EUnetHTA JA3 WP4 - Other technologies, OTCA09
Comments by external experts on the 2nd draft rapid assessment on HIFU for the treatment of prostate cancer

Comments should be submitted not later than time *Weekday 06/03/2018*

The objective of this reviewer form for external reviewers is to standardise the process of reviewing rapid relative effectiveness assessments by external reviewers.

The reviewer form is organised and structured in a similar fashion to the assessment template. The form will consequently address the following:

Part I) Methods (please see Appendix 1 or chapter 2 of the assessment)
Part II) Results: Domain reports
Part III) Summary of relative effectiveness (please see summary section of the assessment)
Part IV) Other considerations

Please use this form for submitting your comments

1. Please put each new comment in a new row.
2. Please insert the page number and section number on which your comment applies. If your comment relates to the document as a whole, please put **'general'** in this column.
3. Please provide a description of your comment as specific as possible and preferably also provide a suggestion for rewording. If you wish to draw our attention to published literature, please supply the full reference.
4. Please **DO NOT** comment on typos or wording as long as they do not affect comprehensibility/readability of the assessment – the document will undergo medical editing prior to publication.

All comments will be formally responded to in a combined document that will be published on the EUnetHTA website, individual names of the reviewers disclosed.

Please add extra rows as needed.

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b "minor": the comment does not necessarily have to be answered in a detailed manner
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Summary					
Scope					
	12	16 Population Rationale	Correct: …NICE guidelines… …S3 Leitlinie (German oncology guideline program) [3]…	2	Corrected.
	12	16 Intervention	Manufacturer of Sonablate is: SonaCare	2	Corrected.
	13	Functional outcomes	IPSS measures symptoms, not incontinence	2	We added this. Urinary (dys)function: urinary symptoms measured by IPSS and urinary incontinence measured by the number of patients with pad usage or the number of new onset urinary incontinence
	14	Procedural complications	First three points: bladder neck stricture, bladder neck obstruction and bladder neck stenosis are the same; urethral stricture and urethral stenosis are the same. Because most studies do not discriminate very well between urethra land bladder neck strictures, my suggestion is to combine thr three points to one: bladder neck/urethral stricture/stenosis	2	Corrected.

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Methods					
	17/18	83-87	Duplicates 75-82: omit …due to language……..	2	Corrected.
Description and technical characteristics of the technology					
	21	148	The correct term is:…power density…	2	Corrected.
	21	154	This probe or MRT in MRT-guided approach enables….	2	Corrected.
	21	156	Replace: "your bladder" by "the bladder"	3	Corrected.
	21	159	Replace: "This works …" by "Most procedures take 1.5 to 4 hours. Depending on equipment and treatment scheme, e.g. half-gland or focal therapy, treatment time can be shorter.	2	Corrected. Added.
	21	165-166	Replace: "Its major limitation…" by "Its major limitation is that visualisation of the prostate cancer using current ultrasound systems is not possible."	1	Corrected.
	22	178	Insert: …lateral "sitting" position…	2	Added.
	22	181-183	Omit: "Afterwards…." This sentence might be useful in a manual, it is of no use because it repeats the treatment principle only.	1	We deleted the sentence.
	22	187-188	The transducer is not available in two focal lengths, it has both focal lengths, the user can use both and switch	1	Corrected.

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			between them to treat the ventral and the dorsal part of the prostate consecutively (read 189-192).		
	22	189	Replace "staring" by "starting"	3	Corrected.
	22	192	Replace: "The maximum prostate size that …" by "The maximum distance from the transducer that …"	2	Replaced.
	22	193	Omit "completely" or better, the whole sentence. In any of the devices, the planning is completely operator dependent. At this place, the reader might have the impression that Sonablate is different from other devices regarding operator dependency. In Ablatherm, the systems presetting	2	We deleted the sentence.
	22	195-206	This sounds like an ad. Replace by: In FocalOne, image fusion of real-time transrectal ultrasound and pretreatment MRT images is achieved by integrated software. This allows an image-guided HIFU treatment of a defined zone and sparing the rest of prostate tissue. The transducer's focal length is 60 mm at maximum and can be modified during treatment.	1	Corrected.

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	23	221-229	Please replace: The technology is designed for the destruction of the whole prostate gland in a single procedure that lasts about an hour, but can also be used for any targeted or focal ablation of cancerous tissue. After the ultrasound probe is placed in the prostatic urethra near the target, the treatment is performed with MRI real-time planning and guidance. The ten ultrasound transducers along the probe are selectively activated to deliver energy to the whole gland or the targeted part of the prostate only, heating it and in the process killing its tissue. The probe slowly rotates in order to deliver the ablative energy across the entire prostate or at the planned target. During treatment, real-time MRI is used to verify that the planned heating pattern is accurately delivered. Although no energy is delivered transrectally, an endorectal cooling device is used to prevent any unwanted destruction of nearby tissues [26]. Final assessment with contrast MRI provides immediate verification of complete ablation.	1	Replaced.

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	23	230	Replace both by all	3	We corrected to "characteristics of HIFU systems..."
	23	231 table header, 2nd column	HIFU needs specification: TRUS-guided with MRI-image-fusion	1	Added.
	23	231 frequency	add MHz to the numbers given in the left three columns or remove MHz from the numbers given in the right two columns	3	Corrected.
	24	231 imaging guidance	In the right column, remove: ultrasound compatible (the ultrasound transducer is MRI compatible, but has nothing to do with imaging) In the right two columns, add "with" MRI, or remove "with" TRUS in the other columns	3	Corrected
	24	231 therapeutic transducer	Right column, replace: NA by Array with 10 transducers (see 221-229)	1	Replaced.
	24	240-246	The type of prostate cancer, which is considered clinically insignificant, has a low risk of progression. Elderly men with low-risk cancer do not need treatment, since any type of treatment is more likely to cause harm than the cancer left untreated. Management of prostate cancer in these cases is called watchful waiting.	1	We split up this paragraph and added relevant information to the text on HIFU, than on AS.

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			Younger men with low risk cancer could also be managed with watchful waiting. However, the general problem with prostate cancer is it can be and often is multi focal and multi clonal, there can also be a shift from low risk to high risk. There is also a sampling error, based on standard biopsy technique. Therefore, younger men with low risk cancer should have a control scheme called active surveillance. This include re-biopsies after 2 years. High risk prostate cancer in younger men requires treatment. Because of the often multi focal and multi clonal nature of prostate cancer, whole gland treatment or□ablation was considered standard. Nevertheless the latest evidence suggests that the □natural history of the disease is predominantly driven by the largest lesion with the highest □grade, the so-called index lesion. Focal therapy is a tissue-preserving strategy to reduce treatment-related toxicity by □minimising the damage		

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			caused to the prostate and adjacent tissues. Focal or targeted treatment is delivered not to the whole gland, but to the target only. This can be all tissue identified as cancerous, or that half of the gland, in which biopsies were positive. However, in cases with multifocal tumors it is also possible, to treat the index lesion only or all lesions with intermediate or high risk cancer and leave low risk cancer lesions untreated.		
	25	249	Omit: The main difference….approach.	1	Corrected.
	25	253	Insert: …indicate relevant progression or potential…	2	Inserted
	25	260	Insert: …node dissection, or so-called extended lymph node dissection.	2	Inserted.
	25	280	Insert:…to ablate the targeted tissue or the index lesion only.	2	Inserted.
	25	281	Correct: …sexual dysfunction…	1	Corrected.
	25	284-285	I do not understand the meaning of the sentence. I suppose: …as well as to limit side effects and to provide a treatment option for patients requiring or deciding for active treatment in which RP and RT is considered overtreatment.	3	Yes, corrected.

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	26	300-301	FocalOne® was the first device ~~to combine imaging and treatment.~~ to implement MRT/TRUS image fusion to guide transrectal treatment.	1	Corrected.
	26	301-302	HIFU performed with real-time magnetic resonance tomography ~~focused ultrasound surgery~~ is the newest and most precise imaging to localize and ablate prostate cancer. In addition, this allows ~~has an improved targeting~~ and real-time temperature monitoring and visualisation of treatment effects.	2	Corrected.
	26	307-308	For image fusion, the radiologist is involved to perform pre-treatment MRI and provide image data the software of the HIFU system requires. If HIFU is performed under MRT guidance, the urological surgeon and the radiologist and their teams are working hand in hand.	2	We added this to the paragraph.
	26	323-328	The required equipment depends on the type of device: ~~a special bed is needed to use~~ The treatment table with the attached probe is part of the Ablatherm® device. The Sonablate® device has a separate probe holder which can be attached to any operating table; therefore the	1	Corrected.

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			treatment can be done in any setting where an operating table is available~~, no special bed is needed~~. MRI-guided HIFU devices require MRI [22]. Most ~~The~~ devices ~~generally have very~~ require few disposables, usually tubing and covers, gels and fluids.		
	27	343	...can be included.... ???	3	Are included. We already corrected.
Health problem and current use					
	28	354-362	Replace by: Prostate cancer (PCa) is the most common non-skin cancer in men in Europe [1]. The malignancy usually originates from glandular epithelial cells, often multi focal and multi clonal. Depending on parameters such as tumor grade, tumor volume and PSA concentration at time of diagnosis, risk stratification is possible. Small low grade cancer is a frequent finding, and usually characterized by slow local growth and the lack of metastasis. This type of tumor is named latent or clinically insignificant, because there is a low risk of progression. With increasing tumor grade, in particular, there is an	1	We replaced the text. References to the textprovided by the reviewer were inserted: • Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santia M, Fossati N, Gross T, Henry AM, Joniau S, Lam TB, Mason MD, Matveev VB, Moldovan PC, van den Bergh RCN, van den Broeck T, van der Poel HG, van der Kwast TH, Rouvie`re O, Schoots IG, Wiegel T, Cornford P: EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol 71 (2017) 618–629 • Cooperberg, M.R., et al.: The University of California,

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			increasing risk of progression. High-risk prostate cancer shows rapid local growth and a high likelyhood of meteastasis. In early stage, prostate cancer is localised and organ-confined [40]. Depending on the risk of progression, the cancerous lesion over time increases in volume and produces more PSA. Depending on localisation of the initial lesion in the prostate, the cancer can infiltrate the central or transitional zone of the prostate, and adjacent tissues and organs as well, then called locally advanced prostate cancer. Depending on the risk of progression, too, the cancer can metastasize early or late, into regional or distant lymph nodes. Metastatic prostate cancer is also very likely to produce bone metastases, these with a high variation in size and numbers, in any location. High-risk prostate cancer carries a high likelyhood of early locally advanced stage and early metastasis. Therefore it is, in general, life-threatening and has a high		San Francisco Cancer of the Prostate Risk Assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. J Urol, 2005. 173:1938. http://www.ncbi.nlm.nih.gov/pubmed/15879786 • D'Amico AV, Chen M-H, Roehl KA, Catalona WJ: Preoperative PSA Velocity and the Risk of Death from Prostate Cancer after Radical Prostatectomy. N Engl J Med 2004; 351:125-135, DOI: 10.1056/NEJMoa032975 • Rodrigues G, Warde P, Pickles T, et al: Pre-treatment risk stratification of prostate cancer patients: a critical review. Can Urol Ass J 6 (2012) 121-127 • Ciezki JP: High-Risk Prostate Cancer in the Modern Era: Does a Single Standard of Care Exist? Int J Radiation Oncol Biol Phys 87 (2013) 440-442 • King CR, Long JP: Prostate biopsy grading errors: a sampling problem? Int J Cancer 90 (2000) 326-330

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			rate of cancer-specific morbidity, in particular if diagnosed in younger men. In contrast low risk prostate cancer, in particular in elderly men, can most often left untreated. It might never cause any problems or affect overall survival [41]. Because risk stratification is based on biopsy findings, however, there is a risk of under or overestimation because of sampling error. During follow-up, a shift of grading can also occur. Recurrence of prostate cancer can be local or due to metastasis. Locally relapsed/recurrent prostate cancer occurs when the cancer is still present or comes back after failed primary therapy. After RP, if it was curative, there is no PSA. After RT, or any other procedure which leaves healthy or noncancerous prostatic tissue behind, PSA is still detectable, the lowest value during follow-up being named the nadir. After RT, any PSA above zero is a proof of recurrence or remaining prostate tissue, either locally or metastatic. In most cases, this is a sign the		• Graham J, Baker M, McBeth F, et al: Diagnosis and treatment of prostate cancer: summary of NICE guidance. BMJ 336 (2008) 610-612 • Horwich A, Parker C, Bangma C, et al: Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 21 (2010) 129-133

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			initial tumor was understaged. After RT, the definition of recurrence is more difficult, the definition of recurrence is based on increasing PSA in consecutive measures Phoenix definition). Biochemical recurrence is a term at first used for patients after RP who had a nadir of zero, showed some PSA increase to a low value which stays on a low level during further follow-up, with no detectable lesion. The term biochemical recurrence is also used for recurrence after other therapies, usually with low tumor burden. (see 451-459)		
	28-29	368-375	At this place, it is alo important to discriminate high and low risk PC. The hereditary PC cited in the manuscript refers to high risk.	1	We changed this paragraph: "PCa can be divided into three groups: hereditary, familial, and sporadic. Positive family history is a strong epidemiological risk factor for prostate cancer. Gene–environment interactions also play a crucial role in cancer development. Hereditary prostate cancer, which is high-risk PCa is demonstrated only in 5 % of cases with family history, whereas familial prostate cancer accounts for about 13–25 % of cases. Hereditary PCa patients have three or more affected relatives or at least two relatives who have developed early-onset disease, i.e. before the age of 55, and have onset usually six to seven years earlier than

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					spontaneous cases. Epidemiologic studies have shown strong evidence for a genetic predisposition to PCa based on ethnic background too [1, 46]."
	29	390-406	The signs and symptoms of PCa are unspecific. In the age group affected by prostate cancer, benign prostatic hyperplasia and chronic prostatitis are common preexisting comorbidities causing LUTS. Patients with the primary diagnosis of locally advanced or metastatic disease might suffer from symptoms of these conditions, such as hematuria, incontinence, urinary retention, uni- or bilateral hydronephrosis, urinary tract infection, skelettal pain at various locations. PCa (especially localised disease) is mostly diagnosed as a result of PSA screening, not based on any perceived symptoms.	1	We added this paragraph. Reference could not be provided by the external reviewer. "This is common knowledge. Guidelines do not even contain a paragraph on symptoms."
	29	394-395	Comment: No! It is not the symptoms of BPH or of other problems in the prostate may be like symptoms of prostate cancer. The common symptoms of BPH are those listed in 397-402, summarized as LUTS. These are bladder related and are discriminated in storage symptoms, emptying symptoms, and others. Apart from	1	IPSS is validated to measure urinary symptoms and quality of life regardless in which disease. Reviewer's answer: Of course, IPSS can measure symptoms, however, the validation was made for "LUTS suggestive of BPH" (Barry MJ, Fowler FJ, O'Leary MP, Bruskewitz RC,

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			BPH, LUTS of any kind and of any degree can be caused by primary bladder disorders including bladder cancer and cystitis, and any disorder of the prostate, including prostate cancer. LUTS can also be caused by diseases of the urethra or the penis, and by diseases unrelated to the genitourinary tract, e.g. diabetes. IPSS is an instrument to measure LUTS in BPH. It is often used as a surrogate to measure LUTS caused by other diseases, but was never validated for this.		Holtgrewe HL, Mebust WK, Cockett ATK, and the Measurement Committee of the American Urological Association: The American Urological Association symptom index for benign prostatic hyperplasia. J Urol 1992; Nov 148(5): 1549–1557 and Cockett ATK et al. Recommendations of the International Consensus Committee concerning Prostate Symptom Score (IPSS) and Quality of Life Assessment; in The 2nd International Consultation on Benign Prostatic Hyperplasia (BPH). Patronized by WHO. SCI 1994: pp. 553–55) We differentiate from the beginnig storage and vioding LUTS from other LUTS, we refer to LUTS as adverse event and urinary symptoms in the functional outcomes. Reviewer's reply: Of course, you are right thar new onset or deterioration of preexisting LUTS is an adverse event. However: In RP, patients have a urinary catheter vor several days. Is this an adverse event or part of the procedure? If a

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					patient has a catheter, he cannot void, he cannot have LUTS. But what's about catheter discomfort? In RT, which is usually done in 30 to 40 fractions, most patients have temporary mild radiation cystitis and LUTS during and some time after this period. This is expected and usually not measured. Usually, this is considered an adverse event only, if it more than the expected level. In HIFU, due to heat application, swelling occurs, leading to an increase of obstruction and LUTS. In some studies a catheter was placed to prevent the risk of urinary retention, in others patients received the catheter only if they experienced urinary retention. It is very diffucult to find a consensus which events are adverse events or are expected as immanent to the procedure or even part of the procedure. I suggest to go with the study authors own definitions of adverse events. If LUTS are reported refore and after, and if they deteriorate, the difference before and after should be reported for the particular time of follow-up, e.g. at 3 months.
	30	436-437	Replace by: Although there is no general agreement on	2	Corrected.

Please add extra rows as needed.

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			the benefit of PSA screening, and no general agreement on the cut-off value to perform a biopsy, it is obvious that higher PSA concentrations indicate a greater likeihood of a positive result, but not definitive sign for PCa [1].		
	30	443	DRE should stand outside the brackets and before "imaging"	3	Corrected
	30	445-447	N-staging: In T and M-staging procedures to achieve information are described, this is missing for N-staging (CT-scan or MRI)	2	We added.
	30	448	~~mp~~MRI	2	Corrected.
	32	472-475	Add: management of prostate cancer also depends on patient's age or life expectancy, respectively	1	Added.
	32	486	Patients preference should be listed as an separate point	2	Modified.
Clinical effectiveness					
	36	628-630	After five years, a more favourable □curve of overall survival was observed in the brachytherapy-group compared to HIFU. The difference, however, was not significant (88 vs. 97.5 %, HR 0.24, CI 0.01-1.34) [13]. Replace by: After five years, overall survival in the	1	Changed.

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			brachytherapy-group compared to HIFU was not significantly different (88 vs. 97.5 %, HR 0.24, CI 0.01-1.34) [13]. Alternatively, add my comment: , ...although patients in the HIFU group were median 5 years and significantly older at time of treatment.		
	36	632-635	Regarding prostate cancer specific survival, after five years, the rate was 89 % for patients in the HIFU-group and 92 % for patients in the brachytherapy-group. ~~Even though the rate was higher for patients treated with brachytherapy,~~ the difference between the study groups was not significant (HR 0.67, CI 0.32-1.29) [13]. Comment: Follow-up was 83 (HIFU) versus 44 (brachytherapy) months. Which patients of the brachytherapy group were included to analyse 5 years follow-up? Only those who completed 60 months?	1	Survival was measured for all 70 patients in the study groups. However, after 5 years some of the 70 patients were dead. Thus, the outcome measure was for all patients, even though some were dead at follow-up.
Safety					
	38	680-681	See comments regarding 38/682-689 and 39/695-697	1	See comment below. We evaluate safety with the functional outcomes defined as urinary dysfuntion and sexual dysfunction (see definitions

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					below).
	38	682-689	Comment: Urinary dysfunction is not a good term or parameter, respectively. The bladder can be affected by storage symptoms, emptying symptoms and others. While in BPH or chronic prostatitis this in one symptom complex or syndrome, respectively, it is called LUTS related to BPH, and measured by IPSS. Any treatment for BPH is aimed on improving LUTS or decreasing IPSS, respectively. In prostate cancer treatment, however, complications affecting „urinary function" can be caused by many unwanted adverse events such as strictures (leading to retention) or sphincter damage (leading to incontinence). Any of these events are reported separatly, It is of no use to summarise these by the term urinary function. It might be necessary to report an increase of LUTS, because this might pe temporary or persistant and different for different procedures. Due to the anatomical region the prostate is located in, usually complications regarding prostate cancer or	1	Functional outcomes, including urinary (dys)function were used in the clinical studies and in other HTAs. Also IPSS score was used to measure functional outcomes. Urinary incontinece when reported with the IPSS score should reflect only question number 4 (frequency). The other IPSS questions do not reflect specifically incontinence. However, incontinence was a major point in all studies. The storage and emptying symptoms are discussed under the term LUTS (which term is now specified and named as "storage and voiding LUTS"). We added the Clavien grades also to the scope. New categorization in the safety domain • Intervention-specific mortality (peri-operative death) (critical) • Anatomical complications: o Clavien-Dindo grade 1-2 adverse events (AEs) affecting the genitourinary tract or the gastrointestinal tract including but not restricted to urinary tract infection, storage and voiding lower urinary tract symptoms (LUTS), acute/chronic urinary retention,

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			prostate cancer treatment are specified in related to the „GU" =genitourinary tract and related to the „GI" = gastrointestinal tract. A total number of GU or GI related complications is sometimes reported, but is not very useful, more important is the discrimination in Clavien-grades. Major complications of any prostate treatment, are anatomical, such as strictures and fistulas, or functional, such as loss of continence or erectile function. Although anatomical complications affect function, these are usually reported separately. Complications like urinary retention and urinary tract infection, and an increase in LUTS require treatment, but are minor and only of temporary character. In addition, temporary retention, caused by thermally induced necrosis, which leads to swelling and hardening of tissue, is imminent to the procedure. Usually, after HIFU a catheter is placed as a routine and left in place for some days. The catheter is part of the procedure. A postoperative catheter is also part of the procedure in RP because of ‚normal' leakage		burn, injuries, bleeding, proctitis, pain, anaesthesia-related complications, thromboembolic disease (phlebitis) (important) o Clavien-Dindo grade 3-4 Serious adverse events (SAEs) including but not restricted to bladder neck/urethral stricture/stenosis, rectal fistula, bladder neck obstruction (critical) • Functional complications (critical) o Urinary dysfunction: urinary incontinence (reported as number of patients with urinary leakage or number of patients with new onset of pads required) or worsening of urinary tract symptoms (increase in the IPSS score) o Sexual (dys)function: loss of erectile function (reported as number of patients with new onset of importance) or worsening in erectile function (decrease in the IIEF-5, IIEF-15, or BMSFI score) Reviewer's reply: categorization is good as long as urinary leakage and worsening of urinary tract symptoms is reported separately. The important point is the following: The question

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			of the urethro-vesical anastomosis in the early postoperative phase. In studies, recatheterisation rates are reported and considered a complication, but these rates depend on the policy, at which day in the postoperative course the catheter is removed. There is no standard. As a result, however, the ‚trial' to remove the catheter as early as possible determines the the ‚error' and therefore recatheterisation rate. Because the reason for recatheterisation is most often retention after HIFU and radiation, but most often leakage after RP, neither retention nor leakage is a good comparator. Your definition of urinary dysfunction is unclear: ...usage of pads and/or physician reported events or with the International Prostate Symptom Score (IPSS)... Is „reported events" the number of patients of the cohort with new onset of pads required (=being incontinent to any degree) or the number of pads? Incontinence could be a yes/no category, but it is also gradual, e.g. no/mild/moderate/severe, and the number of pads per		of the IPSS addressing "incontinence" is to assess storage symptoms being so severe these lead to URGE incontinence. The affected organ is the bladder. Urge incontinence can be a complication of prostate cancer treatment, however, it is always the bladder which is affected. The more important mechanism after prostate cancer therapy which leads to incontinence is damage of the sphincter, this type of incontinence is called STRESS incontinence. Please consider, an increase of IPSS of 3 points or 10 points is not the same.

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			day might help to discriminate the degree of incontinence. What ist he meaning of „with the IPSS"? If IPSS is reported before and after HIFU, how many points increase is „urinary dysfunction". IPSS is not a yes/no category, it is gradual and helps to categorise patients suffering from no/mild/moderate/severe symptoms. „and/or" is difficult, incontinence and symptomatic detereoration are two different categories, although both fit in the category of urinary dysfunction.		
	39	695-697	Please see the comments on 38/680-681. All procedures to locally treat prostate cancer can cause complications which are related to the GI tract and therefore related to bowel function. However, proctitis is a relatively common complication of radiation therapies, but never a complication of RP or HIFU. As a consequence, bowel function is not reported in HIFU studies. I suggest to replace the term "bowel function" by the term "proctitis" throughout your report.	1	Corrected. We deleted bowel function. But if it is a complication in RT, this could have been reported in the brachytherapy study in our understanding. Reviewer's reply: The problem is the term "bowel function". In most studies, complications are discriminated in GU tract related and GI tract related. GI related are fistulas, rectal injury, and proctitis. One could imagine rectal sphincter injury with fecal incontinence, but I am not aware this was ever reported after RP or RT or HIFU. Fistulas and injuries can occur after any therapy, this complication needs to be reported. Proctitis (possible

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					complication of radiation) also needs to be reported, if radiation is involved, but is not a complication of RP or HIFU. Summarizing these complications with the term bowel function, causes misunderstanding, because neither fecal incontinence, nor obstipation or diarrhea are complications seen after local therapies of prostate cancer.
	39	739	Omit duplicate "applied"	3	Corrected.
	40	779-781	?: Urinary dysfunction was higher for HIFU-patients compared to patients who received brachytherapy, the difference between the two cohorts was, however, not significant □(occurred in 7.2% of patients in the HIFU group and 3.8 % in the brachytherapy group, p=0.44). This requires more specific presentation, please see the comment regarding lines 682-689 Alternatively: Urinary dysfunction showed no significant difference in HIFU-patients compared to patients who received brachytherapy □(occurred in 7.2% of patients in the HIFU group and 3.8 % in the brachytherapy group, p=0.44). In addition, I have to refer to 41/789-790. Haemorrhagic	1	We added your suggestions.

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			cystitis is high degree urinary ,dysfunction', but required surgical management.		
	40	784	…and LUTS… My comment: wasn't LUTS not part of urinary dysfunction? Please specify the meaning of LUTS. Do you mean any new onset of LUTS or a decrease in IPSS, of how many points? Comment: 41/792-805 describe the reported IPSS changes, and I understand there were no major IPSS increases in any of th studies. How is it possible LUTS was a common complication?	1	No, LUTS did not contain incontinence. The correct naming would be "other LUTS or storage or voiding LUTS". The studies reported new onset of LUTS. The comparative study and a singlar-arm study that reported LUTS as a common complication did not use IPSS scoring, a single-arm study that reported LUTS showed significant change in the IPSS score. New onset of any degree LUTS, not measured by IPSS, was defined a complication in these studies.
	40-41	788-790	These are the most important complications. They should be reported in an extra paragraph, not in a list of minor complications.	3	No, they were not mean as minor complications. We re-structure the paragraph to highlight these complicatiosn more.
	41	792-805	Please compare 783-788 regarding LUTS	1	We completed LUTS by storage and voiding.
	41	796-797	one study [16] concluded that there was a significant change in the IPSS score from baseline 797 to 12 months post-intervention (95% CI: 1.6; 4.4). Please specify if the significant change was an increase	1	It was improvement, we specified.

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			(worsening) or decrease (improvement) of symptoms.		
	41	799-800	Comment: As mentioned above, IPSS is not an instrument to measure incontinence. Incontinence is a major unwanted adverse event, and as such not part of ,urinary function'. Changes in IPSS, distinct as decrease, are an improvement of bladder related storage and emptying function. An increase stands for more pronounced symptoms.	1	We deleted IPSS as a measurement tool for urinary incontinence. IPSS measures urinary symptoms, therefore the measurement tool for the urinary function outcome.
	41	803-805	Comment: This sounds negative, but the meaning of no change in this case is no deterioration of symptoms, which is a positive result. Replace: could not show a significant effect by did not show a negative effect.	2	We amended to ..study did not show any significant effect..
	41	817	Add: , because this was not an expected side effect. In none of the studies, a rectal fistula was reported.	2	We decided to remove this as we deleted the bowel dysfunctio as an outcome.
	41	820	Remove or explain LUTS: comments see above	1	We decided to remove because the study did not explain it.
	41	836-837	Comment: A second HIFU after primary focal HIFU ablation should not be considered salvage in the same meaning as after RP, ERBT or whole-gland HIFU. It is	1	You are right. We changed this paragraph and added that we found no evidence.

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			more a repeated or two-step treatment. I suggest to separate the list regarding second HIFU after focal HIFU. This discrimination is important (please compare 841-845).		
	42	856-859	Comment, no changes required: This is important and explains most of my comments regarding LUTS. Heat application leads to swelling and hardening, increasing obstruction temporarily and causing emptying symptoms. Radiation may cause any degree of radiation cystitis and causing storage symptoms.		OK.
Tables					
	44	Table 4	LUTS: Please see comments above	1	We added storage and vioding LUTS.
Discussion					
	47	5-6	Add: ...hemiablation, or focal therapy. Replace: The guidance oft he HIFU-device into the ablation area.can... by Treatment planning can... Replace: ...whereas the latter is also appropriate... by ....whereas the latter is more appropriate...	2	Added. Replaced.
	47	24-26	Comment: Patient groups were significantly different	1	Information added in paragraph on interpretation of findings.

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			regarding age, the HIFU groups 5 years older. Overall survival and cancer-specific survival were not significantly different. You should add this information or omit the comments on slightly lower survival rates, because this is without information on age difference misleading.		
	47	27	Omit: ‚even' Unfortunately, the study design did not include rebiopsies. This is a design error, not a reporting error.	3	We deleted even.
	47	33	Omit: ...'but'...(Regarding not reported bowel function in single-arm studies, please see comments above). Changes in bowel function were not reported, because proctitis is not an expected adverse event of HIFU.	2	We deleted the sentence fragment after but.
	47	34-36	Exclude LUTS (see comments above) – does it change the result?	1	No, does not change the results. If we add storage or vioding?
	48	51	Replace: ...which cannot accomplish a high evidence level... by Which is level B evidence only.	3	According to GRADE methodology.
	48	52-54	Evidence levels should be included in brackets (LoE C, lacking LoE A).	3	This is according to GRADE methodology where evidence levels are high, moderate, low and very low.

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	48	89-90	Comment: Please apology, I do not understand. What infomation is missing if the number of adverse events and the number of patients affected by these events is reported? I understand you are missing percentages, but this is most likely my misinterpretation. However, other readers might have the same problem. Please check and clarify.	2/3	We corrected.
	48	93-96	Comment: Your HTA is on HIFU, therefore it is mandatory to include all studies. However, whole gland ablation and hemiablation or focal ablation are different treatment concepts using the same tools, therefore cannot achieve the same outcomes. One concept is radical with the goal of destroying all tumorous tissue. In this type of treatment, ny remaining tumor is failure. The other concept is tissue-sparing and trying to avoid side-effects, even if cancerous tissue may be left untreated. It is even part of the concept, to leave cancerous tissue untreated which has only low risk of progression, and to treat the index lesion only, which is the lesion with		We discriminated whole gland, hemiablation and focal therapy where possible in the description of the technology. The comparative study applied whole gland ablation and the single arm primary studies applied hemiablation, therefore we separated the results and we described them separately. We described the whole gland salvage study also separately. We considered the effectiveness results only for the comparative study, where local recurrence was one of our critical endpoints (showing failure) but was not reported on. Side-effects were considered in comparison to brachytherapy in the comparative study and in general in the single-arm studies. We added in the discussion your suggestion and completed: "Whole gland ablation is associated with a worse side-effect profile (more frequent toxicities, incontinence and

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			intermediate or high risk of progresion, the latter being not the topic of yor assessment. A second treatment can be done to treat any tcancerous tissue which demonstrates progression or was mistakenly spared at first treatment. This is therefore not salvage, but the „second of two treatments" The concept of focal treatment is common, e.g. in colon cancer, or breast cancer, although the treatment is surgical. A common analysis of the results and complications of total colectomy or hemicolectomy would be the same, as the common analysis of whole gland ablation and focal ablation of prostate cancer. Some differences are based on the different concept.		erectile problems) compared to hemiablation. This is natural as whole gland ablation is radical with the goal of destroying all tumorous tissue where remaining tumor means treatment failure. The other concept, hemiablation and FT is tissue-sparing and trying to avoid side-effects, even if cancerous tissue may be left untreated. It is even part of the concept in FT to leave cancerous tissue untreated which has only low risk of progression and to treat the index lesion only, which is the lesion with intermediate or high risk of progression."
References					
	52	158-164	3. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms, Kurzversion 4.0,	2	We corrected the reference list.

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Comments by external experts on the 2nd draft rapid assessment on HIFU for the treatment of prostate cancer

Comments should be submitted not later than time *Weekday 06/03/2018*

Comment from *Insert your name, title and affiliation*	Page number *Insert 'general' if your comment relates to the whole document*	Line/ section number	Comment and suggestion for rewording *Please insert each new comment in a new row.*	Character of comment • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3 *Please indicate your choice by writing the according number in this field, e.g. for major choose "1".*	Author's reply
			2016, AWMF Registernummer: 043/022OL, http://leitlinienprogramm-onkologie.de/Prostatakarzinom.58.0.html (Zugriff am: TT.MM.JJJJ)		
	52	165-167	4. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Konsultationsfassung: Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms, Langversion 4.0, 2016 AWMF Registernummer: 043/022OL, http://leitlinienprogramm-onkologie.de/Prostatakarzinom.58.0.html (Zugriff am: TT.MM.JJJJ)	2	
Appendix 3					
	99	Organisational 2.1.	…HIFU device requires plenty of space in an operating room… This is true for Ablatherm, beause the system is built in	1	We added the information that only Ablatherm device requires plenty of space.

Please add extra rows as needed.

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			the patient table. The Sonablate systems have the size of a laser or other medical device and does not require plenty of space. The systems used with real-time MRI are MRI-compatible and do not require much space.		
	99	Organisational 2.2.	Comment: Having personal experiences in numerous RP, numerous Brachytherapy and numerous HIFU (Ablatherm, Sonablate, TULSA-PRO), I cannot give a statement on RT. Learning curves for all procedures are long. If a urologist is trained in transrectal ultrasound, brachytherapy and HIFU have a comparable learning curve regarding treatment planning, however, in brachytherapy it takes additional learning to reproducibly place the application needles and seeds in the correct position. Brachytherapy requires a team (urologist and radiation oncologist and/or physicist). MRI-guided HIFU requires a team (urologist and MRI-trained radiologist).	1	We added the information on the team composition and deleted the our statement on the learning curves.

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Depending on your expertise, you may want to comment on some of the questions provided below.

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part I: Methods				
1. Are inclusion/exclusion criteria for selection of the studies described in appropriate detail?	X			
2. Are the quality appraisal tools appropriate?	X			
3. Is the type/presentation of evidence (e.g. Meta analysis, qualitative synthesis, GRADE) appropriate for this analysis?	X			
4. Is the risk of bias sufficiently assessed, both on study level and on an outcome level?	X			
5. Is the choice of study types appropriate to the population, intervention(s), comparison(s) and outcome(s)?	X			
6. Are the types of studies to be included (randomised trials, quasi-randomised trials or other designs) described?	X			
7. If it was relevant to include data from indirect comparisons, is this step justified and the methods of indirect comparisons sufficiently described?	X			
8. Are appropriate methods of measuring each outcome and appropriate time points for measurement identified?	X			
Comments:				

9. Are details on sources of information and literature search strategies provided?					
Search strategy	Databases	Year range	Language restriction	Primary data	Other kind of information resources
xO	xO	xO	xO	xO	xO
Comments:					

10. Information on basis for the assessment and interpretation of selected data and information:		
Method of data extraction described?	Critical appraisal method (for quality assessment of the literature) described?	Method of data synthesis described?
xO	xO	xO
Comments:		

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Part II: Results (See Domain Reports)				
Description and technical characteristics of the technology				
1. Does the section describe the intervention under review including how it works and how it may have an impact on potential recipients?	X			
2. Does the section describe the comparator(s) under review including how it works and how it may have an impact on potential recipients?	X			
3. Are the supporting references current and do they provide an international picture of the problem?	X			
Comments:				
Health problem and current use of the technology				
4. Does the section describe the health issue including incidence and prevalence, how it occurs, who is affected (including high-risk groups, vulnerable/disadvantaged populations, where it occurs, how it is diagnosed, symptoms and consequences)?	X			
5. Are the supporting references current and do they provide an international picture of the problem?	X			
Comments:				
Safety and effectiveness				
6. Is the risk of bias clearly reported?	X			
7. Is quality of data sufficiently evaluated?	X			
8. Are both relative and absolute effect measures presented for each dichotomous outcome?	X			
9. Are continuous data reported according to appropriate statistics (e.g. 'standardised mean difference' or 'weighted mean difference')?	X			
10. In case of time-to event analysis, are hazard ratios (HR) and ratios of medians presented?				n.a.
11. Are measures of the precision of the effect estimates presented or, in case of absence of this essential information, is this fact reported?	X			
12. Is frequency of adverse events, frequency of occurrence, relative risk or number needed to harm (NNH) presented for the safety data?	X			

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13. In cases where adverse events are incorporated in utility values of quality of life, is the source of quantification accessible?	X			
14. Was the transformation of the surrogate outcomes into patient-relevant final outcomes considered (if relevant)?	X			
Comments:				
General				
15. Do you agree that the data extracted are relevant to the research questions formulated in the beginning and that analysed and synthesised data still answer the question?	X			
16. Can the results be applied to the intended population?			X	
17. Is the assessment sufficiently transparent and evidence ('facts') distinguished from judgements (including values and preferences)?	X			
Comments: My comment is extremely subjective, but describes every-day-practice. According to current guidelines, in low risk cancer either "no treatment" or "radical treatment" should be offered to patients. Many patients, however, consider AS and WW as undertreatment and RP and RT as overtreatment. In the presence of the diagnosis "cancer", many patients are not rationale any more, and they demand treatment, even after long explanation of the NOT-life-threatening nature of low risk prostate cancer. Focal therapy fits almost perfectly into the gap.The practical problem is guideline recommendation "…in studies". Which studies (?), I am aware of registries only. Unfortunately, the existing evidence is insufficient, and an HTA based on insufficient evidence can only report insufficient evidence. The problem if and how we can implement HIFU in our practice is still present.				
Part III: Summary of Relative Effectiveness				
18. Does the summary present a balanced representation of the content of the report?	X			
19. Does the discussion of the summary clearly address the uncertainty in the available evidence, the evidence gaps and the applicability of the evidence?	X			
Comments:				
Part IV: Other Considerations				
20. Have all relevant ethical, organisational, social and legal aspects been considered? (See Appendix 3 of the Pilot assessment)	X			

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