



Comment from <i>Insert your name, title and affiliation</i>	Page number <i>Insert 'general' if your comment relates to the whole document</i>	Line/section number	Comment and suggestion for rewording <i>Please insert each new comment in a new row.</i>	Character of comment • 'major' ^a =1 • 'minor' ^b = 2 • 'linguistic' ^c =3 <i>Please indicate your choice by writing the according number in this field, e.g. for major choose "1".</i>	Author's reply
T. Tandsat			PSA and overall survival should not be outcomes of the assessment and should be removed		As the outcomes are selected at scoping phase, we are not able to "remove them" now – we will make note in the discussion that these outcomes are rarely evaluated in this type of trials
T. Tandsat			Prevalence of toxicity grade 3&4 is rare (short or long term) and a huge number of participants would be needed to gather statistical significant results – not need to present the results		We will also make not of this in the discussion, however as the studies report grade 3 we will keep the data in the report
T. Tandsat			The report tries to include too much		We followed EUnetHTA template but we will try to cut down and abreviate paragraphs as we can to present a shorter version
T. Tandsat			RT has an effect on short term toxicity and QoL		Thanks, we tried to report both as presented in the studies
T. Tandsat			EUA guidelines, only include disease stage the sapcer is used, meaning localized prostate cancer – too much irrelevant information		Will try focus on localized prostate cancer only. TEC and CUR chapters give an overall description of disease and treatment
T. Tandsat			No value if we include all toxicity – the report will not be taken seriously		We will report according to what was agreed at protocol stage
T. Tandsat			Check the RoB/GRADE for RCT (currently as low), do not agree with blinding rating in particular		Manufacture has provided information about allocation and randomization, so the grading will change in those

Please add extra rows as needed.

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					domains. However overall RoB for the RCT remains High Risk
T. Tandsat			nRCT grading is Ok at very low		Ok – it remains very low
T. Tandsat			Surgery and RT are the only standard options, hormone therapy and chemotherapy are not curative		We will reflect this comment through the assessment
T. Tandsat			Rectal Toxicity should be included in the health problem? No-rectal toxicity should not be included, otherwise incontinence with surgery, or other operative complications should be included as well		Thanks, not included
T. Tandsat			Stereoactive RT should be removed		removed
T. Tandsat			How do you explain the discrepancy between the high proportion of patients who have a clinical relevant change in bowel related QoL in two treatment arms and the reported low incidence of rectal toxicity in the same study? Perhaps this is a matter of patient reported vs physician reported outcomes with patient's been at a lower treshold for reporting. After RT there is inflamation and flatulence is common, so patients will report any changes after RT		We will make note of patient completed assessment and physician completed assessments
T. Tandsat			Rectal dose, late effects-lower dose only reduce by spacer use, but after that is harder to be certain. Mean volume to the rectum, do not know exately what is the best value (dose/volume)		Unclear if rectal dose reduction means clinical benefits
T. Tandsat			In Norway there is 1 centre that does Brachithery because 1 MD is interested , but it is more complex because it requires general anesthesia – Differences between brachithery and EBRT may dimisih with time		ok

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T. Tandsat			Wolf – spacer volume is not a proxy for distance		Ok-thanks
T. Tandsat			PSA values should not be presented		This was established at protocol stage, unable to change now
T. Tandsat			QoL in bowel and overall are better in intervention. At 6 months, after RT there is inflammation, we can see a difference		ok
T. Tandsat			In terms of population the T3 tumors are not included, but would be more interesting to treat – individuals need an evaluation to identify they are a candidate or not. There was a discussion to do it in Norway. Also individuals with large prostate and individuals with IBD		Will include this in conclusion and discussion
T. Tandsat			Comorbidities? Treatment with anti-coagulants will be a consideration, but at this point all patients have had an intervention to insert fiducial markers, so the indication will be the same than for the insertion of the fiducial markers		Ok- will mention in the discussion
T. Tandsat			Patient with diabetes spacer may be more beneficial to get less toxicity and heal faster (they have inflammation and lower healing) also higher risk of infection due to poor circulation, any other autoimmune patient		Ok – will try to add to conclusion/discussion
T. Tandsat			Current practice in Norway is that fiducial markers are inserted through the rectum, if this was done through a perineal procedure there is a higher risk of infection		May mention in discussion
T. Tandsat			Evidence can be put in context, single arm are most valuable to see frequency of complications - safety		Ok – that was the idea of including single arms
T. Tandsat			Historical comparative arm, not useful because of changes on RT		ok
T. Tandsat			RWI, refers to the technique, how often the procedure is ok, and often will be ok earlier on the trial, but RWI is ok as an AE		Outcome in SAFF section

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T. Tandsat			Toxicity higher in the beginning declines and plateaus, then some have toxicity after 5 years, should be low		Ok -
T. Tandsat			Consider in RCT and med technology is hard to blind		We will consider this in discussion/conclusion
T. Tandsat			Believes the conclusion should be moderate evidence		GRADE evaluation not changed
T. Tandsat			Future research must focus on locally advanced cancer, replicate with other RCTs		Will add to discussion/conclusion

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Thariat j					
Summary					
Thariat j			Absorbable ?		Word removed (absorbable)
Thariat j			Aimed to involve patients, but what happened then? if not involved, remove sentence		We included a patient partner from Prostate Scotland /sentence re/arranged
Thariat j			Toxicity does not differ but quality of life shows trend for spacer, it is not a hard		Re/phrased to describe quality of life

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			endpoint		trend for spacer
Thariat j			Safety inconsistently reported in studies, to be stated		Safety regarding rectum spacers only reported in Mariados. Comment suggested added to discussion/conclusion
Thariat j			I don t see the point to write “ overwhelming number of abstracts....” in the conclusion. Why would the conclusions be different” This means this is an area of interest and an update of this assessment 26 should be planned in the near future.”		Re-phrased-This meant the number of items we included but did not process due to time constrains, was higher than expected. The number of conference abstracts and posters indicate research is conducted in the area and there is interest. We suggest our understanding of safety (reason whyt we had originally thought of including single arm studies) would be different would we have the opportunity to look at the evidence. With 15 ongoing trials, an update my be necessary in the near future.
Description and technical characteristics of the technology					
			Please give duration of procedure		Sstated
			Please specify anesthetic protocol in the document instead of only referring to manufacturer's protocol		Addressed
		33	Outline of EBRT critically lacks details on high dose SBRT, which is increasingly used in prostate EBRT		Details added
Health problem and current use					

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			Rectal toxicity being an issue in prostate cancer		Rectal toxicity not included in health problem
			Dosimetric benefit consistently shown but does not translate in clinical benefit		Agreed – we have make a point in the discussion/conclusion
Clinical effectiveness					
			Dosimetric benefit consistently shown but does not translate in clinical benefit		Phrase added
			Quality of life questionnaires do not provide a strong endpoint and are likely influenced positively in the spacer arm, may need to be told		Agree, it is a self assessment and drop out rate at 3 years was high. Will add to discussion/conclusion
			Low ASMR		Unclear what this means
Safety					
			Detailed only for 2 studies ?		One study actually. Only Mariados provides Safety data
Appendix					
			OK		

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