EUnetHTA Joint Action 3 2016-2020

OTCA25 Stereotactic Body Radiation Therapy (SBRT) for lung, prostate and liver cancer

Project ID: ***OTCA25***

Project description and planning

Agència de Qualitat i Avaluació Sanitàries de Catalunya

Agency for Health Quality and Assessment of Catalonia (AQuAS)

Agency for Health Technology Assessment and Tariff System (AOTMiT)

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Version Log

Version number	Date	Modification	Reason for the modification
V1.1	02/09/2019	Preliminary draft sent to co-authors	
V2	25/09/2019		
V3	31/10/2019	First draft sent to dedicated reviewers	Integration of comments and suggestions derived from the internal scoping e-meeting
V4	From 8.11.2019 to 18.11.2019		
V5	11.11.2019	Second draft sent to external experts (clinical experts, manufacturers)	Integration of written comments and suggestions from dedicated reviewers as well as input from a face to face meeting
V6	20.12.2019	Third draft	Integration of comments and suggestions from external experts
V7	03.02.2020	Appendix B inclusion	Inclusion in appendix of outcome ratings
V8	21.02.2020	Fourth draft	Integration of comments and suggestions from assessment team
V9	04.03.2020	Fifth draft	Integration of comments from dedicated reviewers to V8
V10	18.05.2020	Sixth draft	Integration of comments from dedicated reviewers to V9
V11	12.06.2020	Final version	Integration of comments from external experts to V10, Table 1-3 updated

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1. Project organisation

1. Participants

Table 11: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
	Agency for Health Quality and Assessment of Catalonia (AQuAS)	Author	Spain	Develop the first draft of the EUnetHTA Project Plan Develop the CUR domain and the A0020/A0021 questions. Cooperate with Poland with anything needed for the TEC domain. Perform the literature search and study selection and carry out the assessment (data extraction, analysis, synthesis and interpretation of findings and assessment of risk of bias) AQUAS will lead the Prostate and Liver cancer scope; aligned with AOTMIT. Send the first draft to reviewers, compile feedback and perform necessary (found legitimate) changes according to reviewers' comments Send the second draft to external experts and to manufacturers for fact check Prepare final assessment and write a final executive summary of the assessment
	Agency for Health Technology Assessment and Tariff System (AOTMIT)	Co-Author	Poland	Review draft of the EUnetHTA Project Plan Develop the TEC with the support from AQUAS, excluding the A0020/A0021 elements. Perform the literature search and study selection and carry out the assessment (data extraction, analysis, synthesis and interpretation of findings and assessment of risk of bias) AOTMIT will lead the Lung Cancer scope; aligned with AQUAS. Check data extraction Discussion of conclusions Cooperate in the preparation and review of the second draft and final assessment documents together with the author, propose amendments whereever necessary and provide written feedback
	Swiss Network for Health Technology Assessment (SNHTA)	Dedicated Reviewer	Switzerland	Review and comment on EUnetHTA Project Plan, propose amendments wherever necessary. Review and comment on draft assessment, propose amendments wherever necessary.
	Azienda Zero - Regione del Veneto	Dedicated Reviewer	Italy	Review and comment on EUnetHTA Project Plan, propose amendments wherever necessary. Review and comment on draft assessment, propose amendments wherever necessary.
	Agencia de Evaluación de Tecnologías Sanitarias - Instituto de Salud Carlos III (AETS-ISCIII)	Dedicated Reviewer	Spain	Review and comment on EUnetHTA Project Plan, propose amendments wherever necessary. Review and comment on draft assessment, propose amendments wherever necessary.
Contributors				

	Dr Adam Maciejczyk (Lower Silesian Cancer Centre)	External expert	Poland	Review and comment on EUnetHTA. Project Plan, propose amendments wherever Necessary. Review and comment on second draft assessment, propose amendments wherever necessary.
	Dr. Sundaramurthy, Aravindhan (Edinburgh Cancer Centre)	External expert	Scotland	Review and comment on EUnetHTA. Project Plan, propose amendments wherever Necessary. Review and comment on second draft assessment, propose amendments wherever necessary.
	Compuscript Ltd (to be confirmed)	Medical Editor		
	Scientific Advice Unit (Avalia-t) of the Galician Agency for Health Knowledge Management (ACIS)	Project Manager	Spain	Project management

2. Project stakeholders

Table 12: Project stakeholders

Organisations involved	Role in the project
Varian, Elekta, Accuray	Manufacturers. Feedback on the Project Plan and second draft of the assessment (only upon the receipt of a confidentiality agreement)
Spanish group of patients with cancer (GEPAC- Grupo Español de Pacientes con Cáncer). Spain	Patient representative group advocate. Answer HTAi questionnaire, participate in weighting outcomes, participate in the e-scoping meeting and feedback of the Project Plan and second draft of the assessment. Patients who have undergone SBRT (if possible). Answer HTAi questionnaire.

3. Milestones and Deliverables

Table 13: Milestones and Deliverables

Milestones/Deliverables	Start date	End date
Project duration	**22.07.2019**	**August 2020**
Scoping phase	**22.07.2019**	**05.12.2019**
Identification of manufacturers and external experts; *and identification of patients*	22.07.2019	September 2019
Ask patients to fill in a questionnaire describing the disease and its treatment	12.07.2019	20.09.2019
Scoping and development of draft Project Plan incl. preliminary PICO	22.07.2019	31.10.2019
Share the preliminary PICO with external experts *(and patients)* for comments	31.10.2019	7.11.2019
Internal Scoping e-meeting with the assessment team	7.11.2019	
Consultation of drafts Project Plan with dedicated reviewers	23.10.2019	21.11.2019
Consultation of draft Project Plan with external experts and fact check by manufacturers found	22.11. 2019	14.01.2019
Amendment of draft Project Plan & final Project Plan available	22.11.2019	01.06.2019
Assessment phase	**June 2020**	**November 2020**
Writing first draft rapid assessment	15.06.2020	14.08.2020
Review by dedicated reviewer(s)	17.08.2020	28.08.2020
Writing second draft rapid assessment	31.08.2020	11.09.2020
Review by ≥ 2 external clinical experts and fact check by manufacturers	14.09.2020	25.09.2020
Writing third draft rapid assessment	28.09.2020	09.10.2020
Medical editing	12.10.2020	23.10.2020
Writing of final version of rapid assessment,	26.10.2020	06.11.2020
Formatting and Final version of REA	09.11.2020	16.11.2020
Local Reports (if applicable)		
Spanish National REA Nº1 [*AQUAS, Spain*]	Undetermined	Undetermined
Possible adaptation after a submission to local reference committees that will evaluate the opportunity and modality for it [Azienda Zero- Regione del Veneto]	Undetermined	Undetermined

Project Outline

1.1.Project Objectives

The rationale of this assessment is to collaboratively produce structured (rapid) core HTA information on other technologies. The purpose is to apply those collaboratively produced assessments in the national or regional context.

Table 21: Project objectives

	List of project objectives	Indicator (and target)
1.	To jointly produce health technology assessments that are fit for purpose, of high quality, of timely availability, and cover the whole range of health technologies.	Production of 1 (rapid) relative effectiveness assessment.
2.	To apply this collaboratively produced assessment into local (e.g. regional or national) context.	Production of ≥2 local (e.g. national or regional) reports based on the jointly produced assessment.

This rapid assessment addresses the research question: to compare the effectiveness, safety of SBRT and standard of care therapies in lung, prostate and liver cancer.

This topic was chosen based on a request from the Spanish Commission on Benefits, Entitlement and Financing (CPAF) who commissioned AQuAS to do an HTA on SBRT in lung, prostate and liver cancer.

The relevance of the topic lies in the fact that there are uncertainties, controversies and lack of consensus [10–13] on the additional value of SBRT, as it can be considered to be an expensive technology.

Moreover, the number of linear accelerators available in Spain with SBRT has tripled in the last three years, making the technology more available.

1.2. Project Method and Scope

1.2.1. Approach and Method

Table 22: Project approach and method

Project approach and method
The HTA Core Mode Applications for Rapid Relative Effectiveness Assessment Version 4.2. will be the primary source for selecting assessment elements. For this Rapid Relative Effectiveness Assessment we will describe the technical characteristics of technology (TEC) under assessment (i.e. type of device, procedure), the Health problem and current use of the technology (CUR) (i.e. target condition, target group), and assess Clinical Effectiveness (EFF) (i.e. relative benefits) and Safety (SAF) (i.e. unwanted or harmful effects). Clinical effectiveness (**EFF**) and safety (**SAF**) domains: 1. A systematic literature search will be performed. Two reviewers from the authoring team (author and co-author) will carry out the selection of relevant articles by screening the titles and abstracts of the retrieved studies, in accordance with the inclusion / exclusion criteria established according to the previously defined PICOS strategy. Potential eligible studies will be obtained and read at full-text. Reasons for exclusion will be recorded. Disagreement will be discussed and resolved between by consensus. 2. Besides, the Medical Devices Evidence Submission template will be sent to manufacturers of the technology under assessment. Study and outcomes validity and level of evidence will be assessed using EUnetHTA guidelines. The quality of the body of evidence will be assessed using GRADE. The GRADE analysis includes a qualitative view on the evidence for each outcome in regard to risk of bias, imprecision, inconsistency and indirectness. For example, for the risk of bias assessment in clinical trials, the Cochrane Collaboration's tool for assessing risk of bias can be considered, and tools like Robins-I can also be considered for assessing observational studies. To avoid duplicating work, it will be based on prior critically appraised HTA assessments published by European and non-European HTA organizations [6,7,8,9]. In accordance with the main organ to be targeted by the SBRT intervention (lung, prostate or liver), results on 6 subgroups will be assessed (see Table 2-6). Depending on the amount of evidence found, results will be provided segmenting the synthesis of evidence according to the following factors (sorted by priority): 1. operability and level of surgical risk [1–4] 2. type of fraction regime (1 fraction vs more than 1 fraction) 3. type of intervention (surgery vs conventional radiotherapy vs both) 4. tumor location (peripheral vs central [2]) 5. tumor stage 6. purpose of treatment (palliative vs curative) 7. recurrent or not

Table 23: Planned literature search strategy

Literature search strategy
A systematic search will be performed in the following databases: Cochrane Library (Wiley), Medline (PubMed), Embase (Ovid). Likewise, a specific search for ongoing clinical trials will be conducted at: Clinicaltrials.gov, Cochrane Central EU clinical trials and International ClinicalTrials Registry Platform (ICTRP). The search will be completed with a manual revision of the bibliographic references cited in the selected papers, a general internet search for scientific journal articles and a revision of sources and guidelines recommended by the external experts Search terms related to SBRT will be used, combined with terms related to lung, prostate and liver cancer. Mesh terms and free text words will be included in the search strategy. Studies will be included if the criteria resulting from PICOS are met. The following publication types will be excluded: case reports, letters, congress abstracts or editorials. If a published study is associated with sequential publications, in order to avoid overlapping, the publication with the largest number of cases or the longest time-horizon will be chosen.

Table 24: Plan for data extraction

Planned data extraction
The relevant data will be extracted and recorded in evidence tables by one reviewer from AQuAS (prostate and liver cancer) and one reviewer from AOTMIT (lung cancer). The definition of the search strategies will be aligned between the two professionals for coherence purposes. Evidence tables for data extraction will be created according to The Cochrane Handbook for Systematic Reviews for Interventions [14]. The data extracted from the studies will include: 1. Study: authors, year of publication, study design, setting/country, funding, study's registration number in clinical trial database, recruitment period, follow-up duration 2. Population: number of participants undergoing the intervention, age, gender, fragility, tumour type/organ, tumour clinical stage, treatments before the intervention (if any), simultaneous treatments (if any), treatments after the intervention (if any), distance to the organ or the lesion, tumour location (peripheral, central) , recurrent cancer or not, unresectable-inoperable or not 3. Intervention and comparator (if any): description of the procedure (including type of surgery or type of radiotherapy technology and manufacturer and model, Computerized Tomography or Magnetic Resonance Imaging guidance (if applicable), approach of the procedure, Radiotherapy fraction scheme (dose and frequency) and length of follow-up. Purpose of the treatment (palliative or curative) 4. Outcomes: A list critical outcomes have been selected and will be extracted (see Appendix B for average rating for each potential outcome that was considered and table 2-6 for selected outcomes). 5. Study methods: Phase of the trial, propensity score study If information required for the assessment of study eligibility or the risk of bias is missing or if outcome data are incomplete, queries to study authors, investigators or sponsors may be necessary. Queries will only be sent out in case of essential questions that can have a possible direct impact on the assessment's conclusion.

1.2.2. Project Scope

The EUnetHTA Guidelines, available at https://www.eunethta.eu/methodology-guidelines/ **need to be consulted** throughout the assessment process.

Table 26: Project Scope: PICO (please see HTA Core Model® for rapid REA)

Description	Project Scope
Population	Age: Adult >=18 years of age. Diseases of interest (corresponding but not equivalent ICD-10-CM codes are shown in parentheses): 1. Malignant neoplasm of bronchus and lung (non-small cell carcinoma) in two subgroups: a. [LUN.M] Tumors with oligometastases (stage IV), including at least one to bronchus and lung (C78.0) b. [LUN.P] Localized primary cancers (stage I-II) located in bronchus and lung (C34) 2. Prostate cancer in two subgroups a. [PRO.M] Tumors with oligometastases (stage IV), including at least one to prostate (C61) b. [PRO.P] Localized primary cancers (stage I-II) located in prostate (C61) 3. Liver cancer in two subgroups a. [LIV.M] Tumors with oligometastases (stage IV), including at least one to liver (C22.9, C78.7) b. [LIV.P] Localized primary cancers (hepatocellular carcinoma at stage I-II) located in liver (C22) **Rationale:** population has been defined according to ASTRO/ESTRO guidelines [1–4] **Additional information:** Primary tumors up to T2 will be evaluated, according to the TNM classification system. If the TNM classification is not used, equivalent size limits will be used for primary tumors and metastases in target organs.

Intervention	Tumour resection through Stereotactic Ablative Body Radiotherapy, Stereotactic Body Radiotherapy (SABR/SBRT) applied as monotherapy (at any moment and combined with androgen deprivation therapy and/or other type of EBRT but not e.g. chemotherapy). MESH: Stereotactic Body Radiotherapy --- MeSH: Radiosurgery All MeSH Categories Analytical, Diagnostic and Therapeutic Techniques and Equipment Category Therapeutics Radiotherapy Radiosurgery All MeSH Categories Analytical, Diagnostic and Therapeutic Techniques and Equipment Category Investigative Techniques Stereotactic Techniques Radiosurgery Comments on the definitions: - SBRT will be understood as 1–7 fraction schemes, if they are declared as SBRT in the study. - Example of surgical risk definition: “high risk” in lung means to able to tolerate sublobar resection but not lobectomy - Simulators are not considered, Complementary Devices’ effects are not included. Examples of possible CE-marked technologies that enable SBRT: Accelerators such like Tomotherapy, Varian Trilogy, Varian Unique, Varian ix, Varian True Beam, Varian Edge, Elekta Synergy-S, Elekta Axesse, Elekta Infinity, Elekta Versa HD or CyberKnife

Comparison	For cancers located in lung, prostate or liver, different standard of care therapies will be considered for direct comparisons: • Radiotherapy such as conventional, standard, 3D Conformal Radiotherapy, Intensity Modulated Radio Therapy and others • Surgery such as lobectomy, wedge resection, metastasectomy and others • Surgery + conventional radiotherapy Only standard of care therapies will be considered for each population, considering the answers to the PICO reimbursement survey. This survey will be sent to EUnetHTA WP4 OT partners and will define standard of care for each subpopulation using the following table scheme: Population Radiotherapy Surgery Surgery and conventional radiotherapy LUN.M If not operable If operable LUN.P If not operable If operable PRO.M If not operable If operable PRO.P If operable If operable If operable LIV.M If not operable If operable LIV.P If not operable If operable Rationale: ASTRO/ESTRO guidelines [1–4] and feedback from Dedicated Reviewers. The list includes all those interventions that have been considered standard of care during the development of the protocol by the authors, dedicated reviewers and external experts. A PICO survey will be conducted and, if other interventions that are used as a standard of care are identified and source documents are cited to support it (clinical practice guidelines, official reports), this interventions will be included in the list of comparators. Additional comments/clarifications: • We plan not to include “drug interventions” and “other non-drug interventions” such as radiofrequency ablation, microwave ablation, irreversible electroporation or high-intensity focused ultrasound (HIFU). • Intensity Modulated Radio Therapy or Volumetric modulated arc therapy can be combined with SBRT or not. IMRT and 3D conformal radiotherapy in SBRT are considered interventions of interest. On the other hand, IMRT plans that are not combined with SBRT are considered comparators • Brachytherapy or Intra-Operative Radiotherapy are also not considered as comparators • Conventional radiotherapy is understood as any radiotherapy between 8 and any number of fractions.

Outcomes

CLINICAL RELATIVE EFFICACY OR EFFECTIVENESS

Outcome	LIV.P	LIV.M	PRO.P	PRO.M	LUN.P	LUN.M
Number and percentage of patients with tumor response		X				
Overall survival at 5 years		X				
Overall survival at 3 years					X	
Local disease control			X		X	
Distant disease recurrence/metastases					X	
Need for salvage therapy					X	
Disease free survival						X
Overall survival in primary lung tumors (stage I)						X	X
Treatment associated mortality (survival)	X		X		X	X	X	X
Number and percentage of patients with local control (prostate, liver)			X		X		X		X	
Biochemical control (free of BC recurrence survival)						X				
Acute urinary and digestive toxicity (RTOG-EORTC / CTCAE scales)			X		X		X		X	X
Late urinary and digestive toxicity (RTOG-EORTC / CTCAE scales)							X			
Quality of life (SF-36/ EPIC)	X		X		X		X		X	X	
Percentage of patients with privative androgenic treatment due to recurrence									X	X
Change in EPIC questionnaire Quality of life					X		X			
Urinary or bowel symptoms (EPIC-26 questionnaire or separately)							X		X	
Faecal incontinence					X					
EORTC * questionnaire to estimate respiratory difficulties									X	X
Dypnoea						X		X		
Changes in a pain scale	X			X			X			

SAFETY OUTCOMES

Number and percentage of patients presenting grade 4 toxicities				X		X				
Number and percentage of patients with acute toxicities					X					
Major surgical complications (presence or absence of grade >2 event)							X			
Major systemic therapy complications: presence or absence of grade >2 CTCAE v4 complication					X	X				

ECONOMIC OUTCOMES

Cost per QALY	X		X		X		X		X	X

X=included, Ø = not included with an average rating <8 or not applicable.

Rationale: ASTRO/ESTRO guidelines [1–4]. All outcomes with an average score of 8 or higher have been selected. Subsequently, this list of outcomes has been validated with external experts (with a deadline of 15 days) and by means of a PICO survey after project plan publication. With all this information, the authoring team will establish the set of outcomes that will finally be reviewed.

Additional information.

1. No published core outcome sets were found on metastases.
2. The final list of critical outcomes has been established and scored based on GRADE ratings.
3. Appendix B describes the results of the prioritization exercise

Study design	Inclusion criteria:
	
	• Published after 1st January 2015
	• Available full-text version in English, Spanish or Polish
	• Design
	  ○ At least 2 years of follow-up.
	  ○ #1 Randomized prospective controlled trials or non-randomized comparative prospective cohort studies or paired/database/propensity-score matching with at least 40 patients (20 per group).
	  ○ #2 Single-arm prospective with at least 40 patients. For each subpopulation, this second search will be conducted if there aren't included studies after the first search and before data extraction.
	
	Exclusion criteria:
	
	• Preliminary phase dose studies, or studies said to be "Phase I" in the literature
	
	Additional information:
	Searches will be conducted for published articles after 1st January 2009. For each subgroup, if there aren't included studies after the first two selection procedures based on study design, the first inclusion criteria will be modified to include studies from 2009.

Communication and collaboration

Table 31: Communication

Communication Type	Description	Date	Format	Participants/ Distribution
Scoping	To internally discuss and reach consensus on the scoping.	18-10-2019	Face-to-face meeting in Diemen (taking benefit of the WP4 Face-to-Face meeting)	Author, co-author, dedicated reviewers, project manager, external experts
	To internally discuss and reach consensus on the scoping.	8-11-2019	*Short confirmatory e-meeting*	Author, co-author, dedicated reviewers, project manager and patient representative
First draft of the rapid assessment	*To discuss comments of dedicated reviewers*	*20-5-2020*	*E-meeting with project team*	Author, co-author, dedicated reviewers, project manager, external experts
Second draft of the rapid assessment	*To discuss comments from ≥ 2 external clinical experts and manufacturers*	26-6-2020	*E-meeting with project team*	Author, co-author, dedicated reviewers, project manager, external experts

As many additional e-meetings as needed can be scheduled for the assessment team throughout the project.

The EUnetHTA Intranet (https://eunethta.sharepoint.com/Pages/Home.aspx) will be used as primary communication tool.

3. Dissemination plan

The final rapid assessment will be published on the EUnetHTA website: http://eunethta.eu/rapid-reas/ .

All stakeholders and contributors will be informed about the publication of the final assessment by the project manager.

4. Collaboration with stakeholders

Collaboration with manufacturer(s)

Manufacturers will be offered to review the preliminary PICO and carry out a fact check of the 2nd draft project plan and the 2nd draft assessment by the manufacturer(s).

Collaboration with other stakeholders

A patient advocate has participated in outcome prioritization, as explained in Appendix B.

5. Collaboration with EUnetHTA WPs

For the individual rapid assessment, some collaboration with other WPs is planned: WP7 [Implementation] will be informed of the project, in order to prepare activities to improve national uptake of the final assessment. Feedback on the WP4 REA process will be asked from the involved parties by WP6 [Quality Management], and this information will be processed by WP6 to improve the quality of the process and output.

6. Conflict of interest and confidentiality management

Conflicts of interest will be handled according to the EUnetHTA Conflict of Interest Policy. All individuals participating in this project will sign the standardised “Declaration of Interest and Confidentiality Undertaking” (DOICU) statement.

Author, co-author(s) and dedicated reviewers who declare a specific conflict of interest will be excluded from the whole work under this specific topic. However, they still may be included in other assessments.

For external experts, patients or other stakeholders involved, conflict of interest declarations are collected. External experts or patients who declare a specific conflict of interest will be excluded from parts of or the whole work under this specific topic. However, they still may be included in other assessments.

Manufacturer(s) will sign a Confidentiality Undertaking (CU) form regarding the specific project.

3. Preliminary considered references according to the criteria established

Table 41: Preliminary search expected first author and year of publication results (best selection to be further confirmed)

	Prostate cancer	Lung cancer	Liver cancer
P	#1: vs RT Widmark et al. 2019 Brand DH et al. 2019 (Loblaw et al. 2013, 2016 Alongi et al. 2013 Madsen et al. 2007) --- #2: EFFICACY Alayad et al. 2018 Loblaw A et al 2013 , 2017 (Morrison et al. 2018 (ASCO) Fuller DB et al. 2014 Katz AJ et al. 2010, 2011,2014 Lee SW et al. 2014 Mantz C et al. 2014 Meier R et al. 2018 Zimmermann M et al. 2016) SAFETY Alayad 2018 (Madsen BL et al. 2007 Fan et al, 2015 Rana et al. 2015 Koskela et al.2017 Bolzicco G et al. 2013 Chen LN et al. 2013 Davis J et al. 2015 Kotecha R et al. 2016 Alayed Y et al 2018 Boyer MJ et al. 2017 D'Agostino G et al. 2016 Folkert MR et al. 2017 Freeman D et al. 2014 Hannan et al. 2016 Glowacki G et al. 2017 Jackson WC et al. 2018 Joh et al, 2014 Kim YJ et al. 2013, 2014 Lukka H et al. 2016 Murthy V et al. 2018 Musunuru HB et al. 2014-16 Miszczyk et al., 2015, 2017 Paydar et al. 2016 Quon HC et al. 2016 Rucinska M et al 2016 Shikama N et al. 2016 Tree et al 2014 Woo et al 2014)	#1: vs lobectomy Chang et al. 2015 Chen et al. 2018 (16 PS agreggated result) #1: vs sublobar resection/wedge resection (Yerokun JTCVS 2017) #1 vs RT: Nyman et al. 2016 Ball et al. 2019 #2: (Navarro-Martin 2016 Brat et al. 2011 Timmerman et al. 2010 Ricardi et al. 2010 Baumann et al. 2009 Fakiris et al. 2009 Koto et al. 2007 Singh et al. 2017 Videtic et al. 2015 Tekatli et al. 2017)	#1: (Matsuo et al. 2016) #2: Feng M et al 2018 Bujold et al 2013 Weiner et al 2016
M	#1: Ost et al. 2017 Gao et al. 2019 #2: Siva et al. 2018 Ahmed et al. 2012 Pasqualetti et al.2018 Muracevic et al. 2013	#1: vs Surgery Widder 2013 Lodeweges 2017 PS Flannery 2008 #1: vs RT: Siva (2016) SAFRON II (SBRT 4fr vs RS 1fr) Palma et al. 2019 #2: Aoyama (2015) Ricardi 2012 Inoue 2013	#1: #2: Hoyer et al. 2006 Milano et al. 2008 Scorsetti et al. 2018

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5. Appendix A

5.1. Selected Assessment Elements

The table shows the assessment elements and the translated research questions that will be addressed in the assessment. They are based on the assessment elements contained in the 'Model for Rapid Relative Effectiveness Assessment'. Additionally, assessment elements from other HTA Core Model Applications (for medical and surgical interventions, for diagnostic technologies or for screening) have been screened and included/ merged with the existing questions if deemed relevant.

Table 61: Selected Assessment Elements

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
Description and technical characteristics of technology (TEC)					
B0001	Features of the technology and comparators	What is the technology and the comparator(s)?	Yes-Critical	M	What is SBRT and the standard alternative treatment for lung, prostate and liver cancer patients?
A0020	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	Yes-Critical	M	For which indications have SBRT and related devices received marketing authorization or CE marking?
B0002	Features of the technology and comparators	What is the claimed benefit of the technology in relation to the comparator(s)?	Yes-Critical	M	What is the claimed benefit of SBRT in relation to the standard alternative treatment for lung, prostate and liver cancer patients?
B0003	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	No	NM	What is the phase of development and implementation of SBRT?
B0004	Features of the technology	Who administers the technology and the comparator(s) and in what context and level of care are they provided?	Yes	M	Who administers SBRT and in what context and level of care it is provided?
B0008	Investments and tools required to use the technology	What kind of special premises are needed to use the technology?	Yes	NM	What kind of special premises are needed to use SBRT (e.g. 4D, immobilization devices, safe practices [13]…)?
B0009	Investments and tools required to use the technology	What equipment and supplies are needed to use the technology and the comparator(s)?	Yes	NM	What equipment and supplies (including the maintenance of resources) are needed to use SBRT ?
A0021	Regulatory Status	What is the reimbursement status of the technology?	Yes	NM	What is the reimbursement status of SBRT in different EU countries?
Health problem and current use of technology					
A0002	Target Condition	What is the disease or health condition in the scope of this assessment?	Yes	M	What is the type of cancer in the scope of this assessment?
A0003	Target Condition	What are the known risk factors for the disease or health condition?	No	NM	
A0004	Target Condition	What is the natural course of the disease or health condition?	Yes-Critical	M	What is the natural course of the lung, prostate and liver cancer?
A0005	Target Condition	What are the symptoms and the burden of disease or health condition for the patient?	Yes	M	What are the symptoms and the burden of the lung, prostate and liver cancer?
A0006	Target Condition	What are the consequences of the disease or health condition for the society?	No	NM	Addressed A0005

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
A0024	Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	Yes	M	How is the cancer currently diagnosed according to published guidelines and in practice?
A0025	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	Yes-Critical	M	How is the cancer currently managed according to published guidelines and in practice?
A0007	Target Population	What is the target population in this assessment?	Yes-Critical	M	What is the target population in this assessment?
A0023	Target Population	How many people belong to the target population?	Yes	M	How many people belong to the target population?
A0011	Utilisation	How much are the technologies utilised?	Yes	M	How much is the SBRT utilised?
Clinical effectiveness					
D0001	Mortality	What is the expected beneficial effect of the intervention on mortality?	Yes-Critical	M	What is the expected beneficial of SBRT on mortality?
D0005	Morbidity	How does the technology affect patients' symptoms, body function, daily living and findings (severity, frequency) of the disease or health condition?	Yes-Critical	M	How does SBRT affect patients' symptoms, body function, daily living and findings (severity, frequency) of Lung, prostate and liver cancer?
D0006	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	Yes-Critical	M	How does SBRT affect progression (or recurrence) of lung, prostate and liver cancer?
D0011	Function	What is the effect of the technology on patients' body functions?	No	M	Addressed in D0005
D0016	Function	How does the use of technology affect activities of daily living?	No	NM	Addressed in D0005 + D0012
D0012	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	Yes-Critical	M	What is the effect of SBRT on generic health-related quality of life?
D0013	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	Yes-Critical	M	What is the effect of SBRT compared to standard/ conventional radiotherapy or surgery on disease-specific quality of life in lung, prostate and liver cancer?
D0017	Patient satisfaction	Were patients satisfied with the technology?	Yes	NM	How does intervention with SBRT compare to standard/ conventional radiotherapy or surgery in terms of patient satisfaction or other patient-reported experience outcomes of lung, prostate and liver cancer?

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
Safety					
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?	Yes	M	How safe is SBRT compared to standard/ conventional radiotherapy or surgery in lung, prostate and liver cancer?
C0002	Patient safety	Are the harms related to dosage or frequency of applying the technology?	Yes	NM	
C0004	Patient safety	How does the frequency or severity of harms change over time or in different settings?	Yes	M	How safe is SBRT compared to the standard/ conventional radiotherapy or surgery over time or in different settings of use in lung, prostate and liver cancer?
C0005	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	Yes	M	What are the susceptible patient groups that are more likely to be harmed through the use of SBRT in lung, prostate and liver cancer?
C0007	Patient safety	Are the technology and comparator(s) associated with user-dependent harms?	No	NM	
B0010	Safety risk management	What kind of data/ records and/or registry is needed to monitor the use of the technology and the comparator(s)?	Yes	M	What kind of data/records and/or registry is needed to monitor the use of SBRT and the standard standard/ conventional radiotherapy or surgery in lung, prostate and liver cancer?

5.2. Checklist for potential ethical, organisational, patient and social and legal aspects

1.	**Ethical**	
1.	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	[**Yes**/No]
	The limited number of hospitals (sometimes private) able to provide the procedure can lead to an increase in discrepancies in patients' access to the treatment and fulfilment of their needs.	
2.	Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	[Yes/**No**]
	None	
2.	**Organisational**	
1.	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	[**Yes**/No]
	Introduction of the technology could cause organisational and management changes like waiting lists management, as well as to give rise to the need to provide additional devices.	
2.	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	[**Yes**/No]
	In case of a shortage of adequate surgeons the technology may have an organisation relevant impact, due to the number of surgeries reduction. It is not considered relevant enough for making an specific analysis in this assessment.	
3.	**Social**	
1.	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	[Yes/**No**]
	None	
2.	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	[Yes/**No**]
	None	
4.	**Legal**	
1.	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	[**Yes**/No]
	Some professionals working with radiotherapy have not received training on risk analysis techniques, which should be an accomplished legal requirement on the centres acquiring technologies that enable SBRT.	
2.	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	[Yes/**No**]
	None	

6. Appendix B

The list of outcomes was established considering a preliminary SBRT assessment search and considering, for each population those highlighted by the International Consortium for Health Outcomes and the Core Outcome Measures in Effectiveness Trials initiative. No published core outcome sets were found on metastases. During the preliminary SBRT assessment, a prioritization exercise was carried out with 2 oncology radiotherapists in Spain, 1 thoracic surgeon, 1 director plan lead and a Spanish patient advocate.

Table 13: Ratings Average rating for each outcome in each subgroup evidence synthesis.

OUTCOME OR ENDPOINT TO COMPARE SBRT WITH CONVENTIONAL RT AND/OR SURGERY	PRIMARY	METASTASES
CLINICAL RELATIVE EFFICACY OR EFFECTIVENESS	**Average rating**	
LIVER CANCER		
Number and percentage of patients with tumor response	8,0	7,0
Overall survival at 2 years	6,7	6,5
Overall survival at 5 years	7,3	8,0
Time to progression or PFS	7,0	5,0
Disease free survival	6,5	5,0
Time to recurrence	7,0	5,0
PROSTATE CANCER		
Overall survival at 3 years	7,3	8,0
Overall survival at 6 months	3,5	3,5
Survival for specific causes	4,5	2,0
Number and percentage of patients according to functional status	7,0	7,0
Local disease control	8,3	8,0
Number and percentage of patients according to disease progression	6,0	5,5
Death from prostate cancer	5,0	2,0
Death from any cause	7,5	7,0
Local disease recurrence	7,5	6,0
Distant disease recurrence/metastases	8,0	7,0
Disease progression	7,5	7,0
Need for salvage therapy	7,0	9,0
LUNG CANCER		
Disease free survival	8,0	7,5
Overall survival in primary lung tumors (stage I)	8,5	9,0
Number and percentage of patients with cure	6,5	4,0
ALL OR SOME (type of cancer)		
Treatment associated mortality (survival) (all)	8,3	9,0
Number and percentage of patients with local control (prostate, liver)	8,5	8,0
Biochemical control (free of BC recurrence survival) (all)	8,5	8,0
Progression-free survival (all)	7,0	6,0

Acute urinary and digestive toxicity (RTOG-EORTC / CTCAE scales) (all)	8,5	9,0
Late urinary and digestive toxicity (RTOG-EORTC / CTCAE scales) (all)	8,5	9,0
Quality of life (SF-36/ EPIC) (all)	8,5	8,0
Percentage of patients with privative androgenic treatment due to recurrence (all)	8,0	7,0
Other: Years without disease (lung)	7,0	7,0
Other: Expected reactivity to treatment (liver)	7,0	7,0
ECONOMIC OUTCOMES (Type of cancer)		
Cost per QALY (all)	8,0	8,5
Time in the hospital in the end of life (lung)	7,3	7,5
Other: _____		
Other: _____		
SAFETY OUTCOMES (Type of cancer)		
Number and percentage of patients presenting toxicities (prostate)	7,7	7,5
Number and percentage of patients presenting grade 4 toxicities (liver)	8,3	8,0
Number and percentage of patients with acute toxicities (liver)	7,0	8,0
Number and percentage of patients with late toxicities (liver)	7,0	6,0
Major surgical complications (presence or absence of grade >2 event) (lung)	7,5	8,0
Major radiation complications (presence or absence of grade 2 CTCAE v4 complication) (lung)	6,0	6,0
Major systemic therapy complications: presence or absence of grade >2 CTCAE v4 complication (lung)	8,0	8,0
ECOG performance status 1 year post-initiation of treatment (lung)	7,5	7,0
Others: _____		
Others: _____		
PATIENT REPORTED OUTCOME		
PROSTATE CANCER		
Change in EPIC questionnaire Quality of life	8,7	9,0
Emotional functionality and well-being **	6,5	7,0
Physical functionality	6,7	7,0
Sexual dysfunction	6,7	6,5
Sexual domain of quality of life questionnaire	5,5	5,0
Urinary or bowel symptoms (EPIC-26 questionnaire or separately)	8,5	9,0
Urinary function	7,7	8,0
Rectal and/or bowel function	7,5	7,0
Stress urinary incontinence	6,7	8,5
Feacal incontinence	6,5	9,0
Sexual function	6,5	7,0

LUNG CANCER		
Cough	7,7	7,5
EORTC * questionnaire to estimate respiratory difficulties	8,7	8,5
Health-related quality of life through EORTC	7,0	7,0
Social functioning	6,0	6,0
Physical functionality	6,0	6,0
Emotional functioning	5,0	5,0
Cognitive function	5,0	5,0
Pain	7,5	7,0
Dypnoea	9,0	9,0
PROSTATE OR LUNG CANCER		
Fatigue and vitality	7,0	7,0
Changes in a pain scale	8,0	7,5
Others: _____		
Others: _____		