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ROBOTIC STEREOTACTIC BODY TREATMENT FOR EARLY STAGE NON-SMALL CELL LUNG CANCER

ERKEN EVRE KÜÇÜK HÜCRELİ DIŞI AKCİĞER KANSERLERİNİN TEDAVİSİNDE ROBOTİK RADYOCERRAHİ

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Abstract

Objective: In this study, we retrospectively reviewed and statistically analyzed the Cyberknife SBRT outcomes in terms of local control and survival times for the patients with primer lung tumors treated at Anadolu Medical Center.
Methods: We included 135 patients who were treated between 2005 and 2016 and diagnosed primary lung cancer who were judged medically inoperable. median BED10 was 180 Gy (ranging 45-180). The treatment response was assessed using either a CT or a PET-CT scan or both. There were 108 men and 27 women, with an overall median age of 65 years (range 44-88 years). The median follow-up and overall survival were 19 (3-88) and 34 months, respectively.
Results: Overall survival and local control of the patients for 1, 2, 3, 5 years were 88%, 72%, 50%, 39%, and 81%, 54%, 51%, 39%, respectively. 1, 2 and 3 year survival rates for BED10=180Gy group were 89%, 84% and 72% respectively. 1, 2 and 3 year survival rates were found as 88%, 68% and 42% for BED<180Gy, respectively. 1, 2 and 3 year local control rates for BED=180Gy group were found as 92%, 86% and 86% respectively. 1, 2 and 3 year local control rates for BED<180Gy group were found as 78%, 42% and 38%. Local control and overall survival were associated with higher BED10. The difference between survival and local control of BED=180 Gy and BED<180 Gy are significant (p=0.008, p=0.002).
Conclusion: The Cyberknife stereotactic radiosurgery treatment with real-time tumor motion tracking is a promising well tolerated treatment option for inoperable early stage lung tumors.

Keywords: *SBRT, Lung Tumors, CyberKnife*

Öz

Amaç: Bu çalışmada Anadolu Sağlık Merkezi'nde robotik SBRT uygulanan erken evre akciğer kanserli olguların tedavi sonuçları geriye dönük olarak incelenip lokal kontrol ve sağkalım süreleri istatistiksel olarak raporlanmaya çalışıldı.
Yöntem: Kliniğimizde 2005-2016 tarihleri arasında SBRT uygulanan opere edilemeyen ya da cerrahi istemeyen, T1-T2N0M0 evre 135 olgunun incelendi. 87 olgu Synchrony Takip yöntemi ile, 34 olgu X Sight Lung yöntemi ile tedavi edilirken 17 olgu X Sight Spine Takip yöntemi ile tedavi edildi. Medyan fraksiyon sayısı 3 (1-8) idi. Medyan BED10 değeri ise 180 Gy (45-180' di. Tedaviye yanıt BT ve/veya PET/BT ile değerlendirildi. Medyan yaş değeri 65 (44-88) olan olguların 108'i erkek iken 27'si kadındı. Medyan takip süresi 19 (3-88), medyan sağkalım ise 34 ay hesaplandı.
Bulgular: Çalışmaya dahil edilen olgulara ait 1, 2, 3 ve 5 yıllık sağkalım %88, %72, %50 ve %39 iken aynı süreler için lokal kontrol ise %81, %54, %51 ve % 39 olarak elde edildi. BED=180 Gy ve BED<180 Gy olarak tedavi dozunun etkisi araştırıldığında dozun sağkalıma ve lokal kontrole etkisi anlamlı bulundu (p=0,002, p=0,008).
Sonuç: Gerçek zamanlı tümör hareket takibi ile Cyberknife stereotaktik radyocerrahi tedavisi, ameliyat edilemeyen erken evre akciğer olgularında umut verici ve tolere edilebilen bir tedavi seçeneğidir.

Anahtar Kelimeler: *SBRT, Akciğer Kanseri, CyberKnife*

Introduction

Standard treatment of early stage non-small cell lung cancers (NSCLC) is surgical intervention[1,2]. In the conducted studies, local disease control rate is defined as 90% and 5 year survival rates are 60-80% for Stage I, 40-50% for Stage II[3]. Meanwhile, low pulmonary functions, cardiac disorders and/or other diseases like diabetes deem an early stage NSCLC case medically inoperable. Although the optional treatment method for early stage NSCLC cases is not defined clearly today, according to the successful results of the conducted studies, Stereotactic Body Radiotherapy (SBRT) is an alternative treatment to surgery for medically inoperable patients or patients who refuse surgery[4-8]. When the results of SBRT are compared with the results of external radiotherapy, local disease control is 60-70% and 2 year survival rates are less than 40% in conventional fractionation, meanwhile SBRT results performed with the inhomogeneity correction in inoperable Stage I and II cases and applied as 54Gy dose in 3 fractions; 3 year tumor control is reported as 98%, local control is 91% and total survival is 56%[9-11]. High radiation doses are required to achieve local control in SBRT applications in early stage NSCLC cases. SBRT is now considered a standard treatment for inoperable stage I NSCLC and is being explored as a treatment option for medically operable patients[12]. However, the optimal treatment and schedule of SBRT for T1–T2N0M0 lung cancer are still being explored. The treatment success is published as better in the SBRT applications with a Biological Effective Dose value (BED) of BED≥100Gy in the studies conducted by dose escalation to achieve ablative dose with of different dose schedules[13-15].

SBRT or Stereotactic Ablative Radiotherapy (SABR), is frequently utilized for the treatment of primary or metastatic tumors in different anatomic localizations after 1990s with developing technology in radiotherapy and reduced uncertainties in tumor imaging[16]. SBRT aims high dose to the target well designated by different imaging techniques and strictly immobilized cases in a variable low fractions usually ranging between 1 and 5 with highly accurate radiation beam meanwhile exposing nearby critical organs to minimal dose in an attempt to reduce the toxicity caused by treatment. Ablation is achieved in tumor volume with high BED, as well as rapid dose gradient at the immediate termination of tumor borders allowing the critical organs (OAR) to be preserved maximally. The accuracy and sensitivity are important in SBRT applications which utilize high doses to small and moving tumors such as lung tumors when comparing target created with high margins in external beam radiotherapy. Differing from intracranial Stereotactic Radiosurgery (SRS), the designation of the uncertainty in tumor localization, caused by the tumor's or adjacent organs' movements, must be defined with high sensitivity imaging and tracking methods performed before and during treatment in SBRT, since it is the most important factor that affects the treatment success[17].

With CyberKnife, a robotic frameless radiosurgery system (Accuray Incorporated, Sunnyvale, CA), real-time respiration monitoring can be performed with Synchrony Respiratory Tracking system during the treatment of the tumors localized in thorax that move with respiration. Target is tracked with at least three markers placed within the volume or immediate vicinity with periodically repeated orthogonal x-ray graphs while breathing of the patient is tracked by external markers with creating breathing cycle. Therefore, target localization is designated with accuracy lower than 1.5 mm during treatment[18]. Due to this accuracy of CyberKnife SBRT applications, the margins to the target volume can be reduced that helps to reduce the dosage transferred to other critical organs like normal lung tissue, spinal cord and esophagus. In one of the first publications based on early stage NSCLC cases treated with CyberKnife, Phase I study performed by Whtye et al.[19], despite treatment was administered with 15 Gy in single fraction, it is revealed in following studies that local control rate is low if the dose in single fraction is <30-34Gy[18, 20]. Although various dose schedules are utilized in Phase I and Phase II studies conducted [20-24], 60Gy in 3 fractions dose schedule, which is accepted routine treatment schedule in our clinic for robotic radiosurgery in early stage NSCLC cases, is accepted as standard SBRT schedule in early stage peripherally localized NSCLC patients. Lower BED values can be applied in some cases due to tumor localization, size and patient's clinic condition.

For the early stage NSCLC cases who cannot be operated due to medical reasons or unwilling to surgery, SBRT with CyberKnife (Accuray Incorporated, Sunnyvale, CA) treatment was performed in Anadolu Medical Center Radiation Oncology Department since 2005. In this study, we attempt to report the results of the early stage NSCLC cases who had been treated with robotic SBRT between 2005 and 2016 years in Anadolu Medical Center Radiation Oncology Department by retrospectively analyzed in terms of local control and survival rates.

Methods

Patients and Acceptance Criteria

135 cases with T1-T2N0M0 stage disease with complete follow-up data, who received SBRT in Anadolu Medical Center Radiation Oncology Department between 2005 and 2016, who have peripherally localized lesion and who either do not want surgery or cannot be operated due to medical reasons such as poor respiratory functions, cardiac or vascular diseases, are included in this study. Although we were bound to possess a histological diagnosis for treatment, cases who have poor respiratory functions and could not undergo a biopsy, but accepted as T1-T2N0M0 by multidisciplinary approach and morphological findings were also included in this study. In these cases, increasing size or activity value in Computed Tomography (CT) or (18F) Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) imaging was accepted as treatment indications. Each case was evaluated before treatment in terms of respiratory functions and pulmonary sufficiency by Thoracic Surgery and Diseases specialists and SBRT was decided after these values were deemed eligible. CT was used for staging in 42 patients included in this study (32.06%), while PET/CT was used for the others. Cases with a tumor size of >5 cm were excluded. Post-treatment patient follow-up was performed with clinical findings and imaging protocols. Demographic and clinic data of patients included in the study are present in Table 1.

Tumor Marking and Treatment Transmission Methods

Patients were treated with three different imaging guided treatment (IGRT) methods shown in Table 2 that were utilized in extracranial SBRT applications in CyberKnife robotic radiosurgery system. Tumor was tracked by the 3-dimensional translation and 3-dimensional rotational error, actualized by the comparison of real-time orthogonal

radiographic images with Digital Reconstructed Radiography (DRR) images obtained by planning CT images. The tissue heterogeneity differences between vertebral bone and soft tissue was used in X Sight Spine tracking method. 14 patients, who has a lesion in close proximity to vertebral column and unable to implant tumor marking by fiducials due to clinic findings, were treated with X Sight Spine treatment tracking method. Since respiratory tracking could not be performed in this technique, target volume margins to create Planning Target Volume (PTV) differ from other techniques. Another method was used to treat 87 patients (64%) in the study, is the Synchrony Respiratory Motion tracking method which allows the dynamic tracking of moving tumors with respiration during treatment. In this method, fiducials were placed either within the tumor or in close proximity and the orthogonal radiographs were obtained in real-time during treatment allow dynamic tumor tracking. Patient's respiration curve was constructed by the camera which detects the movement of 3 Light Emitting Diodes (LED) placed on the patient. The radiation beams and this curve were synchronized during treatment and respiration was tracked. Additionally, the tumor position was achieved by the match up of 3 or more tumor markers which were placed within the tumor or in close proximity with at least 15 degree angles, with the orthogonal radiographs and DDR images with marked the location of the markers obtained from planned CT images. Tumor marking by fiducials is an invasive procedure which was performed by radiologists under sedation or local anesthesia by CT guidance with percutaneous or intravascular methods. At least 3 markers were placed percutaneously in many patients, but intravascular marking was also used in some cases, which we had been detailed in our previous study[25]. Figure 1a depicts the planning images of a patient treated by Synchrony Respiratory Motion and fiducial tracking system. Ideally, at least 3 markers are recommended, but the presence of more markers increases the treatment accuracy due to displacement, geometric inconvenience or loss. Additionally, it was reported that a single marker that was placed in tumor's center can be used in some studies with adequate accuracy[25]. Another imaging guided treatment tracking method is X Sight Lung treatment technique which does not require any invasive procedure, using the soft tissue (tumor tissue) contrast difference between tumor and surrounding tissue to check tumor motion, also checking the respiratory movement by Synchrony Respiratory Motion, allowing the dynamic tracking of tumor during treatment. 34 cases with peripheral tumor localization and having lesions greater than 1.5 cm were treated with X Sight Lung treatment technique in this study. During the treatment, tumor tracking was performed by the comparison of the DRR images constructed by the utilization of maximum contrast difference with the graphs segmenting the tumor localization by using the orthogonal graphs to determine the contrast difference of the tissues surrounding the tumor. By using orthogonal images, position error was identified by using correlation method to detect the uncertainty in tumor localization caused by the respiratory motion with Synchrony Respiratory Motion system by the designation of both tumor markers that allows to define the error in tumor localization in Synchrony technique and in the error of tumor localization designated by utilizing the contrast difference in Xsight Lung tracking system. This correlation model was refreshed by orthogonal images obtained in set frequencies during respiration. Treatment was stopped in the cases which the tumor markers cannot be found, matched up or the total margin of error exceeded 3 mm during respiration correlation. Treatment was resumed after refreshing the respiration curve following the repositioning of the patient.

Table 1. Patient Demographics and Clinical Characteristics

Variable	Number of Patients (%)
Sex	
Female	25
Male	106
Median Age	65 (44-88)
Median Tumor Volume, cc	33 (2,1-174,4)
Tumor Location	
Right Sup	46
Right Mid	11
Right Inf	29
Left Sup	28
Left Mid	5
Left Inf	11
Broncial Area	5
Histology	
Squamous	44
Adeno	54
Unspecified NSCLC	29
BronchioalveolarCarsinom	2

Table 2. CyberKnife SBRT Characteristics

Variable	Median (Range)
Dose (Gy)	45 (24-60)
Biological Effective Dose	180 (45-180)
BED_{10} (Gy)	
Prescribed Isodose Level (%)	84 (67-93)
Target Coverage (%)	96,2 (86-99,8)
Conformity Index	1,26 (1,02-1,85)
Homogenity Index	1,25 (1,1-1,38)
Non-Zero Beam Number	224 (273-128)
Fraction Number	3 (1-8)
Colimator Size	20 mm (7,5-35 mm)
Tracking Method	
X Sight Spine	14
X Sight Lung	34
Fiducial Tracking (Synchrony Respiratory Motion)	87

Treatment Planning

A simulation was performed by dressing all patients with a vest which LED emitters can be placed on it, except the patients treated with X Sight Spine treatment technique. Planning CT images with 1.25 cm slices to obtain high quality DRR images and a better contouring in smaller target volumes were obtained at least one week after the tumor marking by holding the breath. Pulmonary parenchyma window was used when the Gross Tumor Volume (GTV) defined by the CT images if the patient has no PET images. For the patients with PET images, PET and planning CT images were matched by "point base" matching methods with imaging match program which is a part of the planning system or manual match methods. After the matching of images, accuracy of matching was verified visually and GTV was delineated in appropriate threshold Standart Uptake Value (SUV) by the guidance of Nuclear Medicine specialist. While 5 mm margin was allocated to GTV during the construction of PTV, 5-7 mm margins were allocated for the construction of PTV for the cases treated with X Sight Spine technique. All critical organs in thoracic

region were contoured. The median collimator size was 20 mm (7.5-35 mm) and median beam number was 224 (273-128) for all plans. Although treatment duration depends on dose rate and beam number, treatment duration for single fraction varies for each patient due to patient's respiration order. Non-isocentric beams were used in MultiPlan planning system, which has an inverse planning algorithm, and all plans were done with Ray Tracing algorithm. The Ray Tracing algorithm uses simple pencil beam calculation algorithm that heterogeneity correction is performed with Electronic Path Length (EPL) technique. Since the lateral electron dispersion is not accounted for particularly in build-up, penumbra and regions that cross between tissues in EPL technique, the dose calculation in homogeneous tissue like brain can be performed in high accuracy. When compared to Type-B algorithms, the calculation of treatment regions with heterogeneous regions (air, pulmonary parenchyma) like lung consist errors in form of overestimation about the calculation of target volume coverage. Treatment plans were made by identifying the target dose to isodose line which comprise the 95% of PTV volume in all plans. Critical organ doses were attempted to be kept lower than the tolerance values defined in RTOG 0236[11] protocol provided in Table 3. Since dose is defined as 60Gy in 3 fractions in this protocol; when treatment is performed with lower or higher dose schedules in our clinic, critical organ doses were kept below tolerance levels by calculating the 2Gy Equivalent Dose (EQD2) value. Dose limitation was set in planning for a volume that receives 20 Gy or more dose for entire lung volume (V20) not to exceed 10% of all lung volume or for 15 Gy or more dose for entire lung volume not to exceed 35% of all lung volume.

Table 3. Dose limitation of critical organs

Critical Organ	Max dose constraints, RTOG 0236 (Gy)
Esophagus	27
Trachea	30
Main bronchus	30
Heart	30
Aorta	40
Spinal cord	18

The treatment dose schema such as fraction number and fraction dosage was performed according to tumor localization and critical organs, median treatment dose value is 45Gy as is seen in Table 2 (24-60Gy), with a median fraction number of 3 (1-8). All treatments were performed on consecutive days. In order to compare the treatment efficiency for the cases treated with different doses and fractionation, BED values were calculated with linear quadratic model (LQ) formulation provided in Equation (1). Median BED value is 180Gy (45-180Gy).

Equation 1. $BED = Dx\left(1 + \frac{d}{\frac{\alpha}{\beta}}\right)$

Tumor dose was calculated by accepting α/β as 10. D and d represent to total dose and fraction dose, respectively.

Follow-Up

Every treated patient was followed-up with CT or PET/CT repeated every 3 months in the first year, then with CT or PET/CT imaging repeated every 4 months in following years. All cancer-related deaths during follow-up were recorded. Local control (LC) value was graded as complete response (CR), partial response (PR) or stable disease (SD) after treatment by using CT or PET/CT images. When the lesion has disappeared or has a SUV lower than malignancy threshold, the case was accepted as CR; 30% or more regression in size, regression in SUV in PET-PET/CT imaging was designated as PR; no change in lesion size and stable SUV or lack of significant growth was defined as SD. If the lesion indicated 20% size increase or SUV increase compared to previous pre-treatment values or a new lesion/lesions formed in treatment region, the case was accepted as local progression. Tumor progression was defined in the cases with ground glass appearance in CT imaging and has increased SUV in PET/CT imaging, or stable disease was accepted in the cases according to clinic data which radiation-induced pneumonia or necrosis cannot be distinguished in the images. Side effects caused by treatment were graded in the immediate aftermath of treatment and during follow-ups by the criteria of CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0)[26]. According to this protocol, if radiation pneumonia is asymptomatic and only a radiological finding, it was staged as Grade I, if it is symptomatic but does not interfere with daily life quality, it was staged as Grade II, if symptoms affect daily life quality and need of oxygen arises, it was staged as Grade III and if it is life-threatening and necessitating ventilator support, it was staged as Grade IV. Grade V was staged if the patient is defined as exitus.

Statistical analysis

Statistical analysis was performed according to the findings starting from the day of the completion of CyberKnife and until the day of last follow-up or the day of exitus. All data of 135 cases were examined with Kaplan Meier method and all survival and local control curves were calculated. Additionally, survival and local control differences due to dosage and tumor size were researched. Discrepancy *p* value was deemed significant if it was <0.05. Furthermore, 5 year local control rates were estimated with Kaplan Meier method.

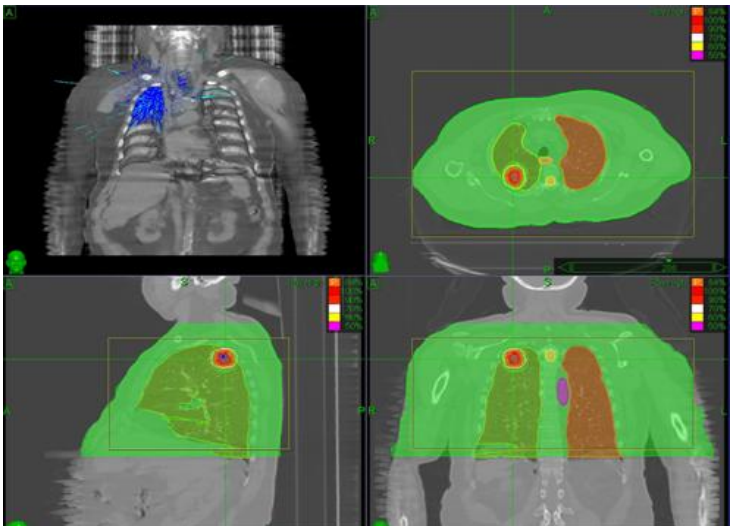
Results

T1-T2N0M0 early stage NSCLC cases treated with SBRT using CyberKnife robotic radiosurgery device in our clinic are included in the study. Median age value of 135 cases was 65; 27 of the cases were female and 106 of the cases were male. Demographic data of the cases were presented in Table 1. 129 of the cases had histopathological diagnosis verified by biopsy, 6 of the cases were accepted as early stage NSCLC with multidisciplinary approach according to radiologic and clinic findings without tissue diagnosis due to risks of biopsy. Of 129 cases, 44 cases with tissue diagnosis were histopathological classified as adenocarcinoma, 54 cases were squamous cell carcinoma, 29 cases were NSCLC without further classification and 2 cases were bronchioalveolar carcinoma. At the time of analyzing, 56

cases were defined as exitus (5 of them have died due to causes unrelated to cancer), 10 cases were out of follow-up after the first follow-up performed in the 3rd month after SBRT. Follow-up PET/CT images of a case, who was treated with X Sight Lung treatment method and 60Gy/3fx dose schedule and with a complete response of 66 months follow-up period were presented in Figure 2.

In the plans of receiving at least 95% of PTV value of designated treatment dosage, this was achieved for most patients, meanwhile 9 of the cases remained below the 95% coverage. Median PTV volume rate received the designated dose was 96.2%, median isodose curve of designated treatment dosage was 84% (67-93). Maximum dose restrictions defined for critical organs were exceeded in none of the plans. Homogeneity Index (HI) defining the dose homogeneity within target volume was calculated with the formulation presented in Equation 2 in MultiPlan. Median homogeneity index of the plans of 135 cases was found as 1.25 (1.1 – 1.38).

Equation 2. $HI = \frac{\text{Maximum Dose}}{\text{Designated Dose}}$



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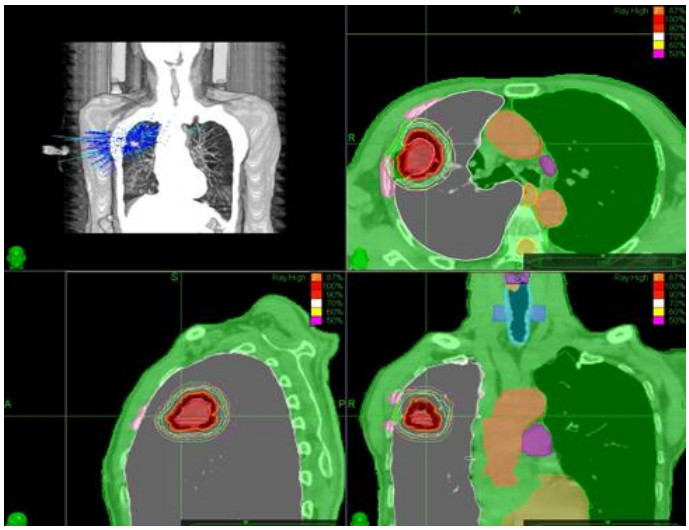

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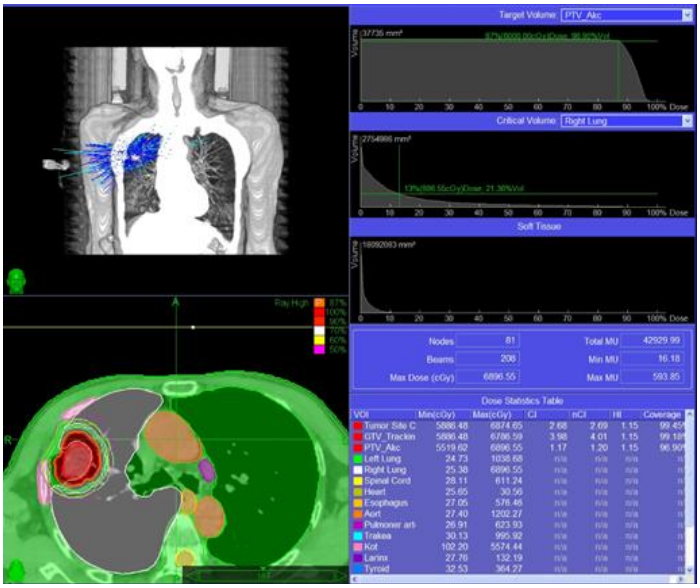
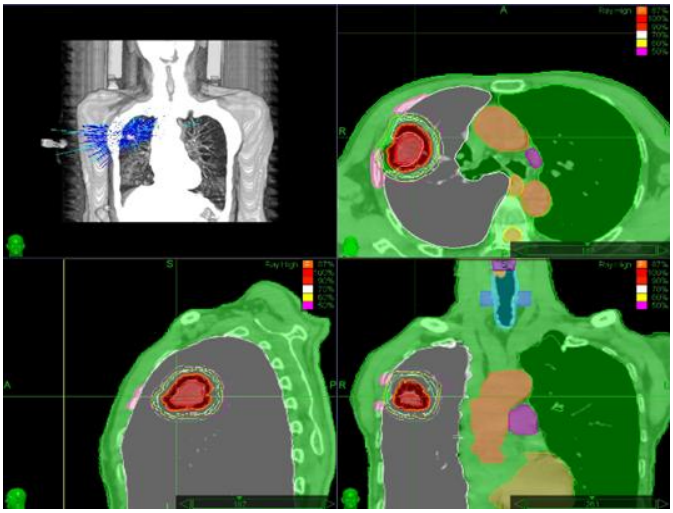


(c)

Figure 1. (a) The planning of a patient who underwent fiducial implemantion and treated with Syhcrony Respiratory Trackin Method. (b) The planning of a patient who treated with X Sight Lung and dose distribution (c).



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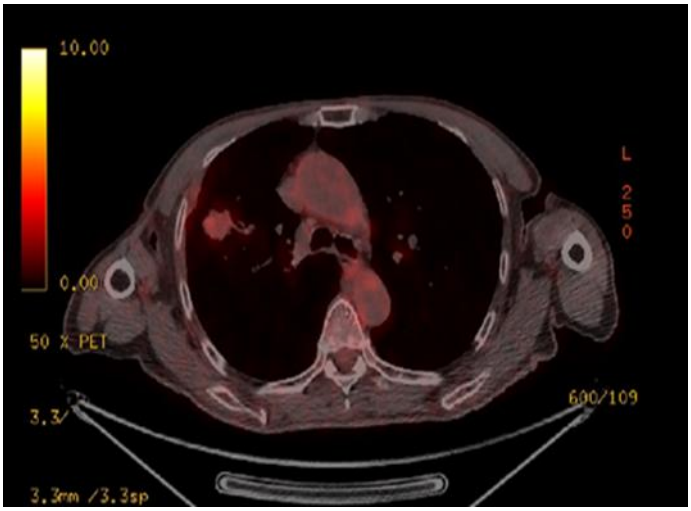

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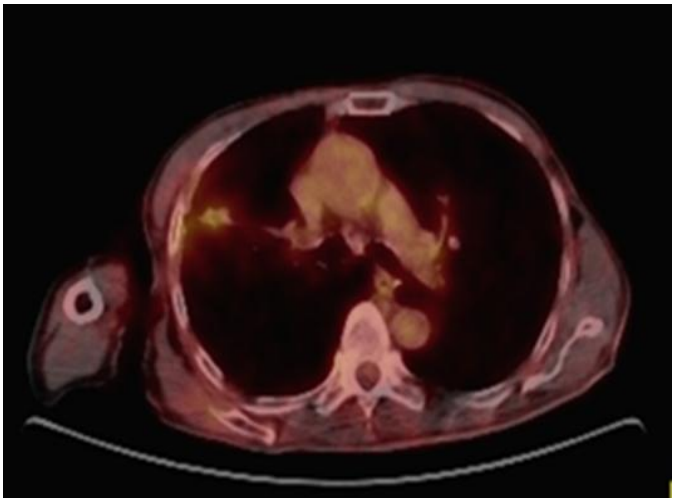

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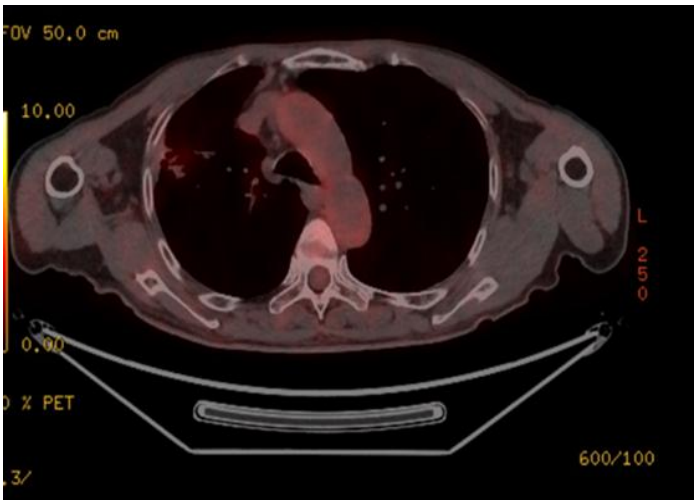

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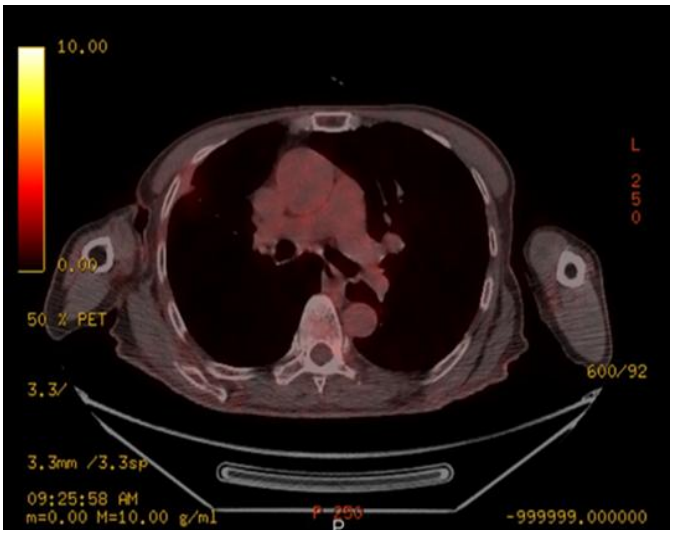
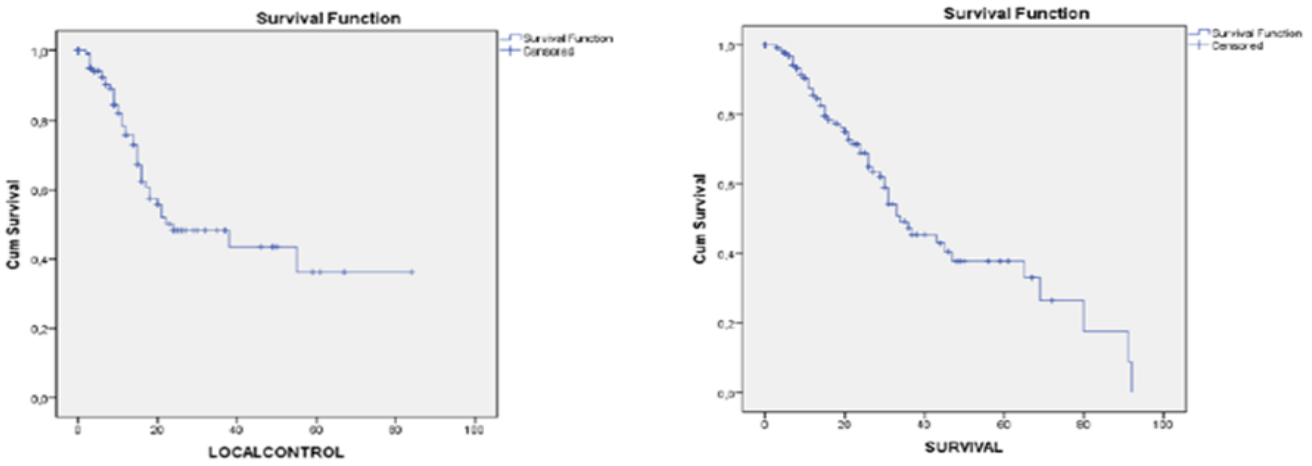


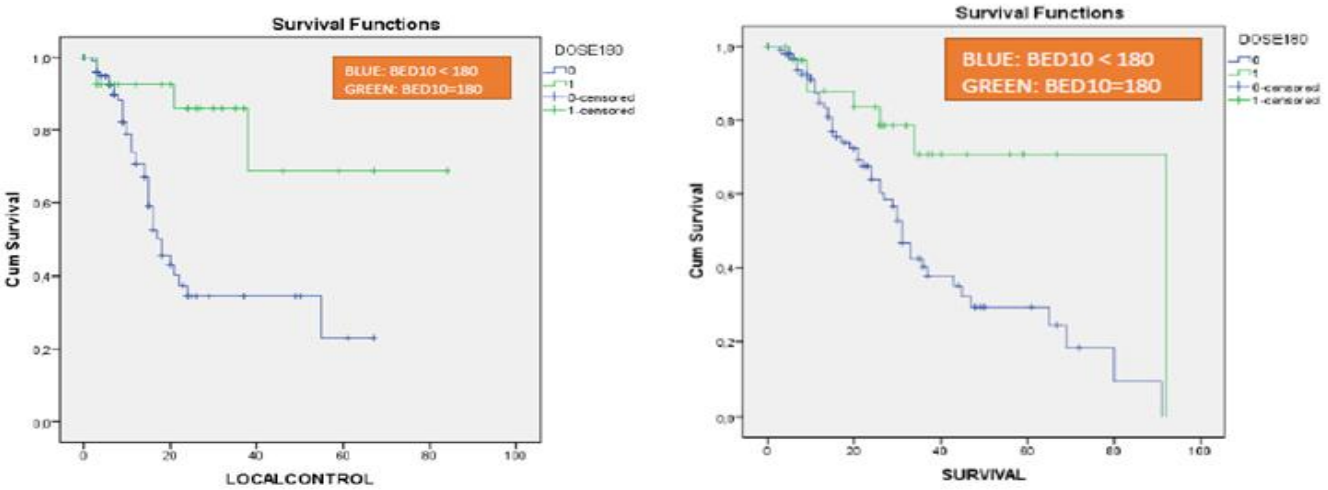
(e)

Figure 2. Treatment planning and follow-up images of the patient who were treated with X Sight Lung tracking method and BED=180Gy. (a) Planning, (b) 3th month control imaging with PR, (c) 12th moths control imaging, (d) 24th month control imaging, (e) 36th month control imaging.



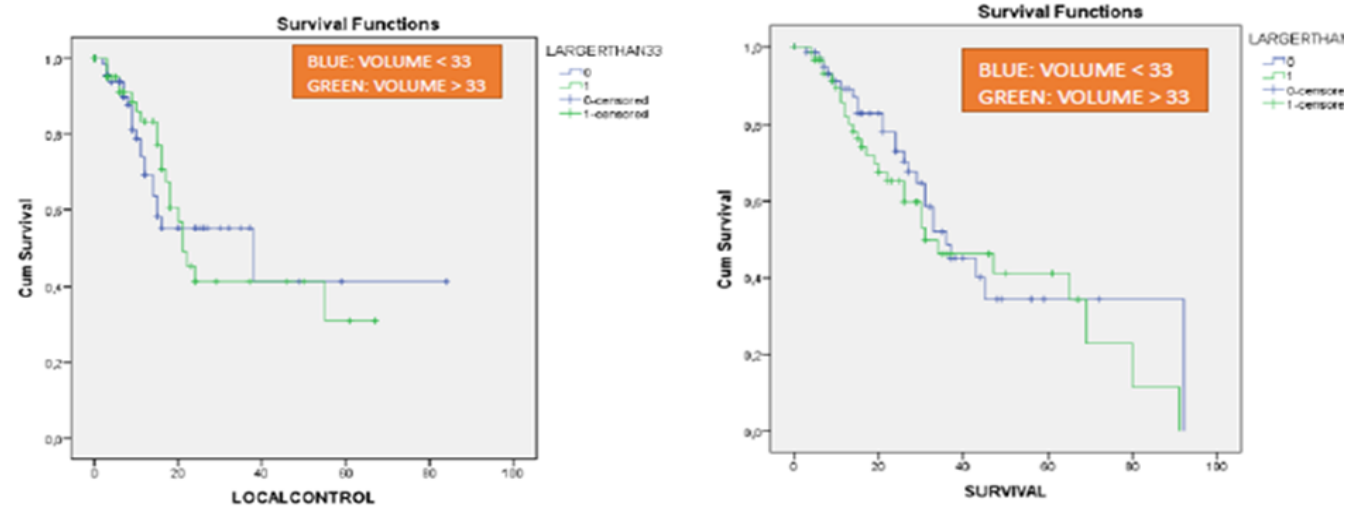
(a) (b)

Figure 3. (a) Kaplan Meier local control and (b) survival graphs of 35 cases



(a) (b)

Figure 4. Effect of treatment dose to local control (a) and survival (b).



(a) (b)

Figure 5. Effect of tumor volume to local control (a) and survival (b).

In MultiPlan, which is the treatment planning system of CyberKnife radiosurgery system, NCI value which provides the coverage of target volume and defined with New Conformity Index was calculated with Equation 3 formulation by Paddick[27] and Nakamura[28] with taking the surrounding critical organs into account. Median NCI value was found as 1.26 (1.02 – 1.85) in the study.

Equation 3. $NCI = \frac{[(\text{Target Volume}) \text{x} (\text{Designated Isodose Volume})]}{(\text{Target Volume Covered By Designated Isodose})^2}$

Local Control and Survival

In 135 cases, 69 of them had CR (51.1%), 50 of them had PR (37%) and 8 of them (5.9%) had SD in first follow-up. In the 8 cases which progression was detected in first follow-up, 3 of them had local progression while others had distant metastasis. In the entire follow-up period, 16 cases had local progression (11%). Local progression period varied between 3 and 23 months. Two cases which were deemed local failure in first follow-up were performed SBRT with CyberKnife again. 3 cases with observed local failure were the cases with 135 cc, 128 cc and 47 cc tumor volumes respectively and were treated with BED<112Gy dose schedule. Local control rates of 1st, 2nd, 3rd, 4th and 5th years were 81%, 54%, 51%, 46% and 39%, respectively. Median follow-up period was 19 months (3-84 months) and median survival was 34 months. Survival rates were calculated as following: 1 year survival was 88%, 2 year survival was 72.3%, 3 year survival was 50%, 4 year survival was 39% and 5 year survival was 39%. Calculated local control rate with Kaplan Meier was shown Figure 3a and survival was shown graphically in Figure 3b.

29 of the 135 cases included in the study were treated with BED10 value of 180Gy dose schedule, 106 cases were treated with dose schedules varying between with BED10 value of 45 and 151. When the effect of treatment dose to local control and survival, using the threshold of median BED10 value of 180Gy dose value was researched; dependency on dosage was found statistically significant for local control and survival. P value was calculated as 0.002 for local control and 0.008 for survival. Kaplan-Meier survival curves for both groups were shown in Figure 4a. 1, 2 and 3 year survival rates for BED10=180Gy group was 89%, 84% and 72% respectively, meanwhile for BED<180Gy, 1, 2 and 3 year survival rates were found as 88%, 68% and 42%, respectively. Kaplan Meier local control curves indicating the difference between local control rates for both groups were shown in Figure 4b. 1, 2 and 3 year local control rates for BED=180Gy group were found as 92%, 86% and 86% respectively, meanwhile 1, 2 and 3 year local control rates for BED<180Gy group were found as 78%, 42% and 38%. Since tumor size is <3 cm in T1 and between 3 cm and 7 cm in T2 stage in T1 and T2N0M0 cases, while looking back at the tumor volumes of 135 cases, median volume was found as 33 cc and distribution was between 2,106 – 174.425 cc. When the effect of this difference on local control and survival was researched by using the threshold of median tumor volume with Kaplan Meier algorithm, no statistical significance was found in both local control and survival in the cases smaller and larger than 33 cc. P value was calculated as 0.934 for local control, it is found as 0.441 for survival. Local control and survival curves according to tumor volume was shown in Figure 5.

Complications

Tumor marking procedure, in immediate aftermath of SBRT application and first follow-up date are included in complications evaluation process for all cases. 4 of the 87 cases, treated by Synchrony Tracking method and tumor marking procedure performed by radiologists, developed pneumothorax during tumor marking. Pneumothorax was treated by aspiration during procedure in 2 of these cases, meanwhile other 2 cases needed tube thoracotomy. After clinic follow-up, all 4 cases started their treatments a week later as planned without problem. SBRT period with median 3 (1-8) fractions and applied consecutively was completed in all cases without any early side effects. Prophylactic subcutaneous injection of steroids was injected to all cases before SBRT application. Fatigue was observed in the majority of cases in 3-6 weeks period after treatment. Grade I radiation pneumonia not requiring any clinic treatment was observed in 15 cases (11%), 8 cases had developed chest wall pain. Additionally, no Grade II and above toxicity caused by treatment has developed in any cases, either acute or late period.

Discussion

Today, SBRT applications are accepted as an alternative treatment to surgery in early stage NSCLC cases[22, 23, 29, 30]. In the phase I/II or retrospective clinic and dosimetric studies conducted, it was shown that local control rates climb above 90-98% with SBRT applications performed with 1-5 fractions with biological effective dose of >100Gy (7) in early stage NSCLC cases with a tumor size smaller than 5 cm, medically ineligible for surgery or do not want to be operated[5, 30-32]. Early stage NSCLC cases or cases with lung metastasis were treated with SBRT with the utilization of real-time tumor tracking ability of CyberKnife radiosurgery system with either fiducial or Xsight Lung techniques in our clinic since 2005. In the lung SBRT applications performed with CyberKnife radiosurgery system, first results were published since 2003[33] but debates about treatment dosage were still ongoing. As it also can be seen in this study, while treatment doses were BED<100Gy in first applications in our clinic, later standard treatment schedule was accepted as 60Gy treatment dose to be applied in 3 fractions. In this study in which the results of 135 cases who have undergone robotic SBRT with median BED=180Gy dose schedule in a median of 19 months follow-up period were examined, local control rates for 1, 2, 3, 4 and 5 years were calculated as 81%, 54%, 51%, 46% and 39% respectively, meanwhile 1 year survival rate was calculated for these years as 88.2%, 72.3%, 50.4%, 39% and 39%, respectively. Due to the difference in both patient groups and treatment doses and techniques in the studies on the results of SBRT-performed cases in literature; local control rates vary between 80-100%. In the study in which the results of 67 cases who had undergone SBRT with CyberKnife are examined by Kelly *et al.* [34], 1 and 2 year local control rates were found as 81.8% and 60.6% respectively, meanwhile 3 year survival rate is reported as 62.4%. Again, in a multicenter study on the results of 283 cases treated with CyberKnife robotic radiosurgery system[35], 2 year survival rate was dropped below this level (54%) due to heterogeneity in both patient stages (T1, T2N0M0) and dose levels (BED=45-180Gy). However, we found 1, 2 and 3 year local control rates in

BED=180Gy group as 92%, 86% and 86%, respectively. Again in the same study, 2 and 3 year survival rates were reported as 75-65% and 64-50%, these rates were also calculated similarly in our study as 72.3% and 50.4%, respectively. Although the treatment dose heterogeneity was high in this study, both local control rates and survival rates were similar to previous studies. As it was mentioned before, it is shown in many studies that local control rate increases simultaneously with BED dose value (5, 30-32). It was similarly obtained in this study that statistically significant BED value of <180Gy group yielded lower local control and survival rates. 1, 2 and 3 year local control rates were found in BED=180Gy group as 92%, 86% and 86%, meanwhile the same rates were 78%, 42% and 38% in BED<180Gy group, respectively. When survival rate was compared for both groups, 1, 2 and 3 year survival rates were 89%, 84% and 72% for BED10=180Gy group, meanwhile these values were 88%, 68% and 42% for BED<180Gy group, respectively. In the study performed by Voort van Zyp et al.[36] which examined the early stage lung cases treated with real-time tumor tracking system; cases treated with BED10=180Gy had a local control rate of 96%, while this number was 78% for the cases treated with BED<180Gy dose. The local control and survival rates obtained by this study conducted by the evaluation of 135 cases treated in our clinic were consistent with the results reported by Erasmus University for 59 cases[36].

In the SBRT applications in which the high doses that will allow ablation of target volume are targeted, geometric accuracy is the single most important factor that affects the treatment success and possible side effects. With the robotic radiosurgery system CyberKnife, intended dose can be transmitted to target volumes with high accuracy in moving tumors particularly like lung tumors using suitable target tracking techniques and IGRT systems, also allowing maximum critical organ preservation. In this study of 135 cases, Synchrony system with respiration tracking treatment is performed for the treatment of 121 cases. However, real-time respiration tracking could not be performed in the treatment of 14 cases who were treated with X Sight Spine technique, who have inappropriate tumor localization and clinically unsuitable conditions for tumor marking. In these cases, 5-7 mm margin values were used instead of 5 mm margins which were used to construct CTV in other techniques. Nevertheless, no correlation between the toxicity and treatment technique was found. In real-time tumor tracking system, the beam positioning is arranged according to the tumor displacement by respiration motion. Therefore tumor is tracked with accuracy under 1 mm, the safety margins to be given to target volumes were drastically reduced. Additionally, high dose gradient was achieved immediately after the tumor by the direction of hundreds of small beams. With these functions of CyberKnife robotic radiosurgery system, maximum preservation is achieved in the critical organs around the target volume. Therefore, high survival is achieved and toxicity caused by treatment can be minimized. Similarly to the study conducted by Kelley et. al.[34] in which the results of 67 cases treated by robotic radiosurgery system are reported; no Grade II or above toxicity was observed after SBRT application in this study either. X Sight Lung tracking methods which do not require tumor marking is available in the CyberKnife system, but these tracking systems are not suitable for every tumor due to some limitations. Therefore, the interventional procedure of tumor marking is inevitable for cases which are nor suitable to treat with X Sight Lung tracking for high accuracy tumor tracking. In this study, 2 of the 4 cases had Grade II toxicity during tumor marking process, but the treatment started without delay after clinic intervention and one week of recovery period. Apart from that, 34 cases are treated with X Sight Lung tracking technique without tumor marking procedure. If the tumor diameter is >1.5 cm and tumor localization is within pulmonary parenchyma, without any junctions to costal region and if the tumor can be seen in 45 degree localized orthogonal radiographs, then lung tumors can be treated with this technique using real-time respiration without any interventional procedures.

Treatment planning of all cases was done with MultiPlan planning system. Planning was done to get the results of median PTV volume receiving the designated dose as 96.2%, median isodose curve that designated the treatment dose as 84% (ranging 67-93), but in this version with calculation algorithm of Pencil Beam used, heterogeneity correction was performed with simple EPL algorithm. Therefore, in these kinds of algorithms, dose calculation accuracy in SBRT applications are lower than more advanced Type b algorithms and complex algorithms such as Monte Carlo which perform 3 dimensional heterogeneity correction in the high heterogeneity difference like lung and in smaller target volumes. In the studies conducted [37-39], when the traditional Ray Tracing algorithm of CyberKnife was compared to the Monte Carlo algorithm which was used as a calculation algorithm in a more advanced version of planning system, this difference reaches 10% in lung SBRT applications. In our clinic, while the aimed dose will be normalized to isodose curve was selected by considering the fact that Ray Tracing algorithm calculates the higher target volume coverage.

One of the deficits of our study was the short period of follow-up. In the study with the median follow-up period of 19 months, follow-up period of 21 cases (15.5%) was 6 months or fewer. Therefore, while estimating the long-term local control and survival rates, these patients had no effect since their follow-ups were shorter than the others. Nevertheless, in this study in which 135 cases treated with robotic radiosurgery system, 1, 2 and 3 year local control rates were found as 9%2, 86%, and 86% respectively for the cases treated with BED=180Gy dose, which was accepted as standard treatment dose schedule. With these high local control rates and low toxicity levels present in our study, early stage NSCLC cases who are ineligible for surgery or reluctant to surgery, robotic SBRT application performed with 60Gy/3 fractionations dose schedule was accepted as routine treatment dose.

According to the dose schedule defined in RTOG0236[11] protocol (60Gy/3 fractions), high local control and low toxicity rates achieved with BED=180Gy SBRT applications and real-time respiration and tumor tracking SBRT applications were found as a safe and efficient treatment option in early stage NSCLC.

Conflict of Interest

We have not had any actual or potential conflict of interest for the article titled “Robotic Radiosurgery in Early Stage Non-Small Cell Lung Cancer Treatment” that we have submitted to you for publishing.

All authors declare no conflict of interest.

We confirm that the material has not been published previously, and will not be submitted for publication elsewhere.

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Author Contributions

CC: Project development, manuscript drafting/writing/editing, data collection, data analysis, literature search, critical revision; AH: Critical revision, data analysis and interpretation; HBA: Study design and conception; KB: Critical revision, data analysis and interpretation; ÖG: study design and conception, supervision, critical revision; KE: Project development, data collection, resources, materials, critical revision, supervision

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