



ESTRO-ACROP consensus guideline

ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer



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ABSTRACT

Background: Stereotactic body radiotherapy (SBRT) has become the standard of care for medically inoperable patients with peripherally located, early stage non-small cell lung cancer (NSCLC), and for those refusing surgical resection. Despite the availability of national and international guidelines, there exists substantial variability in many aspects of SBRT practice.

Methods: The ESTRO ACROP guideline is based on a questionnaire covering all aspects of SBRT implementation and practice ($n = 114$ items). The questionnaire was answered by the 11 faculty members of the ESTRO course “Clinical practice and implementation of image-guided SBRT” and their 8 institutions.

Results: Agreement by >50% of the institutions was achieved in 72% of all items. Only 8/57 technologies and techniques were identified as mandatory for SBRT while 32/57 were considered as optional. In contrast, quality-assurance related elements were considered as mandatory in 12/24 items. A consensus of risk-adapted SBRT fractionation was achieved with 3×15 Gy for peripherally located lesions and 4×12 Gy (PTV D95-D99; $D_{max} < 125\%$ to $< 150\%$) for lesions with broad chest wall contact. For patients free from severe comorbidities and with favourable long-term OS expectancy, use of the maximum tolerated dose of 3×18 Gy should be considered.

Conclusions: This ACROP guideline achieved detailed recommendations in all aspects of SBRT implementation and practice, which will contribute to further standardization of SBRT for peripherally located early stage NSCLC.

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Introduction

Stereotactic body radiotherapy (SBRT) has become the standard of care for patients with medically inoperable early stage non-small cell lung cancer (NSCLC), and for those refusing surgical resection [1]. International, multi-disciplinary guidelines (ESMO, NCCN) support the superiority of SBRT over conventionally fractionated radiotherapy, and SBRT is preferred to other ablative methods [2–4]. As a consequence, SBRT for early stage NSCLC is today practiced by the majority of radiotherapy centers in Europe, Canada and the US [5–8].

Despite the availability of multi-disciplinary guidelines recommending SBRT as the standard of care, and despite rapid and broad adoption of SBRT within the radiotherapy community, there exists substantial variability in many aspects of SBRT [9–11]. Such variations are observed in patient selection, staging, equipment used and methodology of SBRT planning and delivery, quality assurance and patient follow-up schedules. This lack of standardization can be explained by several factors and their interactions [12]: (1) rapid developments in new radiotherapy technologies; (2) lack of large scale studies comparing different workflows, procedures and devices; (3) adaptation of SBRT practice to the local situation and available equipment; 4) lack of comprehensive guidelines.

Several guidelines have been published by national and international bodies aiming to standardize and homogenize the practice of SBRT for early stage NSCLC: American Society for Radiation

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Oncology (ASTRO) and American College of Radiology (ACR) on image-guided radiotherapy and SBRT in general [13,14]; European Organisation for Research and Treatment of Cancer (EORTC) on high precision radiotherapy [15]; American Association of Physicists in Medicine (AAPM) on SBRT in general [16]; UK National Radiotherapy Implementation Group Report on implementation of SBRT in general [17]; Canadian Association of Radiation Oncology (CARO) on practice guideline for lung, liver and spine SBRT [18]; German Society for Radiotherapy and Oncology (DEGRO) on SBRT practice for early stage NSCLC [19]; and Canadian Comité de l'évolution des pratiques en oncologie (CEPO) on SBRT for early stage NSCLC [20].

This Advisory Committee on Radiation Oncology Practice (ACROP) Guideline on SBRT for peripherally located early stage NSCLC aims to address unmet needs in current practice guidelines in radiation oncology. Co-authors of this guideline are faculty members of the European Society for Radiotherapy and Oncology (ESTRO) teaching course "Clinical practice and implementation of image-guided SBRT", and were motivated by the needs and questions of course participants especially in areas where variations in practice exist and strong evidence is lacking. Radiation oncologists and medical physicists contributed equally and comprehensively to the development of this multi-professional practice guideline.

It is evident that the therapeutic ratio of SBRT is favorable despite the observed variations in clinical practice. Nevertheless, we believe that this guideline is worthwhile for several reasons: (1) setting minimum requirements may ensure consistent clinical outcomes as the use of SBRT continues to expand; (2) the availability of minimum requirements may facilitate a more rapid adoption of SBRT; (3) result in SBRT practice being more efficient, and thus cost effective; (4) decreased variability of SBRT will improve comparability of outcome between different protocols and studies.

Materials and methods

This ACROP guideline aims to comprehensively cover the methodology of SBRT for peripherally located early stage NSCLC. All radiotherapy-specific aspects of SBRT implementation and practice are addressed, including equipment selection, quality assurance, staff education, training and credentialing, patient selection, treatment planning, fractionation, treatment delivery and follow-up. Although the guideline does not specifically address the details of SBRT for centrally located tumors, key differences in SBRT practice between peripherally and centrally located tumors are presented. The currently available literature does not sufficiently address and cover all aspects of SBRT: consequently, the recommendations of this ACROP guideline represent the opinions of 11 faculty members of the ESTRO course "Clinical practice and implementation of image-guided SBRT" and their eight institutions.

Guideline development started with a questionnaire, which was answered by all faculty members of the ESTRO course "Clinical practice and implementation of image-guided SBRT". All faculty members and their home institutions have long-standing and extensive experience in research and clinical practice using SBRT for early stage NSCLC. The questionnaire was developed by the course faculty, and discussed via e-mail prior to the ESTRO teaching course in August 2015. In the initial step, the questionnaire was answered as comprehensively as possible by all faculty members during the course in August 2015. Following the course, all faculty members discussed the questionnaire with their multi-professional team at their home institutions to provide a comprehensive and balanced opinion of SBRT practice. Final responses from all institutions were available by January 2016. This practice guideline therefore represents the opinions of 11 ESTRO school fac-

Table 1

Definitions of all categories in the survey.

Category	Definition
Mandatory	Minimum equipment and methodology required to achieve clinical outcome in agreement to published prospective clinical trials
Recommended	Equipment and methodology achieving potentially best clinical outcome and best accuracy currently achievable
Optional	Equipment and methodology that might improve clinical outcome and accuracy of SBRT without clinical evidence available, yet
Insufficient	Equipment and methodology resulting in potentially worse clinical outcome compared to published prospective clinical trials
Discouraged	Equipment and methodology resulting in no improvement in accuracy or clinical outcome and in no other obvious advantage

ulty members (4 Medical Physicists and 7 Radiation Oncologists) and of the 8 home institutions (7 of which University hospitals) from 6 European countries. Results of this practice guideline are reported on the institutional level.

For each aspect of SBRT practice addressed, an attempt was made to differentiate between mandatory, recommended, optional, insufficient and discouraged practice. The level of agreement or disagreement observed in the ACROP guideline serves to demonstrate areas of uncertainty. The definitions of all categories are shown in Table 1.

Results

Equipment

For SBRT delivery, conventional C-arm linear accelerators equipped only with an Electronic Portal Imaging Device (EPID) and 10 mm Multi-Leaf Collimator (MLC) are considered as insufficient for lung SBRT (agreement level 5/8 institutions, 62.5%). A C-arm linear accelerator equipped with image-guidance technology with improved image-contrast compared to an EPID, is considered as mandatory (agreement 75%), whereas a dedicated stereotactic C-arm linear accelerator equipped with more advanced image guidance, a high-resolution MLC of <10 mm and improved mechanical accuracy (according to AAPM Task Group 101 [16]) is recommended for best SBRT practice (agreement 75%). TomoTherapy® or dedicated SBRT devices such as the CyberKnife® or Vero® are considered as optional (agreement 75%).

Only volumetric in-room image guidance (agreement 75%) and respiration-correlated 4-dimensional computed tomography (4D-CT) (agreement 62.5%) are considered as mandatory components of SBRT practice, whereas a high-resolution MLC <10 mm is considered as best practice recommendation (agreement 75%). All other equipment is considered as optional with agreements ranging between 62.5% to 100%: fluoroscopy for pre-treatment tumor motion analysis, abdominal compression, active breathing coordinator (ABC), 4D [¹⁸F]fluorodeoxyglucose positron emission tomography (FDG-PET CT) for treatment planning, implanted fiducial markers, implanted Calypso transponders, audio-visual feedback of individual breathing pattern, surface scanner, in-room breathing monitoring, flattening filter free treatment delivery, very-high resolution MLC < 5 mm and a robotic 6 degrees of freedom couch.

Staff teaching, training and credentialing

Written departmental protocols covering all steps of SBRT practice (agreement 100%), institution-specific SBRT implementation and application based on a multi-disciplinary project team (agreement 100%), structured follow-up, and assessment of clinical out-

comes (agreement 100%) are uniformly considered as mandatory components of developing a lung SBRT program. Participation of staff members at dedicated SBRT teaching courses (agreement 87.5%) and vendor-organized dedicated SBRT trainings (agreement 75%), hands-on trainings at SBRT-experienced institutions (agreement 62.5%), and supervision of the first SBRT treatments by SBRT-experienced colleagues (agreement 62.5%) are recommended. External audits, either after the SBRT implementation phase (agreement 50%) or at regular intervals (agreement 62.5%), are considered as optional. The minimum number of lung SBRT treatments performed per year in order to ensure a high-quality SBRT program, was considered to range from 12 to 50 procedures, with a median of 20 treatments per year for each center.

Patient selection for SBRT

All institutions agree that all eligible patients with early stage NSCLC need to be discussed at an interdisciplinary tumor board (agreement 100%). There is no uniform definition of when a patient is medically inoperable, and most institutions define inoperability based on discussions at the interdisciplinary tumor board. However, all institutions offer SBRT as the treatment of choice for operable patients who refuse surgical resection (agreement 100%). Biopsy confirmation of malignancy is recommended but not mandatory (agreement 87.5%) prior to SBRT, provided that the clinical diagnosis of malignancy is consistent with existing guidelines. There is no consensus whether FDG-PET is mandatory (agreement 50%) or recommended (agreement 50%) for nodal and systemic staging; however, if used, the staging FDG-PET imaging should not be older than median 2 months (range 1–6 months). Cranial MRI is discouraged in patients staged cN0 with early stage NSCLC, and the role of staging endoscopic ultrasound as a routine procedure remains investigational.

Institutions agreed (62.5%–100%) that there are no absolute contraindications for lung SBRT in terms of age, Charlson Comorbidity score, chronic obstructive pulmonary disease (COPD) GOLD classification and pre-treatment pulmonary function. However, the majority of the institutions agree on a minimum ECOG performance status of 3 (agreement 75%) and a minimum life expectancy of 1 year (agreement 75%). SBRT after pneumonectomy (agreement 100%), SBRT for two simultaneous primaries (8/8) and SBRT of centrally located tumors (agreement 87.5%) are practiced routinely by the majority of institutions. The upper limit (agreement 87.5%) of tumor diameter considered acceptable for SBRT is a median of 5 cm (range 5–8 cm).

Patient counseling

Table 2 shows, how the therapeutic ratio of SBRT compared to other treatment options is communicated by the institutions surveyed to their patients. This comparison assumes that the patient is fully eligible for the comparative treatment option, e.g. a resectable and operable patient for lobectomy.

Table 2

Comparison of SBRT with other local treatment options according to the surveyed institutions. One institution remained undecided in the comparison of SBRT and RFA.

	SBRT superior to	SBRT equivalent to	SBRT inferior to
Best supportive care	100%	0%	0%
Conventionally fractionated radiotherapy	87.5%	12.5%	0%
Radiofrequency ablation	75%	12.5%	0%
Wedge resection	50%	50%	0%
Segmentectomy	12.5%	75%	12.5%
Lobectomy	0%	62.5%	37.5%

Overall, a consensus exists between the institutions surveyed that SBRT is superior to options such as best supportive care, conventionally fractionated radiotherapy and radiofrequency ablation, and that it is equivalent to segmentectomy and lobectomy. Whether SBRT achieves superior or equivalent outcome compared to a wedge resection is considered inconclusive.

Treatment planning

The use of SBRT-specific immobilization devices like the stereotactic body frame (agreement 62.5%) or the BodyFix system (50%) are considered as optional, and the same is true for abdominal compression (agreement 87.5%) and administration of intravenous (IV) contrast for CT imaging (agreement 37.5%). Acquisition of a dedicated planning FDG-PET for target volume definition is optional (agreement 87.5%). However, CT imaging with IV contrast and FDG-PET imaging may be more useful for centrally located lesions.

SBRT using population based (i.e. non-personalized) margins without a 4D breathing motion compensation strategy is either discouraged or insufficient (agreement 87.5%). The internal target volume (ITV) concept is mandatory as minimum motion compensation strategy (agreement 87.5%); the mid-ventilation strategy is considered as recommended (agreement 37.5%) or optional (agreement 50%). Gated beam delivery (agreement 75%) or real-time tumor tracking (agreement 87.5%) are optional technologies.

Based on the mandatory use of a 4D breathing motion compensation strategy, respiration correlated 4D-CT imaging for treatment planning is considered mandatory by 50% institutions; the other 4 institutions considered other 4D-imaging approaches such as slow-CT or repeated 3D-CTs as sufficient as well. 4D-CT images should be reconstructed with a slice thickness of 3 mm (range 2–3 mm). Median 6 (range 2–10) respiration phases are reconstructed for evaluation of breathing motion, reconstruction is most frequently performed with a phase-based sorting algorithm (agreement 62.5%) and reconstructions like average intensity projection or maximum intensity projection are not used by the majority of the institutions (agreement 62.5%).

All but one institution use 0 mm GTV-to-CTV margins and the minimum CTV-to-PTV margin is median 5 mm (range 3–7 mm). There is no consensus to whether evaluation of institution-specific CTV-to-PTV margins is mandatory (agreement 50%), recommended (agreement 25%) or optional (agreement 25%) component of an SBRT program.

A 3D conformal technique is mandatory and therefore sufficient for SBRT planning (agreement 75%) whereas VMAT is considered as recommended for best SBRT practice (agreement 62.5%). Non-coplanar beam directions are most frequently considered as optional (agreement 50%). Type A dose calculation algorithms without a 3D-based heterogeneity correction are insufficient (agreement 75%) whereas type B algorithms, e.g. superposition-convolution or collapsed cone algorithms, are mandatory (agreement 87.5%); Monte Carlo dose calculation is optional (agreement 62.5%). Grid size for dose calculation is median 2 mm (range 2 mm–3 mm).

Dose is most frequently prescribed to a PTV encompassing isodose line (agreement 37.5%) or D99%–D95% values of the PTV (agreement 37.5%). The use of a consistent dose inhomogeneity and dose profile within the PTV is recommended by the majority of the institutions (agreement 62.5%).

Dose and fractionation

A risk adapted fractionation strategy is an essential component of any lung SBRT program (agreement 87.5%). We distinguished between peripheral tumor location and peripheral tumor location with broad chest wall contact. An overview of the prescribed doses

and fractionations is shown in Table 3: results are listed for 7/8 institutions, where dose prescription is performed as minimum PTV doses (PTV encompassing isodose or volumetric prescription D99%–D95%). Maximum PTV doses range between $\leq 125\%$ and $\leq 150\%$ of the prescription dose. One institution performs dose pre-

scription to the GTV, which makes a direct comparison difficult (see Table 4).

There are currently no uniformly accepted normal tissue dose constraints, but the majority of the institutions use constraints which were defined and developed in-house (agreement 62.5%).

Table 3
Overview of PTV prescribed doses (PTV D99% – D95%) and fractionations of 7/8 institutions and consensus fractionation of the ESTRO ACROP Guideline. All doses are calculated using only a type B dose calculation algorithm.

Tumor location	Institutional specific fractionations	Consensus fractionation of the ESTRO ACROP Guideline		
		PTV prescribed dose (D99% – D95%)	BED10 of prescribed PTV dose	Maximum doses within the PTV
Peripheral location	3 × 13.5 Gy (n = 2)	3 × 15 Gy	113 Gy BED10	$\leq 125\%$ to $\leq 150\%$
	3 × 15 Gy (n = 1)			
	3 × 17 Gy (n = 1)			
	3 × 18 Gy (n = 2)			
	4 × 12 Gy (n = 1)			
Broad chest wall contact	3 × 13.5 Gy (n = 1)	4 × 12 Gy	106 Gy BED10	$\leq 125\%$ to $\leq 150\%$
	3 × 15 Gy (n = 1)			
	3 × 17 Gy (n = 1)			
	4 × 12 Gy (n = 1)			
	5 × 9 Gy (n = 1)			
	5 × 11 Gy (n = 2)			

Table 4
Overview of all mandatory and recommended work-flow and equipment of SBRT for early stage NSCLC (>50% agreement).

SBRT workflow or equipment items	Mandatory (minimum) requirements	Recommended for best practice
Equipment	C-arm linear accelerator with volumetric in-room image guidance	Dedicated C-arm stereotactic linear accelerator (more advanced IGRT, more precise accuracy)
Staff teaching, training and credentialing	Respiration correlated 4D-CT	High-resolution MLC <10 mm
	Written departmental protocols	Participation in dedicated SBRT teaching course (e.g. ESTRO)
	Multi-disciplinary project team for SBRT implementation and application Structured follow-up for clinical outcome assessment	Participation in Vendor-organized dedicated SBRT training Hands-on training at SBRT-experienced center Supervision of first SBRT treatments by SBRT-experienced colleague
Patient selection for SBRT	Discussion in interdisciplinary tumor board Minimum ECOG 3 Minimum life expectancy of 1 year	Biopsy confirmation of malignancy
Treatment planning	3D conformal treatment planning Type B algorithms Respiration correlated 4D-CT imaging ITV based motion management strategy	Dynamic IMRT planning (VMAT) Use of a fixed dose inhomogeneity in PTV
Dose and fractionation	Risk adapted fractionation schemes for peripheral and central tumors, and for tumors with broad chest wall contact	
Inter- and intra-fraction image guidance	Daily pre-treatment volumetric image-guidance	Daily pre-treatment 4D volumetric image-guidance (in-room 4D-CT, 4D-CBCT)
Follow-up	Follow-up according to published guidelines	Routine biopsy confirmation of imaging-defined local failure only in patients who are likely to undergo salvage therapy
Quality assurance	FDG-PET imaging in case of suspected local recurrence	
	Intensified quality assurance (mechanical accuracy of 1.25 mm and a dosimetric accuracy of 3% in a lung phantom inside the treatment field)	End-to-end testing in a moving 4D lung phantom
	Small field dosimetry detectors for commissioning	
	End-to-end testing in a lung phantom	
	Quality assurance of in-room image-guidance systems and of the 4D-CT scanner	
	Weekly checks of the mechanical accuracy of the delivery system Daily quality checks of the alignment of the IGRT system with the MV treatment beam	

Five institutions used recommendations of the DEGRO Working Group Stereotactic Radiotherapy ($n = 1$), QUANTEC ($n = 1$), Lung-Tech ($n = 1$), RTOG ($n = 1$), TG 101 report ($n = 1$) and ROSEL trial ($n = 1$) for development of in-house normal tissue constraints.

The linear quadratic model is used by the majority of the institutions (agreement 87.5%) for comparison of different SBRT fractionation schedules.

Inter- and intra-fraction image guidance

Patient set-up based only on external stereotactic coordinates is insufficient or discouraged (agreement 75%). Instead, daily pre-treatment volumetric image-guidance using cone-beam technology or in-room-CT is considered mandatory in 6/8 institutions and respiration correlated 4D volumetric image guidance is recommended as best practice (agreement 87.5%). Image-guidance using planar X-ray imaging with tumor-implanted markers is considered as optional (agreement 50%) but this is insufficient when used without implanted markers (agreement 75%), as is portal imaging (agreement 87.5%).

Intra-fraction patient or tumor position monitoring using any available technology is not mandatory (agreement 100%) nor recommended (agreement 75%). In detail, intra-fraction EPID imaging in flight mode, intra-fraction imaging using planar x-rays, use of surface scanners or daily post-treatment imaging are all optional (agreement 62.5%–75%). However, intra-fraction target position verification does play an important role if active breathing motion compensation is used such as gating and real-time tumor tracking. There is no premedication used in routine clinical practice prior to lung SBRT.

Quality assurance

Rigorous quality assurance is a mandatory component of any lung SBRT program. This is because of high requirements in terms of needed mechanical accuracy (vector length) of median 1.25 mm (0.5–4 mm) and a dosimetric accuracy of median 3% at isocenter (2–5%) in a lung phantom inside the treatment field.

Mandatory QA measures are dedicated small field dosimetry detectors for commissioning (agreement 100%), end-to-end testing in a lung phantom (agreement 62.5%), quality assurance of in-room image-guidance systems (agreement 100%), and of the 4D-CT scanner (agreement 87.5%). End-to-end testing in a moving 4D lung phantom, however, is recommended (agreement 75%) but not mandatory. Quality checks of the mechanical accuracy of the delivery system (for example Winston Lutz test) should be performed in minimum weekly intervals (agreement 62.5%) whereas quality checks of the alignment of the IGRT system with the MV treatment beam needs to be performed daily (agreement 50%) or weekly (agreement 37.5%). There is no consensus about patient-individual quality assurance of 3D conformal treatment plans. However, patient-individual quality assurance of VMAT planning is considered as mandatory (agreement 50%) or recommended (agreement 50%).

Follow-up

Patient follow-up according to published guidelines is a mandatory component of any SBRT protocol (agreement 62.5%). Specifically, 4/8 institutions use the algorithm proposed by Huang et al. for follow-up after lung SBRT [58]. It is recommended to perform follow-up imaging, or image evaluation, at the treating center (agreement 50%); detailed knowledge of the patients SBRT dose distribution is considered very important for the correct interpretation of follow-up images.

Specifically, FDG-PET imaging is considered mandatory (agreement 62.5%) in case of suspected local recurrence on CT images

(agreement 62.5%), but it is only optional during regular follow-up (agreement 62.5%). There was no agreement on a fixed SUV cut-off for differentiation between fibrosis and local recurrence. Routine biopsy confirmation of imaging-defined (CT and FDG-PET) local failure is recommended (agreement 62.5%) only in patients who are likely to undergo salvage therapy if recurrence is detected.

Discussion

This ACROP guideline provides comprehensive information on all aspects of multi-professional development, implementation and practice of a SBRT program for peripherally located early stage NSCLC. Good agreement was observed between the 8 institutions involved in establishing this ACROP guideline for the majority, but not all, items: a consensus based on a >50% level of agreement was achieved in 72% of all items. The overall close level of agreement is encouraging as high-level evidence in some areas is lacking, and strengthens the applicability of this guideline. This level of agreement was achieved despite the diversity of SBRT delivery technologies at the authors' institutions: C-arm linac based SBRT using Varian and Elekta technologies, CyberKnife[®], Vero[®] and TomoTherapy[®].

An important message of this guideline is that lung SBRT does not require and is not defined by one or more technologies: high quality SBRT is possible and recommended independently of many technologies, which are marketed specifically for this SBRT indication [21]. This is highlighted by the small number of technologies and techniques, which were identified as mandatory for SBRT in this guideline: when focusing on technological and physics related items, only 8/57 items were identified as mandatory. 6/57 items were recommended for best practice, but the majority of 32/57 technologies and work-flows were considered as optional. This recommendation is in agreement with the excellent outcome of all prospective phase II trials of SBRT for early stage NSCLC: local tumor control was high with a favorable toxicity profile despite the relatively undemanding requirements on the technological aspects of SBRT from a 2016 perspective [22–27]. Consequently, the high investment costs associated with dedicated SBRT technology should not be a barrier to starting a lung SBRT program.

In contrast to the moderate technological requirements and recommendations, this guideline demonstrates the importance of creating a SBRT-adapted, consistent and comprehensive quality-assurance strategy. This involves not only intensified medical physics quality assurance aspects but especially building a multi-disciplinary SBRT team, SBRT-specific teaching and training of all multi-professional team members, integration of lung SBRT into the inter-disciplinary lung cancer care, and structured follow-up for outcome assessment. In questions covering these areas, 12/24 items were identified as mandatory and another 9 as recommended; only 3 items were considered as optional. Financial and human resources required for these areas need to be made available before starting an SBRT program. Continuous education after implementation of the SBRT program was not addressed in our survey, but it is considered important in the rapidly evolving field of SBRT. Finally, a multi-professional team with sufficient experience was considered as important to establish and maintain a high-quality SBRT program: minimum 12–50 SBRT procedures per year for each center, with a median of 20 treatments, are recommended to build-up sufficient experience [21,28].

Patient selection for lung SBRT needs to be performed within the multi-disciplinary tumor board. SBRT is now a guideline-recommended treatment for patients being medical inoperable; however, inoperability is poorly defined in the literature [29] and our guideline was not able to clearly define inoperability. This is

caused by variations in surgical approaches (lobectomy versus sublobar resection), variations in local and regional expertise in thoracic surgery, interpretation of surgical risks of morbidity and mortality and finally variability in interpretation of the existing literature, where highest level of evidence in the form of randomized trials is lacking.

In the pre-SBRT era, a relevant proportion of patients at advanced age or suffering from severe comorbidities were not offered a curative treatment approach but were managed with best supportive care, only [30,31]. SBRT is recommended as curative and well tolerated treatment to this high risk population; only ECOG performance status >3 and estimated life expectancy of <1 year were identified as contraindications for SBRT. Other factors like old patient age [32–34], severe comorbidities and poor pulmonary function should not prevent recommendation of SBRT as a curative and well tolerated option [35–37]. Clinical situations, which are potentially associated with an increased risk for toxicity, do not preclude use of SBRT, for example following a contralateral pneumonectomy [38–40], treatment of two simultaneous primaries [41,42] and treatment of centrally located NSCLC [43,44]. Recently, idiopathic pulmonary fibrosis (IPF) has been identified as a risk factor for severe radiation induced pneumonitis but was not a relative contraindication for SBRT in the majority of the institutions [45–47]. However, all institutions agree that more extensive SBRT experience is required in these situations and institutions starting their SBRT program should refer such patients to more experienced colleagues.

As expected, variability between the institutions was largest in the question of SBRT dose and fractionation. There was a strong consensus that different SBRT fractionation schedules should be compared after conversion of physical doses into 2 Gy-equivalent doses or biologically effective doses (BED) using the linear-quadratic model [48,49]. Additionally, inhomogeneous dose profiles inside the PTV are standard in lung SBRT with maximum doses of <125% to <150% compared to the prescription dose. However, there was less agreement on the methodology how to prescribe dose: the practice was divided into dose prescription to a PTV encompassing isodose, DVH-based dose prescription using D99% – D95% values of the PTV and one institution prescribed dose to the GTV. Despite the known limitations of current dose prescription methods, volumetric dose prescription to PTV D95% – D99% is recommended. Reporting of SBRT doses should include volumetric PTV minimum doses (D95–D99%), PTV maximum doses (D1–D5%) as well as GTV doses (mean or median).

After all authors had stated their institutional dose and fractionation standards, they were asked whether they would also support and recommend one consensus fractionation for each tumor location: 3 × 15 Gy for peripherally located lesions (dose maximum <125% to <150%) and 4 × 12 Gy (dose maximum <125% to <150%) for lesions with broad chest wall contact (Table 3). These values are volumetric dose prescriptions to PTV D95–D99% and both recommended fractionations are above 100 Gy BED10, the dose threshold for achieving >90% tumor control probability [49–55]. Both the 3 [24,27,56] and 4 [57] fraction protocols have been validated in prospective phase II trials for early stage NSCLC and achieved local tumor control rates of about 90%. These consensus doses and fractionations are supported by all eight institutions for patients with medically inoperable disease.

It is important to note that radiation doses cannot be interpreted fully independently from the overall treatment protocol and treatment technique (e.g. the motion-management strategy, treatment planning objectives, margin, and dose calculation algorithm); the dose recommendations above are therefore only valid in the context of this ACROP guideline. Additionally, evidence of SBRT for early stage NSCLC is predominantly based on medically inoperable patients, where overall survival is often limited. How-

ever, SBRT is increasingly being used for operable patients who refuse surgery and their competing risk of death from causes other than cancer is much lower. In patients with peripherally located stage I NSCLC free from severe comorbidities and with favorable long-term overall survival expectancy, use of the maximum tolerated dose of 3 × 18 Gy should be considered.

Although we have addressed aspects of SBRT for centrally located tumors, and despite the fact that SBRT for this indication is currently practiced by the majority of the authors institutions, we acknowledge the fact that substantially less evidence is available to allow for recommendations to be made. Published results of prospective trials e.g. RTOG 0813, HILUS and EORTC LungTech are not yet available. Therefore, even though all authors agreed on a need for conservative risk-adapted fractionation for central tumors, no optimal fractionation schemes have been recommended.

In summary, this ACROP guideline about SBRT for peripherally located, early stage NSCLC aims to improve standardization by providing detailed information on all aspects of multi-professional development, implementation and practice of the SBRT.

Conflict of interest statement

The authors declare that they have no competing interests. None of the authors has any financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work.

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