Web Appendix

Inclusion and exclusion criteria, and clinical trial requirements, per indication.

Indication	*Inclusion criteria*	*Exclusion criteria*	*Only as part of a clinical study?*
Primary tumours			
Primary lung tumour	Multidisciplinary team (MDT) confirmed diagnosis of NSCLC	Any tumour that is not clinically definable on pre-treatment imaging	No
	Clinicat stage T1 or T2/T3 (≤5cm) N0 M0	Significant overlap with previous radiotherapy fields	
	Not suitable for surgery	Advanced interstitial lung disease	
	WHO Performance Status 0-2.		
	Peripheral lesions outside a 2cm radius of main airways/proximal bronchial tree. This is defined as 2cm from the bifurcation of the second order bronchus e.g. where the right upper lobe bronchus splits		
Primary prostate tumour	Localised disease (stage T1/T2, N0 M0)	Previous radiotherapy to the pelvis or brachytherapy to the prostate	Yes
		Prostate surgery	
Primary liver tumour	Histologically or radiologically confirmed unresectable HCC	Previous abdominal radiotherapy that would make delivery of the liver radiotherapy exceed normal tissue constraints	Yes
	ECOG performance status ≤2.0	Inability to meet normal tissue dose constraints	
	Life expectancy >3 months	Previous anti-cancer therapy within four weeks of SBRT	
	≥ 18 years of age	Uncontrolled bleeding disorders, active GI bleeding or PT-INR/APTT ›1.5x upper limit or normal	
	A single lesion with maximum dimension of 6cm or up to three lesions with a summed diameter of 6cm	Pregnant women	
	>700cc normal (un-involved liver)	Patients with signs of liver failure including gross ascites or hepatic encephalopathy	
	Child-Pugh liver function A5 or A6		
	Normal lab work defined locally, but recommended as: leukocytes ≥3000/mcL, absolute neutrophil count ≥1500/mcL, platelets ≥100,000/mcL, haemoglobin ›10g/dL, total bilirubin within normal institutional limits, AST/ALT ≤ 6x institutional upper limit of normal, negative B-HCG for women of child-bearing age		
	Largest burden of disease within the liver		

Primary pancreatic tumour	T1-4 (inoperable) N0 M0 disease. Distant disease should be excluded on CT +/- PET, either before starting chemotherapy, or at time of consideration of SBRT	Any nodal or distant metastatic disease	Yes
	ECOG Performance Status 0-2	Any tumour with an infiltrative pattern of growth such that it is not possible to define the target volume	
	Evidence of partial response or stable disease following primary chemotherapy for at least 5 months, as assessed by CT (and Ca 19-9 if marker was originally elevated)		
	CTV should be < 100 cm3		
	Evidence of response or stable disease following chemotherapy if used		
Primary renal tumour	MDT confirmed diagnosis of renal carcinoma based on CT scan	Primary renal tumours with stage >T1a	Yes
	Clinical stage of T1a (limited to kidney <4cm)		
	Not suitable for surgery because of medical co-morbidity, contralateral nephrectomy, lesion is technically inoperable or patient declines surgery after surgical assessment.		
	WHO performance status 0-2		
	Metastatic disease is not a contraindication if limited (max 3 lesions excluding primary), indolent and local treatment to the primary otherwise indicated		
Primary head & neck tumour	Not appropriate for most sites, but: - Possible use as boost in nasopharyngeal and oropharyngeal sites - Possible use for recurrent disease following conventional radical radiotherapy		Yes
Metastatic lesions			
Lung metastases	Maximum 3 lung metastases, not suitable for surgery	Any tumour that is not clinically definable on pre-treatment imaging	No
	Location criteria as for lung cancer	Significant overlap with previous radiotherapy fields	
		Advanced interstitial lung disease	
Liver metastases	Histologically confirmed liver metastases or histological confirmation of a primary cancer with growing enhancing lesions within the liver consistent with metastases	Previous upper abdominal radiotherapy that would preclude partial re-irradiation of the liver to within normal tissue dose constraints	No
	Tumours which are unresectable (hepatobiliary MDT decision) or medically inoperable intra-hepatic metastases	Progressive extra-hepatic malignant disease which cannot be controlled with surgery, radiotherapy or systemic therapy	

	Patients who have been considered for RFA but found to be unsuitable (lesion diameter ≥ 3cm, lesion adjacent to liver capsule or major bile duct or adjacent to large (≥1cm diameter) blood vessels)	Previous anti-cancer therapy within four weeks of SBRT	
	3 or fewer intra-hepatic lesions	Uncontrolled bleeding disorders or PT-INR/APTT > 1.5x upper limit of normal	
	Maximum individual tumour diameter < 6cm (suggestion only)	Patients with signs of liver failure including hepatic encephalopathy	
	ECOG performance status ≤ 2	Child-Pugh Class B/C (in those patients with liver dysfunction)	
	Life expectancy >3 months	Active hepatitis	
	> 700cc normal/un-involved liver	Gross ascites	
	Adequate organ function: Haemoglobin ≥ 9 g/dL, neutrophils ≥ 1.0 bil/L, platelets ≥ 80 bil/L, AST or ALT < 6 x ULN, reasonable renal function	Pregnant women	
(Para)-spinal metastases*	≤2 spinal segments involved	Previous radiotherapy in the same region, that would make delivery of the spinal/paraspinal radiotherapy exceed normal tissue constraints	No
	Tumour > 3 mm from the cord	Inability to meet normal tissue dose constraints	
	Well defined lesions on imaging.	Previous anti-cancer therapy within four weeks of SBRT	
	No spinal instability.	Pregnant women	
	Limited systemic disease which is controlled = no extraspinal disease activity, not more than 3 metastatic lesions		
Lymph node metastases	SBRT to isolated lymph node metastases from solid tumours, only when clinically relevant		Yes
	In total maximum 3 metastatic lesions		
Other oligometastases	Only if maximum 3 metastatic lesions	metastatic disease (> 3 lesions)	Yes
	(remark: all metastatic lesions count: intracerebral lesions, liver and/or lung metastases…)		

Note:
The in- and exclusion criteria were derived from the then available clinical evidence, summarised by the NHS National Radiotherapy Implementation Group

*primary (para)spinal lesions were accepted in the CED program, following the same criteria defined for (para)spinal metastases

Abbreviations: MDT: multidisciplinary team; NSCLC: non-small cell lung cancer; WHO:World Health Organisation; HCC: hepatocellular carcinoma; ECOG: Eastern Coöperative Oncology Group; SBRT: stereotactic body radiotherapy; PT-INR/APTT: prothrombin time-international normalised ratio/ activated partial thromboplastin time; AST: aspartate transaminase; ALT: alanine transaminase; B-HCG: human choriongonadotrofine; CT: computed tomography; PET: positron emission tomography; CTV: clinical target volume; RFA: radio frequency ablation

Belgian Cancer Registry

Innovative RT – SBRT

The variables with REQ in superscript are required.

The variables with a ❍ are single-select variables; only one answer can be selected.

The variables with a ❑ are multi-select variables; multiple answers can be selected.

Version 29-01--2016

Administrative patient data

Hospital [REQ]: .....
Health insurance institution [REQ]: .....
NISS/INSZ number [REQ]: .....
Last name [REQ]: ..... First name [REQ]: .....
Postal code [REQ]: ..... City [REQ]: .....
Country [REQ]: ..... Health insurance number: .....
Date of birth [REQ]: …. / …. / …. (dd/mm/yyyy) Sex [REQ]: .....

❍ **I confirm that this registration meets the inclusion criteria of the project '2011-26 HTA_Innovative radiotherapy' and is in accordance with the convention for financing of the project 'Innovative techniques in radiotherapy' [REQ].**
An overview of the techniques and cancer indications can be found in the KCE Report 198C (Table 1).
The inclusion criteria and guidelines for each of the applications of SBRT can be found in the NRIG SBRT document on the website of the National Cancer Action Team of the NHS (*http://ncat.nhs.uk/radiotherapy/treatments*) and in attachment 1 of the convention for financing of the project 'Innovative techniques in radiotherapy'.

1. Diagnostics

Lesion to treat [REQ]: ❍ Primary tumor (Complete 1A)
❍ Metastasis (Complete 1B)
❍ Relapse of the primary tumor (Complete 1B)

A. Primary tumor

Incidence date primary tumor [REQ]: ……. / ……. / ……. (dd/mm/yyyy)

Basis for diagnosis primary tumor [REQ]:

- ❑ 1 - Autopsy
- ❑ 2 - Histology of primary tumor
- ❑ 3 - Histology metastasis
- ❑ 4 - Cytology/hematology
- ❑ 5 - Technical (f.ex. CT scan, endoscopy, …)
- ❑ 6 - Clinical
- ❑ 7 - Tumor marker (f.ex. PSA, HCG, AFP, Ig, …)
- ❑ Unknown

WHO score at diagnosis primary tumor [REQ]:

- ❍ 0 - Asymptomatic, normal activity
- ❍ 1 - Symptomatic, but ambulant
- ❍ 2 - Symptomatic, bedbound < 50% day
- ❍ 3 - Symptomatic, bedbound > 50% day
- ❍ 4 - Completely dependent, 100% bedbound
- ❍ Unknown

Primary tumor localization [REQ]: ……..

Laterality primary tumor [REQ]:

- ❍ Left
- ❍ Right
- ❍ Unpair organ
- ❍ Unknown

Histological diagnosis primary tumor [REQ]: ……..

Differentiation grade primary tumor [REQ]:

- ❍ 1 - Well differentiated
- ❍ 2 - Moderately differentiated
- ❍ 3 - Poorly differentiated
- ❍ 4 - Undifferentiated
- ❍ Unknown

Clinical stage primary tumor (cTNM): cT: …….. cN: ……. cM: ……..

Pathological stage primary tumor (pTNM): pT: …….. pN: ……. pM: ……..

B. Metastasis / Relapse

Indication *(only required when it concerns a metastasis)* :

- ❍ Metastatic relapse
- ❍ Metastatic consolidation

Date of metastatic finding/relapse (the one treated within the currently administered dosimetric plan) [REQ]:

- ❍ Unknown
- ❍ Known; Specify [REQ]: ……. / ……. / ……. (dd/mm/yyyy)

WHO score at diagnosis metastasis/relapse [REQ]:

- ❍ 0 - Asymptomatic, normal activity
- ❍ 1 - Symptomatic, but ambulant
- ❍ 2 - Symptomatic, bedbound < 50% day
- ❍ 3 - Symptomatic, bedbound > 50% day
- ❍ 4 - Completely dependent, 100% bedbound
- ❍ Unknown

Disease free interval [REQ]?

- ❍ Yes
- ❍ No
- ❍ Unknown

Earlier metastatic event/relapse [REQ]?

- ❍ Unknown
- ❍ No
- ❍ Yes; Specify [REQ]: ….. / ….. / ….. (dd/mm/yyyy)

2. Treatment specifications

Number of lesions in total to treat with SBRT and/or SRS (cerebral lesions included) [REQ]:
……. (at maximum 3 lesions)

Number of lesions treated within the currently administered dosimetric plan [REQ]: …….

Maximum diameter of the lesion(s) treated within the currently administered dosimetric plan [REQ]:
…… mm

Safety monitoring [REQ]: ❍ Standard indication [REQ]

- ❍ Primary lung (peripheral) lesion (Complete sections: 6)
- ❍ Hepatic metastases (Complete sections: 6)
- ❍ Primary (para-) spinal lesion (Complete sections: 4, 6)
- ❍ (Para-) spinal metastases (Complete sections: 4, 6)
- ❍ Lung metastases (Complete sections: 6)

❍ Study indication [REQ]

- ❍ Primary lung lesion (central lesion and/or lesion >5 cm) (Complete sections: 3, 6)
- ❍ Primary prostate lesion (Complete sections: 3, 6)
- ❍ Primary renal lesion (Complete sections: 3, 6)
- ❍ Primary pancreatic lesion (Complete sections: 3, 6)
- ❍ Primary head & neck lesion (Complete sections: 3, 6)
- ❍ Primary hepatic lesion (Complete sections: 3, 6)
- ❍ Non-standard oligometastatic disease (Complete sections: 3, 5, 6)

3. Clinical trial data

Reference number of the ethics committee approval [REQ]: .....

Reference number of the public clinical trial registry [REQ]: .....

4. (Para-) spinal lesion(s): specifications

Level of the (para-) spinal lesion(s) [REQ]:

- ❑ Cervical
- ❑ Dorsal
- ❑ Lumbar

Localization of (para-) spinal lesion(s) [REQ]:

- ❑ Vertebral body
- ❑ Paraspinal mass

Proximity to spinal cord (in case of multiple lesions: lesion closest to the spinal cord) [REQ]: ..... mm

5. Non-standard oligometastatic disease: specifications

Site of metastatic lesion(s) treated within the currently administered dosimetric plan [REQ]:

- ❑ Other; Specify [REQ]: ……..
- ❑ Bone (non-spinal)
- ❑ Adrenal
- ❑ Lymph node

6. Technical aspects

A. Technical aspects of the tumor localization

Identification of tumor motion [REQ]:

- ❑ kV fluoroscopy
- ❑ 4D-CT
- ❑ Cine MRI
- ❑ Maximum inspiration/expiration breath hold CT
- ❑ None or not applicable
- ❑ Other

Specify [REQ] : ……

Tumor motion compensation strategy [REQ] :

- ❑ Abdominal compression
- ❑ Breath hold
- ❑ Gating
- ❑ Tracking
- ❑ None or not applicable
- ❑ Other

Specify [REQ] : ……

Imaging modalities for treatment planning [REQ]:

- ❑ CT-scan
- ❑ MRI
- ❑ Bone-scan
- ❑ PET-CT
- ❑ Other

Specify [REQ] : ……

Personalized immobilization [REQ]? ❍ Yes
❍ No

Image fusion for target delineation [REQ]? ❍ Yes
❍ No

Markers [REQ]: ❑ Implanted markers
❑ External skin sensors
❑ No markers

B. Applied technique and treatment specifications

Technique [REQ]: ❍ 3D-CRT
❍ IMRT
❍ Rotational IMRT
❍ Rotational 3D
❍ Other
Specify [REQ]: ……

Centre where the RT was performed [REQ]: ……

Centre that referred the patient to the RT [REQ]: ……

Number of fractions delivered [REQ]: ……

Total dose delivered for the currently administered dosimetric plan [REQ]: …… Gy

Start date of RT for the currently administered dosimetric plan [REQ]: …. /…… / …. (dd/mm/yyyy)

End date of RT for the currently administered dosimetric plan [REQ]: …. /…. / …. (dd/mm/yyyy)

C. Dose specific aspects

Dose calculation algorithm [REQ]: ❍ Pencil beam algorithm
❍ Convolution superposition algorithm: Anisotropic Analytic Algorithm – AAA
❍ Convolution superposition algorithm: Collapsed Cone Convolution – CCC
❍ Monte Carlo (f.ex. Voxel Monte Carlo – VMC+++)
❍ Other
Specify [REQ]: ……

Patient specific Quality Assurance (QA) prior to start [REQ]:

- ❑ 1D (point) verification
- ❑ 2D verification
- ❑ 3D verification
- ❑ 4D verification
- ❑ None

Type of IGRT [REQ] :

- ❑ CBCT
- ❑ EPID
- ❑ Exactrac
- ❑ No IGRT
- ❑ Other

Specify [REQ] : ……

7. Nomenclature

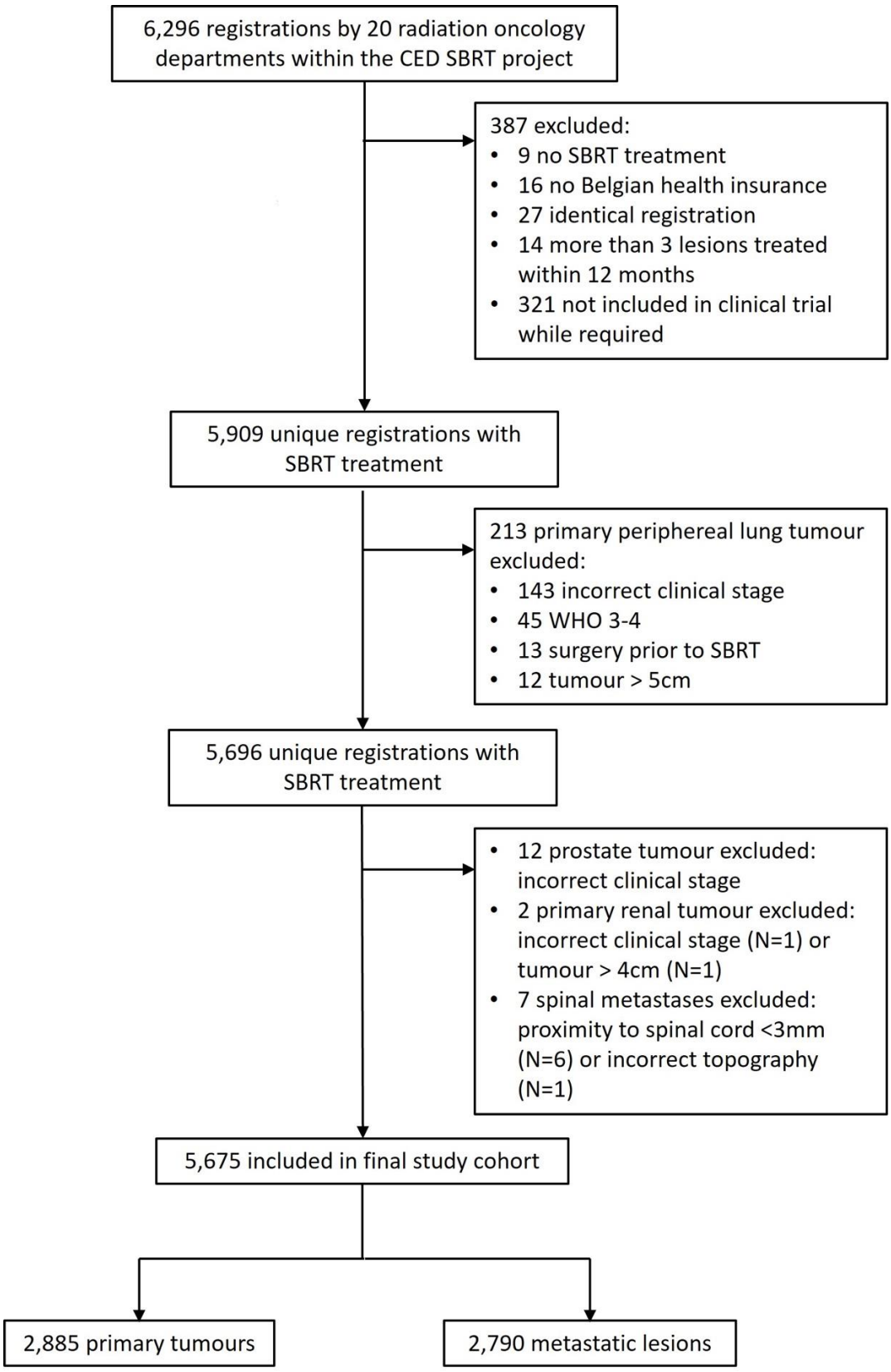
Nomenclature number(s) used [REQ]:

- ❑ 444172 or 444183
- ❑ 444356 or 444360
- ❑ 444393 or 444404
- ❑ 444415 or 444426
- ❑ 444430 or 444441
- ❑ 444452 or 444463
- ❑ 444496 or 444500

……. times charged

- ❑ 444570 or 444581

Supplementary figure: Prisma flow chart of registered and analysed cases.



Abbreviations:
CED: coverage with evidence development, SBRT: stereotactic body radiotherapy, WHO: world health organisation

Supplementary table: Overall survival up to 5years for the different indications.

	1y OS [95%CI]	2y OS [95%CI]	3y OS [95%CI]	4y OS [95%CI]	5y OS [95%CI]
Primary lung (peripheral)	87% [85%,88%]	70% [69%,72%]	56% [54%,58%]	45% [43%,47%]	36% [34%,38%]
Primary prostate	98% [94%,100%]	96% [90%,100%]	92% [84%,100%]	85% [76%,96%]	85% [76%,96%]
Lung metastases	87% [86%,89%]	69% [67%,71%]	56% [53%,58%]	45% [42%,47%]	39% [36%,41%]
(Para)-spinal metatases	87% [84%,90%]	79% [76%,83%]	70% [66%,74%]	60% [56%,65%]	52% [47%,56%]
Non-standard metastases	90% [87%,93%]	82% [79%,86%]	77% [73%,81%]	70% [66%,74%]	60% [54%,65%]
Hepatic metastases	75% [70%,80%]	50% [45%,56%]	33% [28%,38%]	23% [18%,28%]	19% [15%,24%]