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Clinical outcome of stereotactic ablative radiotherapy with CyberKnife® for lung tumors: A single center experience

Akciğer tümörlerinde CyberKnife® ile stereotaktik ablatif radyoterapi sonuçlarımız: Tek merkez deneyimi

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Abstract

Aim: To evaluate retrospectively clinical outcomes of treated with stereotactic ablative radiotherapy (SABR) using the CyberKnife® (Accuray, Sunnyvale, CA, USA), for early primary and oligometastatic lung tumors.

Methods: This descriptive study included thirty tumors from 29 patients with primary lung cancer (n=21) or oligometastatic lung tumors (n=9), who underwent SABR with robotic linear accelerator between March 2011 and July2015. Out of the 30 tumors, 21 were NSCLC, 9 were metastatic lung disease. Treatment was given using different tracking methods including fiducial tracking with Synchrony (21 patients), Xsight lung with Synchrony (4 patients) and Xsight spine (5 patients). Treatment was delivered two to three fractions per week and with different fractionations depending on location and other tumor related factors. Factors, potentially effective on local control and overall survival were investigated.

Results: Median follow-up time for local control was 11 months (2.4-39 months). Of 25 patients with known follow-up data, local control (LC) rates for 1, 2 and 3 years were 82.8%, 82.8% and 55.2 %, respectively. Overall survival (OS) rates for primary lung tumor patients 1, 2 and 3 years were 72.2%, 64.2%, 51.4% and metastatic lung tumor patients for 1 year was 71%, respectively. Except for gender, none of the factors were statistically significantly associated with local control in univariate analysis; female gender was associated with worse local control (p=0.001). Also in univariate analysis of overall survival, there was a trend for worse survival in females, too (p=0.07).

Conclusion: This small study may give some idea about utilizing different tracking ways for CyberKnife® with less toxicity.

Keywords: CyberKnife®, Lung tumor, Stereotactic ablative radiotherapy

Öz

Amaç: Primer ve oligometastatik akciğer karsinomu tanısıyla CyberKnife® (Accuray, Sunnyvale, CA, USA) kullanarak stereotaktik ablatif radyoterapi (SABR) ile tedavi edilen olgularımızın tedavi sonuçlarımızı değerlendirmek.

Yöntemler: Bu tanımlayıcı çalışmaya Mart 2011- Temmuz 2015 tarihleri arasında robotik lineer akselatör ile SABR tedavisi alan primer akciğer kanserli (n=21) ve oligometastatik akciğer tümörlü (n=9) 30 hastanın 29'u dahil edilmiştir. 30 tümörden 21'i KHDAK, 9'u metastatik akciğer hastalığı idi. Tüm tedavi adımları aynı doktor tarafından kontrol edildi. Tedavi, Synchrony (21 hasta), Synchrony ile Xsight akciğer (4 hasta) ve Xsight vertebra (5 hasta) ile fidusiyal izleme dahil olmak üzere farklı izleme yöntemleri kullanılarak verildi. Tedavi, lokal ve diğer tümörle ilişkili faktörlere bağlı olarak, haftada iki veya üç farklı fraksiyonlarda verildi. Lokal kontrol ve genel sağkalım üzerinde potansiyel olarak etkili faktörler araştırıldı.

Bulgular: Lokal kontrol için medyan takip süresi 11 ay (2,4-39 ay) idi. Bilinen takip verileri bulunan 25 hastanın 1, 2 ve 3 yıllık lokal kontrol (LC) oranları sırasıyla% 82,8, % 82,8 ve % 55,2 idi. Tüm sağkalım oranları primer akciğer tümörlü hastalar için 1, 2 ve 3 yıllık sırasıyla %72,2, %64,2 ve %51,4 ve metastatik akciğer tümörleri için 1 yıllık %71 idi. Cinsiyet haricinde, tek değişkenli analizde faktörlerin hiçbiri lokal kontrol ile istatistiksel olarak anlamlı bir şekilde ilişkili değildi; kadın cinsiyeti daha kötü lokal kontrol ile ilişkiliydi (p=0,001). Ayrıca genel sağkalımın tek değişkenli analizinde, kadınlarda da daha kötü bir sağkalım eğilimi vardı (p=0,07).

Sonuç: Bu küçük çalışma, CyberKnife® için daha az toksisite ile farklı tedavi takip yöntemlerinin kullanımı hakkında biraz fikir verebilir.

Anahtar kelimeler: CyberKnife®, Akciğer tümörü, Stereotaktik ablatif radyoterapi

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Introduction

Although surgery is the standard treatment for stage I non-small cell lung cancer (NSCLC) [1]. Stereotactic ablative radiotherapy (SABR) is an increasingly used and revolutionary treatment modality for early stage non-small cell lung cancer (NSCLC) with high rates of local control [2]. Conventional radiotherapy was reported to result in much more lower local control and overall survival rates than surgery [3]. However SABR, with reported high rates of local control, can improve survival even in medically inoperable patients having multiple comorbidities [4-7].

In addition to early primary lung cancer patients, SABR is also revealed with favorable results for oligometastatic lung disease [8]. The CyberKnife, frameless stereotactic radiosurgery system, can track the tumour and motion real time via different tracking methods [9-11].

In our institution we use 3 different target tracking methods of CyberKnife® for lung SABR: Fiducial tracking with Synchrony® (FTTS), Respiratory Tracking System (Synchrony), Xsight® Lung Tracking System (XLTS) with Synchrony and Xsight spine.

For fiducial tracking, fiducial markers were implanted inside or near the tumor by CT guidance [9-10]. Whereas XLTS, capable of tracking the tumour directly instead of fiducials is completely uninvasive method [10]. For Xsight spine method, position of the tumor can be evaluated and corrected relative to the spine location [9].

The purpose of the current study is to document our treatment practices on LC, OS and different tracking methods of central and peripheral located early-stage NSCLC and lung metastases from patient undergone to CyberKnife® for lung SABR.

Materials and methods

We reviewed treatment plans and electronic medical database of 29 lung SABR patients with 30 tumors treated between March 2011 and July 2015. Out of 30 tumors, 21 (70%) had been treated for primary lung cancer and 9 (30 %) for metastatic disease. Some patients had recurrent primary lung cancer (7 patients) and had prior thoracic radiation therapy or lung surgery. Patients' characteristics are listed in table 1.

Table 1: Baseline characteristics

Factor	n	%
Total patient number	29	100
Total number of lesions treated	30	100
Age (years)	Median:68	Range:49-82
Gender (male/female)	22/8	73/ 27
Tumor greatest dimension(mm.)	Median:20.7	Range:8-53.4
Tumor volume (mm^3)	Median:6216.5	Range:904-55980
Primary lung cancer/lung metastasis	21/9	70 / 30
Central /peripheral located tumor	7 / 23	23.3 / 76.7
Histology (known/unknown)	19/ 11	63.3 / 36.7
Pretreatment SUVmax	Median:4.96	Range:1-20.90
BED10 (Gy)	Median:105.6	Range: 59.5-180
Fraction numbers	Median:4	Range:3-7
Tumor follow-up method		
Fiducial	21	70
X sight lung	4	13.3
X sight spine	5	16.7

All patients with lung primary were considered inoperable or preferred SABR over surgery. 23 (77%) patients' tumor were considered peripherally located and 7 (23%) were centrally located according to Radiation Therapy Oncology Group (RTOG) 0236 study definition [12].

All patients were treated with SABR via CyberKnife® (Accuray, Sunnyvale, CA, USA) robotic linear accelerator. Patients underwent computed tomography (CT) or 4-dimensional computed tomography (4DCT) scan for treatment planning with 1.5mm slice thickness. In our department we are using 4DCT (Brilliance CT Big Bore, Philips Healthcare, Cleveland, OH) since January 2014. Gross tumor volume (GTV) was delineated on lung window setting. Clinical target volume (CTV) was not used (GTV=CTV). We used 4DCT, just to have an idea about tumor motion and didn't generate an internal target volume (ITV). General margin for PTV was 5 mm. in all dimension. Occasionally, in case of little movement of the tumor we used narrower margin of 1-2mm. The dose was prescribed to isodose line (median: 81.5%; 75%-97%) covering PTV. As a tumor tracking methods; fiducials tracking, Xsight lung and Xsight spine systems (Figure 1) were used for 21 (70 %), 4 (13.3 %) and 4 (13.3 %) tumors, respectively. One week after fiducial placement, planning CT was performed. Depending on the clinician's discretion, dose and fractionation schedules were varied. But all treatment steps, including contouring, dose scheduling, and plan evaluation were checked by the same physician experienced about stereotactic treatment. Median prescribed dose was 48 Gy (35 to 60 cGy) given in median 4 fractions (3 to 7 fractions). Most common fractionation scheme was 48 Gy in 4 fraction (for 17 tumors).

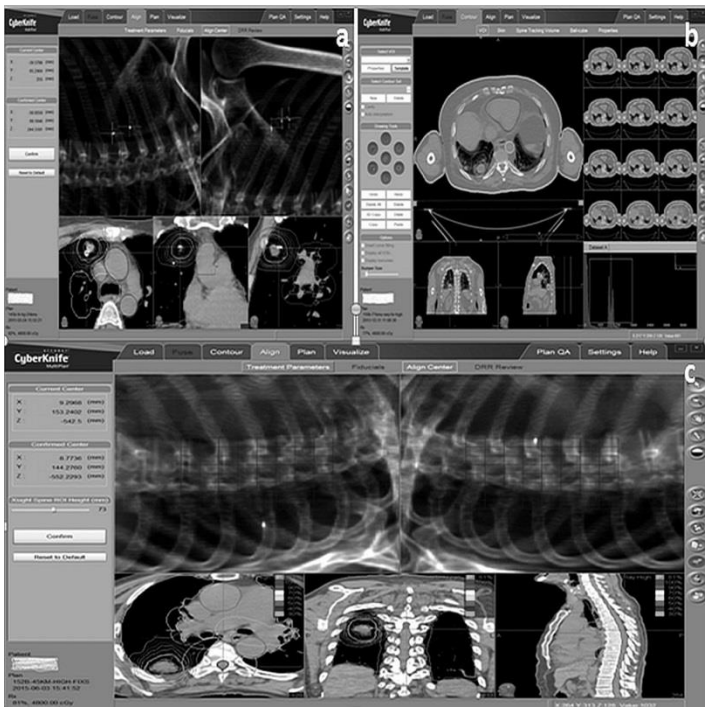

Figure 1: It was shown that the tumor tracking methods as fiducials tracking (a), as Xsight lung (b) and as Xsight spine systems (c)

Follow-up

Follow up data were collected starting from March 2011 to January 2016. Data were obtained from institutional electronic records and via direct/ telephone contact with patient and or family. For the first two years after treatment 3 monthly and every 6 to 12 months visits were planned thereafter. CT scans or PET/CT scans were scheduled initially at 3 to 6 months after treatment and with longer intervals afterwards. Chest x-rays were done more frequently. Treatment response was evaluated

according to Response Evaluation Criteria In Solid Tumors (RECIST) [13].

Statistical analysis

The primary end point of the study was local control and the secondary endpoint was overall survival and also giving an idea about different tracking methods of CyberKnife®. Local failure was defined as disease progression or recurrence in the originally irradiated tumor with SABR. Thus, if the tumor receiving SABR was stable, smaller or disappeared afterwards, it is thought to be locally controlled. Local control and survival analysis were evaluated with Kaplan-Meier for univariate analysis. For multivariate analysis of local control, Cox regression including all the factors in the univariate analysis were carried out. Statistics were analyzed using SPSS version 15 (IBM,USA) software.

Results

All 29 patients were assessed for survival, but 25 patients could be assessed for local control due to lack of follow-up radiologic imaging information. Median follow up time for local control was 11 months (2.4-39 months). Totally 21 (72.4%) male, 8 (27.6 %) female patients with 30 tumors and a median age of 68 (range, 49-82) were included in this study. One male patient with adenocarcinoma of the lung received SABR for two tumors at different sites of the lung with four months break. Out of 30 tumors, 21 (70%) were primary lung cancer and the rest 9 (30%) were lung metastases from different primary sites. 3 (10.4 %) of the patients had received lung radiotherapy for their lung cancers previously. Also 4 (14 %) patients had lung surgery for lung cancer and 2 (7%) two patients had lung surgery for lung metastases, before SABR. Between metastatic tumors, 4 tumors (44.4%) were from colon primary, 1 (11.1 %) tumor was from lung primary and the rest 4 (44.4%) metastatic tumors derived from different primary sites.

For all study population, 21 (70%) of the tumors were treated with fiducial tracking. Xsight spine and Xsight lung tracking systems was preferred for 5 (16.7%) and 4 (13.3%) tumors, respectively. One patient experienced a pneumothorax when fiducial markers were implanted and needed tube placement. After recovering, this patient received treatment without problem and had complete response.

After SABR, one (3.5 %) patient who received 2 SABR for right and left sided tumors received chemoradiotherapy (56 Gy) for progressive right sided lesion, one year later. Another one (3.5%) patient with complete response of the treated tumor, eleven months after treatment, received stereotactic radiotherapy for a new lung lesion, outside of our hospital. One (3.5 %) patient received imatinib for colon primary and 4 patients (14 %) received chemotherapy. Two patients underwent chemotherapy due to progressive metastatic disease although partial response after SABR. Other patient undergoing chemotherapy had progressive tumor at the irradiated site and the new lung lesions. Although progressive disease this patient is alive and has shortness of breath only after serious activity. Remaining one had two primary sites in lung and colon and adjuvant chemotherapy was given.

Mean and median follow-up times for local control were 14.3 months and 11 months, ranging from 2.4 to 39 months, respectively. Of 25 patients with known follow-up data, local control rates for 1, 2 and 3 years were 82.8%, 82.8% and 55.2 %, respectively. Local control for all SABR patients with known local control data is shown figure 2. Crude rate of locally uncontrolled patients was 4/25 (16 %). Remaining 21 patient's tumors was smaller (7/25) accepted as partial response, stabile (7/ 25) or had complete response (7/ 25) after SABR.

Overall survival rates for primary lung tumor patients for 1, 2 and 3 years were 72.2%, 64.2%, 51.4% and patients with lung metastases for 1 year was 71%, respectively. Mean overall survival time for primary lung cancer patients is 34.3 months and for patients with lung metastasis is 19.7 months after SABR until data collection time, respectively. The Kaplan-Meier OS curve is shown in figure 3a and 3b.

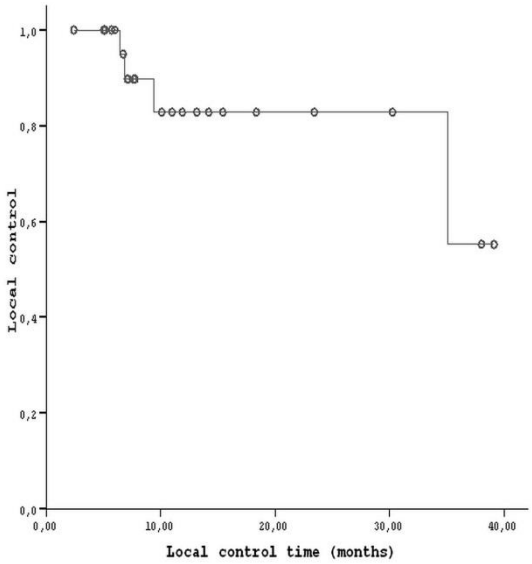

Figure 2: Local control for all SABR patients with known local control data

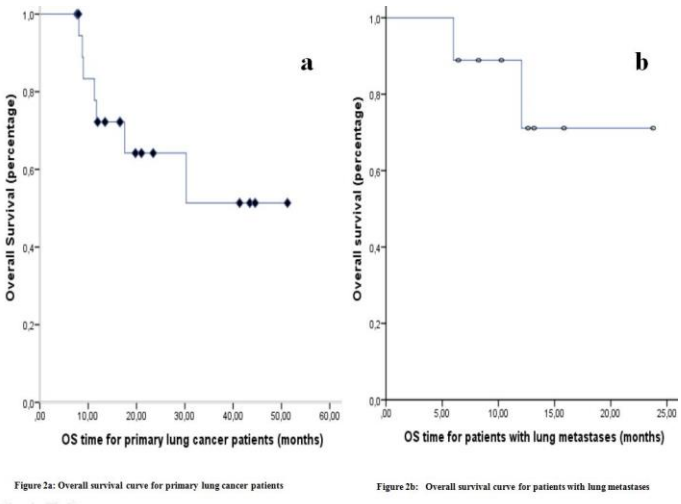

Figure 2a: Overall survival curve for primary lung cancer patients

Figure 2b: Overall survival curve for patients with lung metastases

Figure 3: Overall survival curve for primary lung cancer patients (a), overall survival curve for patients with lung metastases (b)

Table 2 summarizes the univariate analysis of patient, tumor and treatment related characteristics on local recurrence and overall survival. Except gender, none of the factors were statistically significantly associated with local control. Female gender was associated with worse local control (p=0.001) (Table 2). In multivariate analysis for local control including all of the factors, none of the factors was found significantly effective on local control.

Table 2: Results of univariate analysis for local control

Factor	Local Control P value	Overall survival P value
Age (<66 vs.≥66)	0.320	0.841
Gender	0.001	0.073
Tumor greatest dimension (≤24 vs.>24mm.)	0.355	0.307
Tumor volume (≤ 6500mm^{3}vs.>6500mm^3)	0.791	0.922
Pretreatment SUV max. (≤5 vs.>5)	0.333	0.323
Histological diagnosis (yes vs.no)	0.689	0.459
Primary lung cancer vs. lung metastasis	0.651	0.980
PTV dose (BED10, not categorised)	0.340	0.990
Fraction numbers (≤4 vs >4)	0.158	0.182
Tumor follow-up methods(fiducial vs. others)	0.204	0.410
Pretreatment neutrophile/ lymphosite ratio (≤3 vs >3)	0.353	0.794
Peripheral central located	0.464	0.124

Between fiducial implanted patients (21 patients), effect of fiducial numbers on local control was investigated with univariate analysis. There was no relationship between fiducial numbers and local control when categorized (≤3 vs.>3; p=0,547) or not categorized (p=0.983).

We could grade acute side effects retrospectively from patients' records or telephone contact. As an acute side effect we didn't observe Grade 4 or 5 side effects according to Common Toxicity Criteria Version 4. Out of 29 patients, Grade 2 dyspnea was seen in 2 patients (7%) and Grade 3 in 1 patient (3.5%) with all of these patients alive at least 8 months after treatment. One patient (3.5 %) with chronic obstructive lung disease had Grade 2 cough without dyspnea or pain. Apart from these we observed one pneumothorax requiring tube placement at the time of fiducial implanting as mentioned earlier.

Discussion

SABR, with high local control rates, has become a very attractive treatment option not only for early stage primary lung cancer but also for patients having oligometastatic lung tumors [4,5,8]. Due to respiratory motion, conventional radiotherapy has a low conformity and frequently increasing the dose is challenging. CyberKnife®, having ability to tract the tumor and motion is one of the very useful systems for SABR [9-11].

CyberKnife® has a different tumor tracking options. CyberKnife with Synchrony® Tracking System with capacity of real time motion follow-up is capable of delivering high doses of radiation accurately. Compared with linac-based system using breathold technique or respiratory gating, with Synchrony, CyberKnife® gain facility to trace tumour motion in real time which causes reduced margin (typically 3-10 mm.) [14-16]. By means of narrower margins, one can protect adjacent normal tissues more than other systems, resulting in decreased toxicity [17,18].

In our department we use Synchrony® along with Fiducial and Xsight Lung Tracking Systems. For fiducial method, percutaneous transthoracic fiducial implanting by guidance of CT is used [19,20]. Subedi et al. [21] in their phantom study aimed to present data on targeting algorithm accuracy, as a function of image parameters and reported that false locks are more likely to occur with a single fiducial than with multiple fiducials. Therefore, using multiple fiducials helps to be certain about reliable targeting. So, we investigated if the fiducial numbers effect local control or not (≤3 fiducials vs. >3 fiducials) between 16 tumors which treated with fiducial tracking and did not found significant relationship (p=0.547).

Although implanting a gold fiducial allow us to track the tumor accurately, there are some defined side effects related with this intervention like pneumothorax, migration of fiducials and hemorrhage [19,20]. In the current study, out of 21 patients treated with fiducial implanting we saw one pneumothorax requiring tube thoracotomy (5%). This rate is little bit lower than literature as far as we know. Collins et al. reported that after insertion of fiducial markers pneumothorax was seen 25% of the patients [22]. Another stereotactic radiosurgery revealed this rate as 13% [10]. Also, we haven't seen hemorrhage by the time of procedure or afterwards.

For XLTS, similar intensities of digitally reconstructed radiograph (DRR) images match with position of tumor, thus the tumor can be tracked directly. Recently reported lung phantom study from Jung et al. [23], the XLTS was found to have comparable segmentation accuracy with FTTS.

XLTS, is a fully noninvasive method requiring criteria like enough tumor contrast in X-ray images for soft tissue follow up, tumors bigger than 15 mm.in all dimensions and peripheral location of tumor [23].

In the current study XLTS was used for four peripherally located tumors with one of them having a smaller tumor (biggest dimension was 10 mm.) than 15mm. In a study from Korea, done with 58 CyberKnife patients, the authors also reported that they used XLTS for tumors less than 15 mm with high local control rates (1 and 2 years local control rates were 94% and 90.6 %, respectively.) [11].

In our study we have follow-up data for local control for 3 of 4 patients treated with XLTS together with Synchrony. All of these 3 patients were locally controlled at the time of last follow-up.

Another tracking method is Xsight spine by means of which, tumor's position can be assessed based on its location relative to the spine [9]. In Yihang Guo et al.'s study [9] reporting influence of different image guided tracking methods on local control for CyberKnife in lung tumors; they found targets smaller than 15 mL were better controlled with Synchrony than Xsight spine (p=0.038). Whereas in the current study 5 targets between 1.5 and 12.5 mL were treated with Xsight spine tracking and all of them were locally controlled at the end of last control time (3 complete response and 2 partial response).

In this study totally 21 tumors (70%) were treated using Fiducial tracking and we have local control data for 17 of them. 4 tumors were not controlled with SABR and actuarial local control rates for Fiducial tracking ones was 74.6% and 74.6% for 1 and 2 years. Although these were lower than local control rates of tumors tracked with Xsight lung and Xsight spine (all 8 patients were locally controlled), there was not statistically difference between tracking methods.

Between other factors investigated for the effect on local control, only gender was the statistically significantly effective one (p=0.001) and males were doing better than females. In this study we have 6 tumors from female patients and 19 tumors from 18 male patients with known local control follow-up data. Again for overall survival there was a trend towards better survival for males (44.4% vs. 79.4 % at one year) similarly. Whereas in the literature there are studies with both

stereotactic radiotherapy and conventional methods reporting better survival with female patients for lung cancer [24]. In addition, Shibamoto et al. [25], in their multicenter study with stage I NSCLC patients found both overall survival and local control results superior in females. Our study includes not only primary lung cancer but also lung metastatic patients, this heterogeneity and small numbers of patients could be probable explanations for this result. In addition we couldn't see any relationship between tumor's greatest dimension or tumor volume and local control even the fact that we treated tumors with dimension bigger than 50 mm. But there is studies in the literature defining tumor diameter as one of the most significant factors affecting outcome after SABR [26,27].

Dose effect on overall survival and local control was well described in the literature for both early stage primary lung cancer and patients with lung metastasis [24,28]. Onishi et al. in their study with stage I NSCLC patients found that patients receiving a dose greater than BED 10Gy of 100 Gy or more had significantly better overall survival and local control rates than patients receiving lower doses. In our study median BED 10Gy was 105.6 and 4 patients (13.3%) with centrally located tumors had received doses lower than BED 10Gy of 100 Gy. These patients' given doses as BED10Gy were in increasing order; 59.5, 83.3, 86.4 and 94.1 Gy. We couldn't find significant effect of BED10Gy on local control; most probable reason is small sample size.

Due to lower BED10Gy, one can expect lower local control rates with increasing fraction numbers. In our study the most frequently used fraction scheme was 48 Gy in 4 fractions (BED10Gy of 105.6 Gy) with 17 tumors (57%). When we compared patients receiving treatment with bigger than 4 fractions to patients receiving smaller or equal to 4 fractions, although not significant local control rates for 1 year were 62.5% and 92.3%, respectively (p=0.158). A single institution study using CyberKnife® with XLTS from Bibault et al. [10] also showed significantly better local control rates with 3 fractions than with more than 3 fractions (p=0.006).

Treatment was well tolerated and all patients completed the planned course of SABR. Apart from grade 2 and grade 3 dyspnea in 2 and 1 patients, respectively and one pneumothorax we didn't see another severe acute side effect. All of the patients were alive at least 6 months after treatment. Our local control rates for 1,2 and 3 years were 82.8%, 82.8%, 55.2% and overall survival rates for primary lung tumor patients for 1, 2 and 3 years were 72.2%, 64.2%, 51.4% and patients with lung metastases for 1 year was 71%, respectively. First 2 years local control rates look close to literature which is between 83% and 93% while survival rates look fairly well if we take into account the vulnerability of these population and literature again [29-31].

Main limitation of this study was small patient numbers, heterogeneous patient population including both primary lung cancer and lung metastatic patients and retrospective data collection. We thought small patient numbers was the potential main reason for some nonsignificant values of univariate analysis. Otherwise this small study with all patients' treatment procedure checking by the same physician, may give some idea about utilizing different tracking ways for CyberKnife®. As in literature, SABR with CyberKnife® improves survival and local control even for central located and metastatic lung tumors with limited side effects.

Conclusion

Stereotactic ablative radiotherapy with CyberKnife® for the treatment of primary and metastatic lung tumors is a reliable and efficient treatment method for medically inoperable patients. To evaluate tracking methods of CyberKnife® system more comprehensive studies are awaited.

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