Are three doses of stereotactic ablative radiotherapy (SABR) more effective than 30 doses of conventional radiotherapy?

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Abstract: In early stage non-small cell lung cancer (NSCLC) definitive radiation therapy is an appropriate alternative to surgery. Recent studies show, that in such patients hypofractionation schedules (for example 3 times 18 Gy or 5 times 12 Gy), can be safely applied, without causing severe toxicities and achieving high local control rates of up to 90% and more. In the last couple of years a lot of knowledge about the cancer biology, technical aspects, clinical outcomes and toxicities has been accumulated from different clinical trials. The purpose of this review is to summarize recent outcomes and developments in stereotactic radiation therapy for patients with early stage NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); stereotactic ablative radiotherapy

Introduction

Lung cancer continues to be the leading cause of cancer-related mortality in men and women, whereby the rates recently showed a significant decline in women after continuously increasing since the 1930s (1). For stage I non-small-cell lung cancer (NSCLC), surgery alone results typically in a 5-year overall survival (OS) of 60-70% (2).

For patients with stage I NSCLC who cannot undergo radical resection e.g., for medical reasons, definitive radiation therapy is the appropriate alternative to surgery. For these patients standard fractionated radiotherapy alone can lead to a 5-year OS of 8-15% and a cancer specific survival rate in the range of 30-55% (due to competing risks of death) (3,4). Recent publications also support the strategy of treating only the primary tumor and PET positive lymph nodes (involved node radiotherapy; INRT) instead of treating the elective nodal regions (elective nodal irradiation; ENI) to reduce the volume of irradiated healthy tissue especially keeping the volume of lung that receives more than 20 Gray (Gy) below 35% (using conventional fractionation) (5-8). However, local tumor control after a conventional treatment with 55 to 70 Gy delivered over 4 to 7 weeks is as shown above suboptimal. Available data suggest that conventionally fractionated doses of >70 Gy might be necessary to control >90% of tumors locally (9-11).

Already in 1995, Blomgren *et al.* showed improved local control rates for patients with lung cancer treated with stereotactic hypofractionated radiotherapy compared with conventionally fractionated radiation (9). After a phase of careful dose escalation, single dose treatments at doses of 30 Gy (12) and fractionated treatments with 5×10^{-12} Gy or 3 times 20 Gy are currently applied on various institutional protocols and seem to be reasonably safe, with increase of the tumor control (SBRT prescription of 60 Gy in 3 fractions equates to as much as 150 Gy delivered in conventional fractions) (10,11,13).

The aim of this review is to summarize the updates of the radiobiology, technical aspects and clinical outcomes of SBRT.

SABR/SBRT

Stereotactic body radiation therapy (SBRT) or SABR (stereotactic ablative radiotherapy) is a relatively novel concept in which high doses of radiation are directed focally onto malignant lesions in organ sites other than the brain, including lung, liver, and spine tumors. The idea of SBRT is derived from the experience in treating metastatic lesions in the brain by SRS (stereotactic radiosurgery). In SRS very high radiation doses are

delivered to small brain lesions in a single session, with the intent to ablate all malignant tumor cells in one setting. The success rates of this treatment approach, with local tumor control rates as high as 93.3%, have made SRS a standard of care for limited metastatic disease to the brain (14-16).

SBRT as discussed here will largely adhere to the accepted definition in the United States as the delivery of high-dose focused radiation in one to five fractions onto small malignant lesions. High-dose delivery is most often understood as single fraction doses exceeding 5 Gy. Small lesions are most often defined as being less than 5 cm in maximum diameter. Focal radiation delivery refers to narrow planning target volume (PTV) margins added to a target volume delineated in consecutive slices of a CT, MRI or PET radiation planning dataset. Additionally, SBRT is a radiation therapy modality for which a target has to be directly or indirectly localized before the radiation dose is delivered.

Steep dose gradients between the lung lesions and surrounding normal tissue are a hallmark of SBRT dose distributions, and achieve excellent normal tissue sparing. This is accomplished by using multiple radiation beams which are shaped according to the tumor outline, and are all centered upon the lesion. While each of the radiation beams delivers a small fraction of the cumulative radiation dose, the dose at the target, where all radiation beams intersect, is summing up to high tumoricidal dose levels. Similar dose concentration can be achieved using arc delivery techniques during which a multi-leaf collimator, a radiation beam shaping device, continually adjusts the radiation port to the shape of the target from a given beam's eye view. SBRT radiation plans use 7 to 11 individual radiation beams arranged coplanar or non-coplanar around the target lesion, with little incremental plan quality gained when the number of radiation ports exceeds 9 (17-21).

Extracranial stereotactic radiotherapy poses several challenges for patient immobilization and tumor localization. Framed and frameless systems have been developed for this purpose. In 1995, Blomgren et al. described a technique of SBRT using a custom-made body cast and stereotactic coordinates (22). Lohr et al. introduced in 1999 a body cast and head mask system with a stereotactic body frame for patients with paraspinal tumors in the thoracic and lumbar spine, the same group treated also liver tumors with single dose stereotactic irradiation using a vacuum pillow and an abdominal compression. Both groups reported an acuracy of ≤5 mm (23,24). For the lung, Uematsu et al. introduced 2001 a frameless approach using the FOCAL unit, a combination of linac, kV simulation and a CT-scanner. Breathing with an oxygen mask and an abdominal compression belt allowed the intrafractional tumor motion to be less than 5 mm (25).

The growing interest in SBRT has been driven by advances in the radiotherapy planning imaging techniques and delivering techniques, which allow increasing treatment precision (26). A matter of concern by the use of SBRT technique in the treatment of lung tumors is their potential susceptibility to breathing-induced target movements, which might lead to dosimetric uncertainty and discrepancies between planned and delivered doses. This problem is a major concern for all tumor sites in the thorax (27). In 50% of lung tumors, a movement of 0.5 to 1 cm is observed, in 10% of more than 1 cm (28). While a broad spectrum of movement patterns is observed, by far the predominant direction of movements is longitudinally in the cranio- caudal direction (29). One solution of the breathing motion problem is the use of four-dimensional computed tomography (4D-CT) scans that correlate CT images with respiratory phases, allowing the visualization of the tumor motion (30). The concept of gating uses this information, and will enable radiation beam delivery only when the lung, and thus the target, are in a defined proportion of the breathing cycle (31).

Real-time target tracking (continuous adapting of the radiation beam to the tumor position) or positioning with a fully robotic patient positioning system with six degrees of freedom are methods used to reduce the treatment margins but are not widely clinically implemented (32-34).

Another approach is the use of the breath-hold and respiration-synchronized gating. A breath-hold technique using ABC© (Active Breathing Control, Elekta, Crawley, UK) has been shown to be an accurate and clinically useful tool. It has the advantage of reducing the target motion such that the gross tumor volume (GTV) resembles a primarily static tumor on the planning CT scan. Intra- and interfractional reproducibility of this system is 1.7 and 3.7 mm (35-37).

Clinical experience and toxicity

One of the first SBRT trials for patients with medically inoperable NSCLC was the trial of the University of Indiana. The group recently updated the results of the phase II study. A total of 70 medically inoperable patients were included in the study. The SBRT treatment dose of 60-66 Gy was prescribed to the 80% isodose volume in three fractions. Median follow-up was 50.2 months and the local control at 3 years was 88.1%. Median survival was 32.4 months, the 3-year overall survival was 42.7% and the cancer-specific survival at 3 years was 81.7%. There was no difference in local control or survival between the T1 and T2 tumors, by tumor volume or by peripheral or central location. Grade 3 to 5 toxicity occurred in 5 of 48 patients with peripheral lung tumors (10.4%) and in 6 of 22 patients (27.3%) with central tumors (38).

The Scandinavian group also updated their results from a phase II trial. They treated 57 patients with NSCLC with SBRT with 15 Gy times three with a dose prescription at the 67%

Table 1 Summary of the results of the prospective trials of SBRT for NSCLC

Author [Year]	No. of patients	Dose	Median follow-up	Outcomes
Fakiris *et al.* [2009] Phase II	70	T1: 3x20 Gy T2: 3x22 Gy DP at 80%	50.2 months	3-year LC : 88.1% 3-year OS 42.7% 3-year CSS: 81.7%
Baumann *et al.* [2009] Phase II	57	3x15 Gy DP at 65%	35 months	3-year LC: 92% 1-, 2-, 3-year OS: 86%, 65%, 60% 1-, 2-, 3-year CSS: 93%, 88%, 88% 3-year PFS: 52%
Timmerman *et al.* [2006]	70	3x20 Gy 3x22Gy	17.5 months	2-year LC 95% 2-year OS 54.7%
Koto *et al.* [2007] Phase II	31	3x15 Gy 8x7.5 Gy DP at 80%	32 months	3-year LC: 77.9% (T1) 3-year LC: 40% (T2) 3-year OS: 71.7% 3-year CSS: 83.5%
Ricardi *et al.* [2010] Phase II	62	3x15 Gy DP at 80%	28 months	3-year LC: 87.8% 3-year OS: 57.1% 3-year CSS: 83.5%
Timmerman *et al.* [2010] Phase II	55	3x18 Gy DP at 80%	34.4 months	3-year LC: 97.6 % 3-year OS: 55.8%

Abbbreviations: LC, local control; OS, overall survival: CSS, cancer specific survival; DP, dose prescription.

isodose of the planning target volume. Overall- and cancer-specific survival at 1, 2, and 3 years was 86%, 65%, 60%, and 93%, 88%, 88%, respectively. There was no statistically significant difference in survival between patients with T1 or T2 tumors, but the estimated risk of all failure (local, regional, or distant metastases) was increased in patients with T2 (41%) compared with those with T1 (18%) tumors. Local control at 3 years was 92%, local relapse was observed in four patients (7%) (39).

In 2006, Timmerman *et al.* reported the results of 70 patients treated with SBRT with a dose of 60 to 66 Gy total in three fractions during 1 to 2 weeks. The 3-month major response rate was 60%, the local control at 2 years was 95%. Median overall survival was 32.6 months and 2-year overall survival was 54.7%. Grade 3 to 5 toxicity occurred in a total of 14 patients. Among patients experiencing toxicity, the median time to observation was 10.5 months. Patients treated for tumors in the peripheral lung had 2-year freedom from severe toxicity of 83% compared with only 54% for patients with central tumors (40).

A group from Japan, reported their results of another phase II trial. They performed SBRT for 31 stage I NSCLC patients. SBRT was administered as 45 Gy in 3 fractions, however, when the tumor was close to an organ at risk, 60 Gy in 8 fractions were used. The doses were prescribed at the center of the tumors. The 3-year local control rates of T1 and T2 tumors were 77.9%

and 40.0%, respectively. The 3-year overall and cause-specific survival rates were 71.7% and 83.5%, respectively. Five patients developed acute pulmonary toxicity ≥ grade 2 (41).

Ricardi *et al.* published in 2010 the final results of the phase II trial, where they included 62 patients with stage I NSCLC and treated them with three fractions of 15 Gy each, given every other day during a 1 week time, up to a total dose of 45 Gy. The dose was prescribed to the 80%-isodose encompassing planning target volume. At 3 years, local control rate was 87.8%, cancer-specific survival 72.5%, overall survival 57.1%, the majority of patients did not experience any toxicity; mild skin reactions, fatigue, dyspnea/cough or transient thoracic pain were recorded in approximately 10% of patients (42).

Recently, Timmerman *et al.* published the results of the RTOG 0236 trial. A total of 59 patients accrued, of which 55 were evaluable (44 patients with T1 tumors and 11 patients with T2 tumors) with a median follow-up of 34.4 months. The 3 year primary tumor control rate was 97.6%, the 3-year rate of disseminated failure was 22.1%. The rates for disease-free survival and overall survival at 3 years were 48.3% and 55.8%, respectively. The median overall survival was 48.1 months. Protocol-specified treatment-related grade 3 adverse events were reported in 7 patients, grade 4 adverse events were reported in 2 patients. No grade 5 adverse events were reported (43). *Table 1*
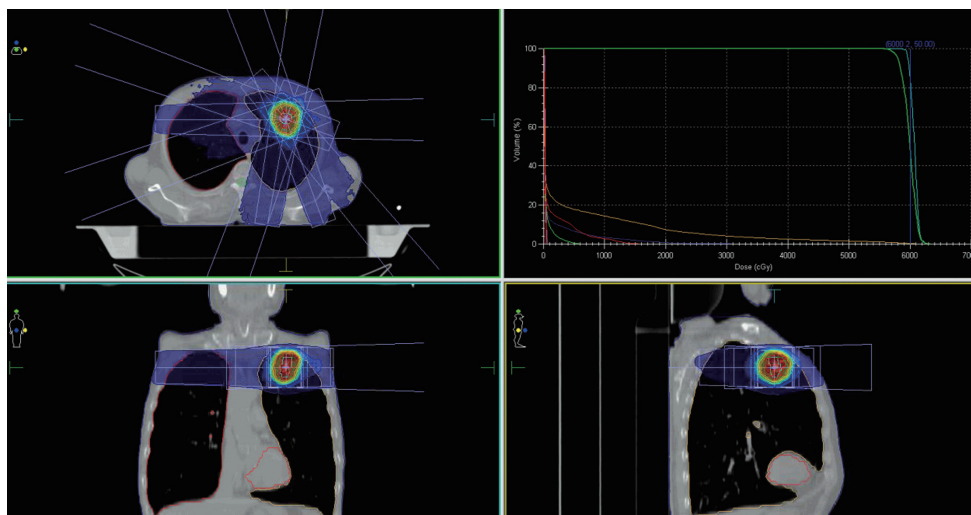
Figure 1 Dose distribution and DVH for one patient, treated with 5×12 Gy SBRT for lung metastases.

summarize the results of the prospective trials of the SBRT for patients with early stage NSCLC.

In a study, accomplished in our department, we included patients with 50 lung lesions who were treated with image-guided breath-hold SBRT with a regimen of 60 Gy in five fractions (*Figure 1*). Breath hold was performed with Active Breathing Control (ABC®, Elekta). Two year overall survival rate was more than 40%. Two-year local control rate was more than 80% without significant toxicity (44).

As shown above, the local control rates are more than 90%, when total doses from 54 to 60 Gy in three fractions are used. Currently, the RTOG 0915 trial is comparing two different SBRT fractionation schedules: 34 Gy in 1 fraction *vs.* 48 Gy in 4 fractions for patients with peripheral stage I NSCLC. The fractionation that proves to be less toxic, will be compared to the SBRT treatment schedule recommended by the RTOG (54 Gy in 3 fractions) in a phase III RTOG trial. The Dutch trial ROSEL (Radiosurgery or Surgery for Early Lung cancer) will compare surgery and SBRT for patients with stage I NSCLC. Primary objectives of the trial will be the local and regional tumor control, quality of life and treatment costs of 2- and 5-years. A similar study is the STARS (Stereotactic Radiosugery *vs.* Surgery) trial, which is comparing surgery and radiosurgery with CyberKnife. Endpoint is the overall survival at 3 years.

High single doses radiation therapy of lung tumors is a special challenge because of diverse reasons such as the highly volume dependent radiosensitivity of the healthy lung tissue and surrounding organs at risk (oesophagus, heart), the breathing-induced motion of pulmonary targets and the dosimetrically difficult situation of a soft-tissue lesion surrounded by low-density lung tissue.

Besides the vital organs at risk heart and oesophagus, the lung itself is one of the most radiation-sensitive organs with two distinctive manifestations of radiation damage with different time frames. As a severe early (subacute) side effect of radiation therapy, pneumonitis occurs in 5-15% 4-6 weeks after conventionally fractionated large-volume thoracic irradiation. Symptoms include dyspnoe upon activity, cough and subfebrile temperatures. The incidence of radiation pneumonitis depends on the radiation dose and the irradiated volume of the normal lung tissue (45). As a late side effect and consequence of radiation pneumonitis, pulmonary fibrosis may arise, rendering the affected tissue without function.

Tumor location is a well known predicting factor, which predicts severe toxicities, when using SBRT (54-60 Gy in 3 fractions) for patients with stage I NSCLC. Voroney *et al*. reported chest wall pain and rib fractures in patients with peripheral lung lesions (46). There is also a higher incidence of severe toxicities, when treating patients with 60 Gy in three fractions with central lung tumors, adjacent to mediastinal structures, defined as within 2 cm of the proximal bronchial tree, brachial plexus, or vertebral body. It seems, that in this cases, it is safer to apply the dose in more than 3 fractions (for example 12 times 5 Gy, 8 times 7.5 or 60 Gy in 4-5 fractions) (40,47,48).

Biological rationale

Over the last decades new insight into biological effects of irradiation in tissue has led to a paradigm change. The single target cell theory and solely cell kill from DNA damage is not sufficient to explain the complex biological effects of radiation. Furthermore, and specifically in SABR, the linear quadratic

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model-which is based on this rather simple theory and obtained from *in vitro* studies-may not be appropriate to assess *in vivo* data from SABR studies (49).

The importance of the tumor-microenvironment, the cross talk of malignant cells and host cells, the tumor bed effect, and the importance of other target cells than cancer cells are focus of intense ongoing research.

In addition, the radiobiology behind the effectiveness of high single doses or a small number of fractions of radiation may be very different from that underlying conventional fractionated non-ablative radiotherapy.

In this respect, endothelial cell apoptosis and micro-vascular dysfunction is observed only after high single doses of at least 8-10 Gy contributing significantly to tumor cell lethality and tumor cure by SABR (50-53). Although, the underlying mechanism of successive tissue damage and conversion of sub-lethal damage in tumor cells to lethal damage is not clear, it might involve leakage of circulating factors, a bystander effect of endothelial damage and ischemia induced complex cellular and molecular signalling.

In this respect, SABR might improve the elimination of potentially existent radio-resistant tumor stem cells which is a prerequisite for cancer cure. Tumor stem cells are thought to have better DNA repair mechanisms (54,55). In between fractions of conventional radiotherapy tumor (stem) cells try to repair sub-lethal damage, they can proliferate and transform into even more radio-resistant cells which possibly might facilitate tumor cell spread. After SABR and consequent micro-vascular dysfunction less repair and even direct apoptosis of cancer stem cells is conceivable. Chang *et al.* observed stem cell apoptosis after single doses of 17 Gy and higher (56).

In summary, endothelial cells and cancer stem cells may require a threshold dose to be crossed before their death is triggered which only can be accomplished by SABR.

Another aspect refers to radiation induced inflammatory and immune response. Radiation-induced inflammatory cytokine production is generally considerably stronger at higher radiation doses. It seems likely that dose fractionation may minimize the damage that results from this source by allowance of tissue repair.

Although likely to generate more inflammation, high local doses may be superior at generating "danger" signalling and rapid cell death and promoting anti-tumor immunity (57,58). Radiation induced massive tumor cell death by SABR leads to release of HMGB1 proteins among others from dying cells. Next to other proteins HMGB1 acts as a danger signal, a so called endogenous damage-associated molecular pattern (DAMP). Dying cells are phagocytosed by immature dendritic cells (DCs). DAMP signal through toll like receptors (TLR4 and TLR2) and are mandatory for host dendritic cells to mature (59). As a result antigen presenting cells (APCs) develop as targets for antigen specific CD8⁺ cells leading to a specific immune response.

As for apoptosis, it was shown that an immune response was optimal after doses of 8-10 Gy and higher.

Altogether, there are several biological aspects that might explain the excellent clinical tumor control rates after SABR.

Technical advancement

Accurate dose delivery to the patient is of utmost importance in external beam radiotherapy (EBRT) particularly if hypofractionated treatment techniques and/or dose escalation are used as in stereotactic body radiation therapy (SBRT). A precise dose calculation, delivery with steep dose gradients between tumor and healthy tissue and accurate tumor localization is essential.

In the last few years a lot of new methods and techniques were introduced in radiotherapy including intensity-modulated delivery (IMRT) with its steep dose gradients. IMRT offers the possibility to shape the dose distribution exactly around the target structures while organs at risk (OAR) are mostly spared. The full potential of IMRT can only be used when safety margins around the targets are reduced.

Image-guided radiotherapy (IGRT) offers the potential to reduce planning margins due to exact patient positioning and thus further helps to increase the therapeutic window (60-62). It has become clinical practice to re-position the patient according to 3D imaging data. To detect internal misalignment of organs relatively to the bony structures, it is preferable to use an image guidance system which is able to discriminate soft tissues. The common systems which can be used for online position correction are CT-on-rails (63), conebeam CT (CBCT) (*Figure 2*) (64-66), ultrasound (67,68) or electromagnetic signals (69). The positive effects of IGRT on the therapeutic dose distribution and the additional imaging dose have already been analysed (70-72).

An exact image guided (or stereotactic) positioning of the patient is rather easy to achieve in rigid structures such as the skull but is a major challenge for mobile organs. Tumors in the thorax and abdomen can move significantly with respiration. This has to be taken into account during the treatment planning process and treatment delivery (73). Several approaches use four-dimensional (4D) CT- or CBCT-datasets, that allow the determination of tumor position in different breathing phases (74-76). However, sometimes the increased time for processing the large amount of data and also the extended and more complex workflow limit the usability in clinical routine (62,74). In contrast to those approaches breathhold techniques (77) have been suggested to reduce the effect of breathing motions while maintaining tight PTV margins around the tumor. With inspiration-breathhold treatment techniques ITV and thus PTV
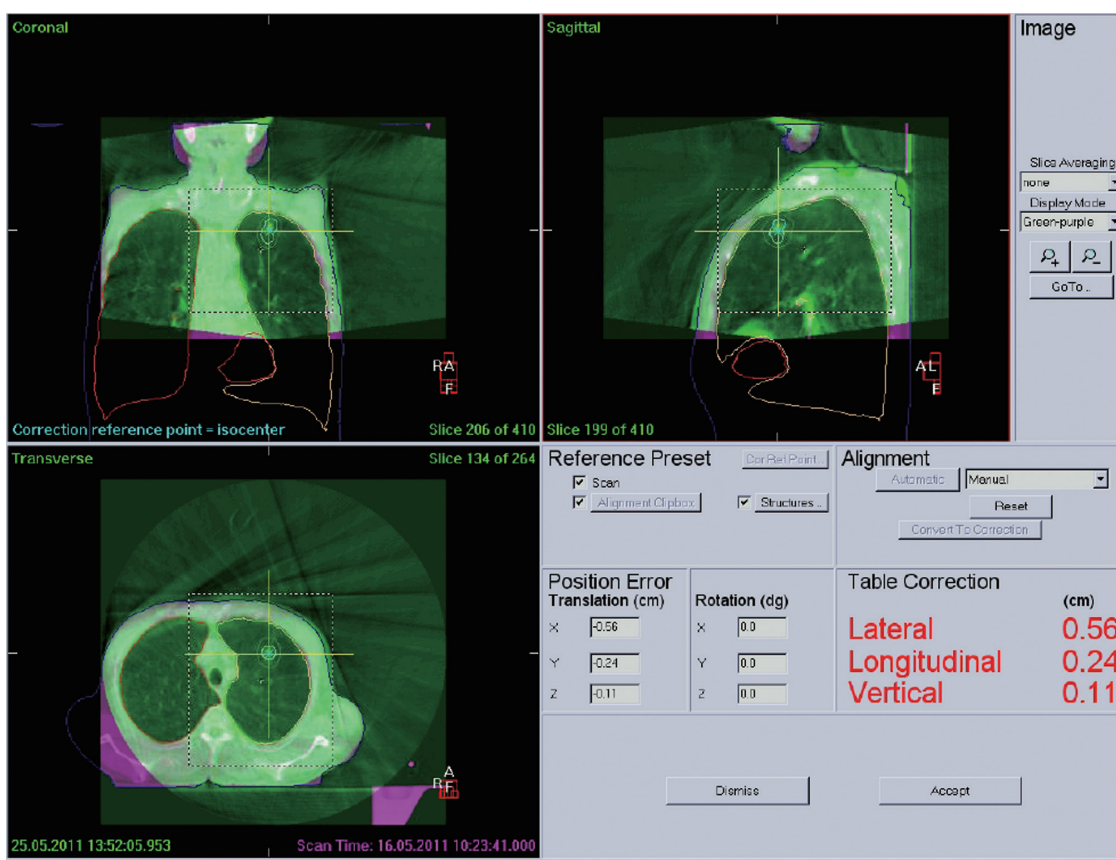
Figure 2 Planning CT (purple) matched on the Cone Beam CT (green) of one patient treated with SBRT for single lung metastasis.

margins can potentially be reduced and doses can be escalated resulting in better tumor control rates. In addition, the total irradiated lung volume and, importantly, lung mass can be kept to a minimum (77-80).

Up to now long image acquisition times of ~60-120 s (kV-CBCT) limit the number of patients who can undergo volume image guidance under breathhold to eliminate motion artefacts. Therefore a new approach was suggested to combine the kV and the MV source of the linac for a simultaneously acquired, fast (~15 s) and accurate kVMV-CBCT reconstruction for image guided patient positioning. kVMV-CBCT based on a standard linac is promising and can provide ultra-fast online volume image guidance with low imaging dose and sufficient image quality for fast and accurate patient positioning for patients with lung cancer under breathhold (81,82).

Conclusions

Highly conformal body-stereotactic treatment with only a few or even single fractions has been successfully applied to extracranial lesions such as lung tumors, achieving high local control rates of more than 90% (97-98% at 3 years). The recommended from the RTOG fractionation schedule of 3 times 18 Gy, can be safely applied, whereby in patients with central tumors it is recommended to use more than 3 fractions (for example 5×12 Gy) to avoid severe toxicities. Additionally, despite comorbidities, SBRT is well tolerated even in patients with lower performance status, due to the less number of fractions (3 to 5). Breathhold techniques can help to reduce the effect of breathing motions while maintaining tight PTV margins around the tumor. During imaging they help to hold the tumor in a quasi stable position and thus reduces motion artefacts to a minimum. However, Long image acquisition times of currently ~60-120 s limit the number of patients who can be imaged with standard on board kV-CBCT for patient positioning at the linac during one breathhold phase. With the implementation combined kVMV-CBCT in the future, a shortening of the imaging time to ~15 s can be expected.

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