and ROSEL) comparing surgical intervention (lobectomy) and SBRT, 3-year overall survival rates (95% vs.78% surgery) was found out to be promising. When long-term side effects were evaluated, 10% of the patients treated with SBRT, grade 3 chest wall pain, cough, dyspnea, costal fracture and fatigue reported. Whereas in 44% of patients treated surgically, (grade 3 and over) dyspnea, chest pain, and infection have been reported. A mortality which was associated with the treatment had been reported after surgery. These two studies were terminated early due to inadequate sample collection [15,16].

In a Dutch study examining the outcomes of these two studies conducted in 2015, 3-year survival rates were found out to be 95% regarding the SBRT group and 78% regarding the surgical intervention group ($p = 0.037$). While 1 local recurrence, 4 regional recurrence, 1 distant metastasis were found in the SBRT ($n = 31$) group out of 58 patients, 1 regional recurrence and 2 distant metastases were seen in the surgical group ($n = 27$), respectively. Grade 4-5 toxicity was not observed at all in the SBRT group whereas a single mortality was reported in the surgical group[16]. The meta-

analysis report from China supports these findings[17].

A study by Shaverdian et al. provided an insight for the question, "What are the preferences of patients?"[18]. 102 patients who were delivered SBRT at early stage or after a surgical intervention were evaluated. 56% of the cases reported that they had not known such a treatment before visiting the radiation oncologist. All of the 39 patients who underwent both surgical intervention and who were delivered SBRT, reported SBRT as a less stressful method with faster recovery, while 2/3 of the cases found SBRT to be more satisfactory.

Surgical intervention will still be preferred as the standard treatment method regarding early stage patients until reliable data is established. On the other hand, patients with small peripheral tumors, with limited pulmonary function, co-existing comorbidities and surgical/general anesthesia risks taking into consideration particularly elderly patients, a non-invasive SBRT should be preferred[19].

Is Histopathological Diagnosis Crucial in Patients Delivered Stereotactic Body Radiotherapy (SBRT)?

Current American College of Pulmonary Physicians recommend the evaluation of >8mm nodules, which are not stable for the last 24 months, with PET/CT. Lesions less than 4 mm, with a low probability of malignancy should be tracked by serial, low dose CT. Moreover, biopsy is recommended for suspicious lesions[20]. However, medical reasons making surgical intervention difficult also aggravate pathological diagnosis.

There are many SBRT studies, including patients without tissue diagnosis. In these studies, 22% - 69% of the patients had no tissue diagnosis[21,22]. Biopsy is recommended to confirm the histological diagnosis of malignant lung nodules before delivering a treatment of SBRT if possible, as of 2017 guideline by ASTRO (The American Society for Radiation Oncology). This guideline also supports the use of SBRT in a patient group not accepting biopsy or has biopsy-associated risks. It is also recommended to examine the patient through a multidisciplinary approach, considering all tumor and patient related, or environmental factors; and to provide consensus with the radiological and clinical evidences whether the case is a malignant lung lesion[23].

Therefore, SBRT can be performed without a biopsy in cases where patient morbidity is impeding biopsy, biopsy is not accepted by the patient and clinical suspicion is high enough for malignancy.

Can Stereoactic Body Radiotherapy (SBRT) be Administered Safely Regarding Centrally Located Tumors?

Tumors being 2 cm or less distant from the proximal tracheobronchial area (carina, right and left main lobe bronchus, right and left upper lobe bronchus, intermediate bronchus, right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchus) are referred to as centrally located tumors. For early-stage SBRT delivery, a 10-fold increase in morbidity and mortality was reported after administration of 60-66 Gy (with fractions of 20-22 Gy) to centrally located tumors[24]. In Japanese and German studies, it was

reported that a daily dose of SBRT of 6.0-7.5 Gy, totally 60-66 Gy could be administered safely[25,26].

Senthi et al., from Amsterdam reviewed a total of 20 studies and when 563 cases were examined where SBRT was delivered to centrally located tumors, it was reported that either the central or peripheral location of the tumor had no effect on recovery rates. A toxicity of grade 3 or above was reported below 9%. When BED was 100 Gy or more, local control would be determined as minimum 85% and the treatment-related mortality would be 1%[27]. These values are acceptable when compared to 25% complication and 4.5% mortality associated with surgical intervention [28].

Haasbeek et al. suggested that there was no difference in survival rates following SBRT, regarding central and peripheral tumors (3 years overall survival 64% vs. 51%, p = 0.09)[29]. Data on regional and distant metastasis rates following SBRT is limited in the literature in terms of early-stage and centrally-located tumors. Two-year regional local control rate was found to be 91% and distant metastasis control rate was to be 73%. This rate was found to be 86% and 75% in peripheral tumors respectively (p = 0.47 and p = 0.72)[30]. Although the risk of severe toxicity due to SBRT is low in centralized tumors, possible risks should be discussed with the patient[19]. It is believed that the long fractionation (between 5-8) will be safer relatively.

3. Single Fraction Lung Stereotactic Body Radiotherapy (SBRT): The studies on doses still continues for peripheral lung tumors . In a study from Ohio, the doses of 30 Gy (n = 55) and 34 Gy (n = 25) administered in a single fraction were compared on 80 medically inoperable, early-stage lung cancer patients. One-year local recurrence rates were found to be 2% vs 13.8% respectively, whereas overall survival rates were found to be 75% vs 64% and cancer-specific mortality was found to be 2% vs 13.8% respectively (p> 0.05, no statistical difference was found). There was no difference in terms of toxicity between the groups. It has been reported that single fractionation may be considered safe in tumors less than 5 cm in diameter and more than 2 cm distant from the tracheobronchial area without any mediastinal lymph node involvement[31].

Hara et al. reported only a single (1.7%) grade 3 dispnea following a study conducted on 59 patients (11 in early stage lung cancer, 48 in metastatic cases) administered a single fraction 30 Gy (Range 30-34 Gy dose) SBRT. Small lung tumors (88.1% of being less than 3 cm) may be responsible for this limited toxicity[32]. A tumor diameter greater than 4.5 cm, and prior RT with thoracic radiation is a risk factor for increased toxicity in single fraction applications[33].

4. Stereotactic Body Radiotherapy (SBRT) in patients with single lung: Patients undergoing surgical resection for early stage lung cancer are at 20% lifetime risk of developing a second primary lung cancer[34]. In patients with previous pneumonectomy, there is a risk of second primary lung cancer in the remaining single lung. Although surgery is

a potential treatment option, many patients who have previously undergone pneumonectomy are not eligible for a second surgery due to insufficient lung reserve. Donington et al. reported that operation complications increased to 40% after wedge resection, segmentectomy, or lobectomy in single lung patients, and operation mortality was 8%. In addition, it was reported that 25% of the cases who underwent surgery required oxygen use at home[35].

Although radiofrequency ablation, wedge resection and conventional fractionated radiotherapy are treatment options in these cases, SBRT is less invasive and provides higher local control rates[36].

Testolin et al. evaluated 12 patients who underwent pneumonectomy with the diagnosis of NSCLC and who were found to develop secondary lung cancer in the contralateral lung during follow-up and treated with SBRT. The median maximum tumor size was 2.1 cm (1-4.5 cm). Five patients underwent 26 Gy in a single fraction, and the remaining group underwent 30 Gy in 3 fractions, 40 Gy in 4 fractions and 48 Gy in 4 fractions. 2-year local control rate was 64.5% and 2-year overall survival rate was 80%. Severe toxicity (>Grad 2) was not observed in patients. In this study, BED_{10}> 100 Gy was recommended for good local control[37]. In the series presented by Thompson et al. in 2014, SBRT was applied to 14 tumors with new lung cancer development after pneumonectomy. SBRT doses were 60 Gy in 3 fractions, 54 Gy in 3 fractions, 48 Gy in 4 fractions, 60 Gy in 8 fractions, and a total of 50 Gy in 10 fractions. Median survival was 29 months and 1- and 2-year overall survival rates were 69% and 61%, respectively. Grade 3 radiation pneumonia developed in two patients three and four months after the treatment and these patients died one and three months after the diagnosis due to myocardial infarction and congestive heart failure. In order to prevent lung toxicity, it was suggested that the mean lung dose in the remaining lung should not exceed 4.5 Gy[38].

In selected cases, SBRT is a treatment option provided that lung V5<50%, V10<20% and V20<7%, mean lung dose is <8Gy, and SBRT dose to be applied is BED_{10}>100 Gy.

5. SBRT in elderly patients: Two-thirds of lung cancers are seen over 65 years of age[39]. In the United States, the number of NSCLC cases over 65 years of age is 163,000, and it is estimated to increase dramatically to 271,000 in 2030. This is due to the aging population and more frequent use of low-dose CT scanning in the community[40].

When the current series are examined, it can be seen that the use of SBRT increases in the age group of 75 years and older. While the rate of RT use was 26% between 1999-2001, it increased to 42% between 2005-2007. Surgical intervention rates did not change during these periods. Ratio of untreated patients decreased from 38% to 26%. Median survival increased from 26 months to 31 months. In the same period, the use of SBRT among RT methods increased from 23% to 55% [41].

In the report published by NCDB, 616 stage I NSCLC cases ≥90 years of age were examined. The cases were divided into groups receiving local treatment (SBRT, surgery), other treatments (conventional RT, chemotherapy), and observation alone. While median survival was 34.9 months, 20.6 months, and 11.8 months, the 5-year overall survival rate was 22.7%, 12.8% and 8.3%, respectively. Subgroup analysis revealed no difference between SBRT and surgery[42].

When we look at studies comparing treatment options in elderly patients, Shirvani et al. evaluated five different treatment modalities in 10,923 patients aged 66 years and older with stage IA-IB NSCLC using SEER data (between 2001 and 2007). The median age was 75 and 29% of the patients had severe medical comorbidity. Lobectomy (59%), sublobar resection (11.7%), conventional RT (14.8%), follow-up (12.6%) and SBRT (1.1%) treatment modalities were compared. After a median follow-up of 3.2 months, the group with the lowest mortality rate in the first 6 months after the diagnosis was the SBRT subgroup. At follow-up after 6 months, lobectomy subgroup was the best group in both overall survival and disease-free survival. Conventional RT and follow-up gave the worst results in all analyses[43].

Out of 158 SBRT patients treated at Rush University, 31 patients over the age of 80 were evaluated for complications (CTCAEv4 scales). The median dose was 54 Gy in 3 fractions (range 50-60 Gy in 3-8 fractions). Local control rates were 100% in the 1st year and 92.3% in the 2nd year. Median survival was 29.1 months. 5 patients (16.1%) had grade 1 weakness, 12 patients (38.7%) had asymptomatic (radiologic) RP, and 2 patients (6.5%) had dyspnea. Grade 2 and above toxicity was not seen in any patient[44].

In conclusion, regimens containing BED ≥100Gy can be conveniently applied to patients aged 80 years and above while paying close attention to lung V20 and "mean" doses.

6. Adjuvant Treatment after Stereotactic Body Radiotherapy (SBRT): Despite the successful results of SBRT in local control, 20% risk of regional/distant metastasis observed during follow-up suggests that these cases require systemic treatment[45]. According to "National Cancer Database" data, when SBRT was compared with SBRT+Adjuvant Chemotherapy in T2bN0 NSCLC cases, median overall survival was 16.5 months vs. 24.2 months, respectively (95% confidence interval [CI]: 14.1-20.1 months and 18.8-33.3 months, respectively; $P < 0.001$). Similar results were also obtained in the T3N0 group (Median overall survival 13 months vs. 20.1 months) (95% CI: 11.7-14.5 months and 17.7-21.9 months, respectively; $P < 0.001$). Adjuvant chemotherapy after SBRT had a beneficial effect on survival in (Lymph Node negative) tumors larger than 4cm (15.9 months vs. 19 months, $P < 0.001$), whereas adjuvant chemotherapy shortens survival in tumors smaller than 4 cm (28.5 months vs 24.3 months, $P < 0.001$). In this study, it was concluded that adjuvant chemotherapy after SBRT increased survival in tumors larger than 4 cm, similar to post-surgery findings [46].

There is still limited information on this subject in the literature. Adjuvant chemotherapy seems to be beneficial in tumors larger than 4 cm. An ongoing study by "University of Louisville" (ClinicalTrials.gov Identifier: NCT01300299) will provide additional information on this subject.

7. Post-Stereotactic Body Radiotherapy (SBRT) follow-up: Post-SBRT follow-up has two purposes. The first is to determine the treatment response, and the second is to detect secondary developing lung cancers. However, there is still no clear consensus. In the "Delphi Consensus Study", a board of 11 experts consisting of Radiation Oncologists and Radiologists presented their opinions on this issue. A vote of ≥75% (in terms of acceptance or rejection) was accepted as unanimity in this consensus. In conclusion, the consensus decided that thoracic tomography should be performed at follow-up, FDG-PET-CT (fluorodeoxyglucose- positron emission tomography) should be performed if there is suspicion of local reccurrence (infiltration into adjacent structures, bulging margins, sustained growth, mass-like growth, spherical growth, craniocaudal growth, and loss of air bronchograms), tomographic follow-up should be performed at 3rd, 6th, and 12th months in the first year, every six months in the second year, and once a year in years 3-5. A consensus was reached that rescue treatment can be performed without pathological confirmation if the imaging findings contain high suspicion, if the biopsy is not appropriate, and if the diagnosis cannot be made with the performed biopsy. It was decided that follow-up tomography should be continued after five years, but there was no clear consensus on the frequency of these examinations[47].

8. Stereotactic Body Radiotherapy (SBRT) Toxicity: Although findings of radiological pneumonia in the lung after SBRT were found in nearly 60% of cases, clinical pneumonia was found in 10%[48]. The complication may not be so frequently seen but life-threatening. Possible complications include bronchial stenosis / necrosis, atelectasis, hemoptysis, esophageal stricture, perforation, trachea-esophageal fistula, aortic aneurysm / rupture, severe skin toxicity, chest pain, costal fracture, radiation pneumonia (RP), brachial plexopathy and spontaneous pneumothorax[49-54].

Furthermore, RP is the most common adverse effect of SBRT. In severe RP cases, there may be a history of pneumonia in or outside the RT area, and a rarely accompanying pulmonary edema and infection. The clinical presentation may rarely result in mortality. Onishi et al. reported fatal RP in 1.3% (28 patients) of 1789 cases who were delivered SBRT. Median RP development time following the treatment was found out to be 75 days (Range 14-204). In half of the patients who developed mortal RP, interstitial lung changes were detected before SBRT[55].

Zhao et al. reviewed 88 studies including 7752 patients who underwent SBRT through their lungs (cases with early-stage lung cancer and lung metastasis). Prevalence of grade 2 and above, radiation

induced lung toxicity (RILT) is reported as 9.1%, whereas grade 3 and above is reported as 1.8% . Elder patient age ($p = 0.044$) and large tumor size ($p = 0.049$) were found out to be associated with grade 2 and 3 RILT development. RILT was found to be lower ($p < 0.0001$) in stage IA cases compared to stage IB cases. Regarding patients with Grad 0-1 RILT, the Mean Lung Dose (MLD) ($p = 0.027$) and V_{20} dose (dose of 20 Gy) was found to be lower ($p = 0.019$). In this study, factors such as elderly age (over 74 years), large tumor size (> 3 cm), MLD and V_{20} were found out to be associated with RILT development[56].

In a study conducted in Amsterdam, the development of RP following SBRT delivery in relatively large tumors (PTV> 80 cm^3) was examined. Following the volumetric modulated arc therapy planning conducted on a limited number of patients (n = 18), the most important two criteria were determined as the dose of V_5 (volume of lung, receiving 5 Gy or more) for the entire lung dose and contralateral lung dose (intact lung lobe); and, regarding all cases with entire lung V_5 <37% and contralateral lung V_5 <26%, acute RP development possibility was found to be quite rare[57].

When esophageal dose limits in SBRT is taken into consideration, the data is very limited. In the Memorial Sloan-Kettering Cancer Center, 125 patients with centrally located lung tumors and SBRT-treated lung were examined. The prevalence of acute oesophageal toxicity was found to be 12% (n = 15). In order to keep the esophageal toxicity below 20%, it was suggested that the dose of esophagus 5ml should be kept below <16.8Gy for 3-fraction treatment, 18.1 Gy for the 4-fraction treatment, and 19.0 Gy for the 5-fraction treatment[58].

The radiation doses the heart is exposed may be the cause of cardiovascular mortality in the long term. In a RTOG 0813 study, it was noted that the heart volume being exposed to a dose over 32 Gy should be <15 cm^3 following 5 fractions of SBRT[59]. Tembhekar et al. followed 102 early-stage lung cancer cases following SBRT for a median time of 27.2 months. They could not conclude on an association between maximum dose, average dose, V_5, V_{10}, V_{20} and V_{30} doses to which the heart was exposed, and cardiac morbidity / mortality. In the dose / volume analyzes, no cardiac mortality was reported regarding 13 patients whose heart was exposed to EQD_2> 80 Gy radiation. They soon concluded that small volumes of the heart tolerate high-dose radiation[60].

9. Stereotactic Body Radiotherapy (SBRT) Cost Effectiveness: With the increasing pressure on health care costs worldwide, the economic impact of SBRT should also be taken into account. Many studies evaluated the cost effectiveness of SBRT compared to other treatment methods.

When Stage I NSCLC Treatment Costs in Canada were compared, it was found that Conventional RT cost $ 7,646.98 (Canadian Dollars), SBRT cost $ 8,815.55, Sublobar resection cost $ 12,161.17, Lobectomy cost $ 16,266.12, pnomonectomy cost $ 22,940.59, and Supportive treatment cost $ 14,582.87. Although conventional RT had the lowest cost, the most cost effective

treatment was SBRT when increased recurrence rates and treatment cost of the recurrent disease were taken into account, and SBRT was also recommended in terms of cost in the treatment of medical inoperable and borderline operable Stage I NSCLC[61].

MD Anderson Cancer Center examined localized (<5 cm tumor) cases of NSCLC above 66 years of age, that were treated between the years of 2003-2009. Lobectomy, sublobar resection and SBRT costs were evaluated in these cases. Cost evaluation included the 60 day period before the diagnosis of lung cancer, treatment and subsequent death or last follow-up period or 5 year period after diagnosis. The mean cost at the end of treatment or the following 5-year period was $ 55,120 (USD) for SBRT, and $ 77,964 for sublobar resorption ($p < 0.001$). Pre-treatment examination costs were $ 7,838 and $ 9,615 respectively ($p = 0.02$), treatment costs were $ 12,436 and $ 26,522 respectively ($p < 0.001$), and costs for the first year after treatment were $ 18,698 and $ 18,861 respectively ($p = 0.05$). This cost-effectiveness in favor of SBRT during the treatment period does not differ from sublobar surgery in the follow-up period of 2nd to 5th years after treatment. When SBRT was compared with lobectomy, the average 5-year cost was $ 54,968 and $ 82,641 respectively ($p < 0.001$). While there was no difference in the pre-treatment period ($ 7,558 vs. $ 8,381; $p = 0.41$), SBRT was significantly cheaper in the treatment phase ($ 12,468 vs. $ 29,551; $p < 0.001$). There was no difference between the treatment modalities in the first 4 years of follow-up. Costs of SBRT were lower in the fifth year ($ 3,967 vs. $ 10,125; $p = 0.03$), but the limited number of cases in this period (11 SBRT cases) reduced the statistical confidence. No statistical difference was found between SBRT and lobectomy in terms of median survival (3.8 years vs 4.7 years) ($p = 0.81$)[62].

In a study published in Boston in 2011, treatment costs of 65-year-old medically inoperable lung cancer patients were compared, and SBRT was found to be more cost effective than conformal 3D RT and radiofrequency ablation[63].

In conclusion, SBRT is a more cost effective treatment in elderly patients with early stage NSCLC. However, lobectomy also exhibits favorable cost effectiveness in fit patients who may undergo an operation (taking into account the survival advantage). However, sublobar resection surgery is an expensive method in terms of cost effectiveness in patients who cannot be lobectomized.

10. Results:

In accordance with 2017 guideline of ASTRO [23];

1. Stage I, NSCLC patients should be evaluated by a thoracic surgeon preferably with a multidisciplinary team in terms of the decision of surgery.

2. In cases where there is a high risk regarding the standard operation (Mortality risk 1.5%), SBRT except for the clinical trial is definitely not an alternative treatment for the surgery. Lobectomy +

mediastinal lymph node sampling should be performed for this patient group.

3. Regarding patients with a high risk of surgery (not tolerating lobectomy but sublober resection), in stage I cases, SBRT is an alternative treatment for surgery.

Suggestions added to ASTRO guideline by ASCO (American Society of Clinical Oncology):

1. In accordance with the results of a multidisciplinary consultation and patient preference, when the decision is to perform resection in high-risk patients, limited resection (segmentectomy or wedge resection) rather than lobectomy is more frequently preferred. A prospective randomized study comparing SBRT or lobectomy to that of limited resection is still insufficient.

2. Although it has not been recognized as a definition by physicians, the high risk of surgery may be defined as, "a combination of predicted FEV_1 <50%, an estimated DLCO <50% or elderly patient with impaired lung function, pulmonary hypertension, and inadequate left ventricular function". Operational risks should be assessed by a thoracic surgeon specialized in lung resections.

11. Conclusion:

It could be stated that lobectomy is still a standard treatment for early-stage NSCLC. However, there is no direct evidence on its superiority compared to that of SBRT, and many studies indicate that these procedures may have similar results.

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