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Title page

Delphi study to identify consensus on patient selection for hydrogel rectal spacer use during radiation therapy for prostate cancer in the UK.

Short title: Delphi study on hydrogel rectal spacer use (UK)

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Delphi study to identify consensus on patient selection for hydrogel rectal spacer use during radiation therapy for prostate cancer in the UK.

Structured abstract *(Word count: 268, max 300)*

OBJECTIVES

To identify consensus on patient prioritisation for rectal hydrogel spacer use during radiation therapy for the treatment of prostate cancer in the United Kingdom.

DESIGN

Delphi study consisting of two rounds of online questionnaires, two virtual advisory board meetings and a final online questionnaire.

SETTING

Radical radiation therapy for localised and locally advanced prostate cancer in the United Kingdom.

PARTICIPANTS

Six leading clinical oncologists and one urologist from across the UK.

INTERVENTIONS

Rectal hydrogel spacer.

PRIMARY AND SECONDARY OUTCOME MEASURES

NR

RESULTS

The panel reached consensus on the importance of minimizing toxicity for treatments with curative intent, and that even low-grade toxicity-related adverse events can significantly

impact quality of life. There was agreement that despite meeting rectal dose constraints, too many patients experience rectal toxicity, and that rectal hydrogel spacers in eligible patients significantly reduces toxicity related adverse events. However, as a consequence of funding limitations, patients need to be prioritized for spacer use. A higher benefit of spacers can be expected in patients on anticoagulation, and in patients with diabetes or inflammatory bowel disease, but consensus could not be reached regarding patient groups expected to benefit less. While radiation therapy regimen is not a main factor determining prioritization, higher benefit is expected in ultra-hypofractionated regimens.

CONCLUSION

There is a strong and general agreement that all prostate cancer patients undergoing radical radiation therapy have the potential to benefit from hydrogel spacers. Currently, not all patients who could potentially benefit can access hydrogel spacers, and access is unequal. Implementation of the consensus recommendations would likely help prioritise and equalise access to rectal spacers for patients in the UK.

ARTICLE SUMMARY: STRENGTHS AND LIMITATIONS OF THIS STUDY

- The Delphi panel is a recognised method in developing NICE guidelines and is utilised here to gather insights from a diverse panel of UK radiation oncology and urology experts who are experienced users of hydrogel spacers.
- This study included seven panel experts and their experiences may not reflect all users of hydrogel spacers.
- To help reduce bias, answers and opinions were assessed by two researchers working independently.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

- Radiation toxicity to nearby healthy tissue is a potential problem when undertaking radical radiotherapy with curative intent for prostate cancer.
- Biodegradable spacers are used to separate the prostate and the rectum, thus reducing radiation exposure to a primary dose-limiting organ.
- Spacer funding and capacity are limited and there is a need to understand which patients to prioritise for use of a spacer.

WHAT DOES THIS STUDY ADD?

- Expert consensus opinion can help to guide strategy in areas of care where the evidence base is lacking.
- There was consensus that increased benefit from spacers is expected in patients on anticoagulation and/or with diabetes and/or inflammatory bowel disease.

INTRODUCTION

Prostate cancer burden

Prostate cancer is the second most common cancer in men globally,[1] and the most common in the UK.[2] More than 47,500 UK men are diagnosed with prostate cancer every year and over 400,000 men are living with and after prostate cancer.[3] The 5-year survival rate for localized prostate cancer in the UK is almost 100%,[4] with three quarters of men diagnosed at any stage expected to survive 10 years.[2] In England, 97%, 87% and 78% of men diagnosed with prostate cancer survive their disease for more than one, five and ten years, respectively.[2] Given the high likelihood of curative therapy, a key treatment goal is to prevent potential adverse events from impacting patient quality of life after treatment.

In addition to the patient burden, prostate cancer is a costly disease with the European costs of care for prostate cancer estimated at EUR 199 billion in 2018.[5]

Radiation therapy for prostate cancer

Choice of treatment for prostate cancer is complex and involves multi-factorial considerations including presenting cancer stage (localised, locally advanced or metastatic), risk stratification, life expectancy, comorbidities, and other patient-specific factors, such as lifestyle, patient preference and treatment goals.[6] For localised and locally advanced prostate cancer, treatment options include active surveillance, surgery, and radiation therapy (RT), with or without hormone treatment, as well as multimodality treatment combining surgery or RT with systemic therapy.[7-9] RT with radical intent is a first-line treatment for localised and locally advanced prostate cancer.[8] Intensity-modulated RT (IMRT) with image guidance (IGRT) is considered the gold-standard form of external beam RT (EBRT).[10] Of the circa 18,000 men identified as having received radical RT for prostate cancer in England and Wales between April 2018 and March 2019, over 90% were treated with IMRT.[11] Whilst stereotactic body RT (SBRT) is not currently routine practice in the UK, its use is increasing and it is now delivered

in several NHS centres.[12] Circa 95% of UK men with intermediate-risk disease receive a hypofractionated radiotherapy regimen.[11]

The success and clinical outcomes of RT depend on several factors, including radiation dose to the tumour and the extent of irradiation affecting nearby normal-tissue, particularly the rectum.[10] Dose-escalated EBRT is a highly effective curative treatment, with higher doses providing better biochemical control.[13] Higher doses can, however , increase radiation toxicity to nearby tissues. Despite substantial advancements in RT, acute and reversible, as well as rare but severe, long-term adverse effects of radiation toxicity such as urinary and bowel incontinence remain problematic. In 2021, The National Prostate Cancer Audit (NPCA) reported that 11% of prostate cancer patients experienced ≥1 severe gastrointestinal complication (defined as a confirmed diagnosis of radiation toxicity and requiring a procedure to the large bowel) within two years after radical RT.[11] Due to its proximity to the prostate, the anterior rectal wall is especially vulnerable to irradiation effects and the rectum is a dose-limiting organ at risk.[14]

Hydrogel spacers

One way of reducing the unwanted radiation dose to the rectum is by increasing the space between the prostate and the rectal wall. This can be achieved by use of a rectal spacer, with three currently indicated for use during RT for prostate cancer in the UK: biodegradable balloons, hyaluronic acid gel, and polyethylene glycol (PEG) hydrogel.[15] In the UK, the use of biodegradable spacers to reduce rectal toxicity during RT for prostate cancer is accepted (IPG590) by NICE, based on safety and efficacy data on the use of PEG hydrogel spacers.[15] Use of rectal hydrogel spacers has been evaluated in a single-blind, phase III trial in image guided IMRT (N=222).[16] The spacer-placement success rate was 99%, and no device-related adverse events occurred.[16] Late (three to 15 months) rectal toxicity severity was significantly reduced in the spacer group.[16] At three years follow-up, decreased bowel toxicity and fewer declines in urinary and bowel quality of life were observed in the spacer group.[17]

Lack of routine reimbursement has led to restricted patient access to hydrogel spacers in the UK. Therefore, there is a requirement to prioritise patients for hydrogel spacer use in the UK, and attempts have been made to identify optimal usage. A secondary analysis of the hydrogel spacer trial data tried to identify the patient subgroups most and least likely to benefit from the intervention but found generally homogeneous results in bowel quality of life with benefits in all assessed subgroups.[18]

The aim of this study was to identify consensus on patient prioritisation for rectal hydrogel spacer use during RT for the treatment of prostate cancer in the UK.

METHODS

The Delphi technique and panel experts

The Delphi technique is a structured, iterative, multistage process using rounds of questionnaires to collect opinions and to stepwise develop consensus among a pre-defined panel of experts.[19] For this study, experts were approached and asked to participate in the panel based on being a UK radiation oncologist or urologist having experience with rectal hydrogel spacers. To ensure a diverse panel, experts were sought to represent different geographies within the UK and use different types of RT modalities. There is no defined optimal panel size for a Delphi study,[20] but the selection of an odd number of experts ensured that a majority outcome could be reached.

Steps in the Delphi process

There is no fixed number of rounds in a Delphi survey.[20] As depicted in Figure 1, our study adopted a five-stage approach to elicit consensus, consisting of two pre-advisory board questionnaires administered through a web-based survey program, two virtual advisory board discussions, and a final concluding questionnaire.

The first questionnaire provided some background information on the experts, such as their most used RT modalities and open-ended questions to capture a broad understanding. The

open-ended questions related to key treatment aims, which patient and treatment characteristics to consider when prioritising hydrogel spacer, factors typically deterring them from recommending hydrogel spacer use, and factors predictive for toxicity. Additionally, experts were asked to rank treatment modalities in order of how much patient benefit they would expect from hydrogel spacer use, on a scale from 0 (no patient benefit) to 100 (maximal patient benefit).

In the second questionnaire, the responses to the open-ended questions from the previous questionnaire were presented, and the experts asked to rank them by order of importance. In addition to follow-up questions, the second questionnaire included questions on perceived barriers to hydrogel spacer use.

Figure 1: Overview of Delphi panel process

Analysis and scoring

Qualitative content analysis was used to analyse responses to open-ended questions. Two researchers independently analysed responses and interpreted consensus. At the advisory board meetings, results from the questionnaires were presented together with initial drafted consensus statements for discussion. Then followed moderated discussions which led to revisions of the consensus statements. In the final online questionnaire, the consensus statements were presented, and the experts asked to select a level of agreement: “I fully agree”, “I partially agree” or “I disagree”. Upon selecting “I partially agree”, experts were asked to give a comment and/or update the wording of the statement. The responses were linked to an agreement score, based on the answer selected, and the comment given if “I partially agree” was selected (Table 1).

Table 1: Consensus statement scoring key

Score	Answer selected	Description
4	"I fully agree"	
3	"I partially agree"	With minor word change
2	"I partially agree"	With minor change to statement interpretation/meaning
1	"I disagree"	

Consensus definitions vary between studies[21-25], with percent agreement being one of the more common approaches.[25] Based on the results of our final online survey, statements were categorised into four levels of consensus (strong, moderate, low, and no consensus). This study scored the level of consensus in terms of percent agreement, and additionally that consensus could not be reached in case any expert disagreed with a statement. Figure 2 depicts the consensus statement scoring for this study. Only statements grouped as either **Strong** or **Moderate** are considered statements where consensus was reached. **Weak** or **No** consensus mean that there was still substantial discussion or divergence of opinion among the experts.

Figure 2: Consensus statement scoring, decision tree

Consent, privacy, and data security

The panel experts were informed about and consented to the full Delphi process, including length and time of surveys and details on the data collected, stored, and deleted. The retention periods of collected data were pre-defined. Questionnaire responses were anonymised and securely stored on the survey software provider's server in Germany. Audio recordings were stored for 60 days on the conference provider's EU based server. All experts were contracted for this study and reimbursed at fair, local market rates for their time commitment during the Delphi process. The study was approved by an independent review board (HML IRB Review #952SCGC21).

Patient and public involvement

No patients involved.

RESULTS

Panel expert characteristics

All approached experts agreed to participate (N=7). Details on the panel experts' treatment practices are presented in Table 2. The majority of the panel (N=6) exclusively use rectal

hydrogel spacers in their practices. One uses rectal hydrogel spacers as well as biodegradable balloons. Participation rates were high, with only one dropout (one expert did not complete the second questionnaire but participated in all other steps).

Table 2: Panel experts treatment practice

Geographical setting, N (%)	
England	5 (57)
Northern Ireland	1 (14)
Wales	1 (14)
Public or private setting, N (%)	
Public only	1 (14)
Private only	0 (0)
Both	6 (86)
Most frequently used RT modalities, % of patients (N experts using modality)	
IMRT	25–95 (6)
EBRT (not specified)	90 (1)
IMRT and HDR BT boost	15–30 (2)
SBRT	45 (1)
BT monotherapy (LDR)	10–20 (2)
PBT	10 (1)

Key: *IMRT, intensity-modulated radiation therapy; EBRT, external beam radiation therapy; HDR, high dose rate; BT, brachytherapy; SBRT, stereotactic body radiation therapy; LDR, low dose rate; PBT, proton beam therapy.*

Key treatment aims, besides curing or controlling cancer and increasing overall survival, were to minimise the risk of side effects and toxicity.

Questionnaire outcomes shaping the consensus statement discussion

Questionnaire outcomes showed that the panel estimated considerably less toxicity in patients with hydrogel spacer, as compared to those without (Figure 3). All experts agreed that hydrogel spacers reduce grade 1 and 2 late rectal toxicity, 86% agreed that it reduces grade 3 toxicity and 71% grade 4 toxicity.

Figure 3: Expected level of late (after 3 months) rectal toxicity in patients with and without hydrogel spacer

The panel considered toxicity a considerable issue, and underlined that also low-grade toxicity-related adverse events may significantly worsen patient's lives:

'I ask them [my patients], when you're out and about, is the first thing you think of where the toilet is?... And a remarkable number of patients say yes to that question, and it is affecting their quality of life.'

In the first questionnaire, the panel estimated that an average of 83% (SD: 13%) patients who could potentially benefit from a hydrogel spacer were denied access. Throughout the discussions, patient access in general and equal access in particular were central themes. The panel voiced their concern, for example regarding differences between NHS and private practice:

'In my private practice, every patient gets it [hydrogel spacer] unless there is a reason why they should not get it. Whereas in my NHS practice, unfortunately no patient gets it, unless there is a reason why they should get it.'

The main barrier to hydrogel spacer use was funding and resource constraints, followed by lack of trained staff.

'The ideal way to go would be to offer it to every eligible patient. But given that this is not currently feasible in our centre, there has to be some kind of categorisation.'

As seen in Figure 4, a trend towards hypo-fractionated external-beam regimens, with potential increased bowel dose and toxicity being associated with more potential benefit for spacers was apparent. This was also reflected in the outcome of the conjoint analysis. The absolute variation between expected benefit was, however, relatively low, ranging from 67 (BT monotherapy LDR) to 80 (SBRT/SABR) on average. This was reflected in later discussions, where experts agreed that RT modality is not the main consideration when prioritising patients for hydrogel spacer use.

Figure 4: Expected patient benefit from hydrogel spacer use, by treatment modality

When asked about patient characteristics to consider when deciding whether to recommend using hydrogel spacer the experts gave a wide range of suggestions, including comorbidities (age, diabetes, high bleeding risk, hip prothesis, inflammatory bowel disease and rectal and

bowel problems, normal erectile function), cancer stage, localisation, and heavy smoking. This was narrowed down in subsequent discussion, with general agreement that patients with certain comorbidities (diabetes, inflammatory bowel disease) or on anticoagulation may have higher benefit from hydrogel spacers.

Consensus statements

Upon being shown the results of the questionnaires, two rounds of moderated discussion followed, resulting in 13 consensus statements. These statements were subsequently voted on in a final questionnaire, and a final scoring was assigned as described in the method section.

The following eight statements reached strong consensus:

- Our consensus opinion is that for treatments with curative intent, focus should be on minimising toxicity and the risk of side effects.
- Our consensus opinion is that use of spacers in eligible patients significantly reduces radiation dose to the rectum and toxicity-related adverse events.
- Our consensus opinion is that despite meeting rectal dose constraints, too many patients continue to experience rectal toxicity.
- Our consensus opinion is that certain grade 1 toxicity-related adverse events[1] can still have a significant impact on patient quality of life.
- Our consensus opinion is that any toxicity grading system in use should be complemented by patient-reported outcomes.

[1] Bowel frequency and urgency, diarrhoea, flatulence, radiation cystitis, radiation proctitis, rectal bleeding, rectal mucus.

- Our consensus opinion is that patients receiving long-term anticoagulation therapy with medications such as direct oral anticoagulants (DOACs)[2] should be considered for spacer use if their anticoagulation can be safely paused.
- Our consensus opinion is that spacers are useful in eligible patients with T1-T2 disease. Spacer use in patients with T2+ disease should not be excluded but should be assessed on an individual basis by a team proficient in inserting spacers.
- Our consensus opinion is that patients should have the opportunity to take part in the discussion regarding the use of a spacer.[26]

For the following two statements, moderate consensus was reached. Each statement is followed by an explanation on why strong consensus was not reached.

- Our consensus opinion is that a higher benefit of spacers is expected in eligible patients with certain comorbidities[3] and/or longer expected overall survival.

Six experts (86%) fully agreed with the statement. One expert (14%) only partially agreed and suggested removing “and/or longer expected overall survival”. This was deemed a change to the statement interpretation.

- All eligible radiotherapy patients should have equal opportunity to access spacers, independent of socio-economic factors.

Five experts (71%) fully agreed with the statement. While there was an overall agreement that lack of equality in access to spacers is currently an important issue, two experts (29%) had rewording suggestions that would have impacted the statement interpretation. One proposed to add more detail on eligibility, and to add that patients suitable for a spacer implant should have access, irrespective of whether they can afford it. The other expert expressed some

[2] The reason for prescribing the DOAC, rather than the medication itself, is more important for the decision. All patients on DOACs, except for cardiac stent and prosthetic valve replacement patients may be able to safely pause their anticoagulation.
[3] Anticoagulation, diabetes, inflammatory bowel disease (ulcerative colitis and Crohn’s disease)

uncertainty regarding the term “socio-economic factors” and would have preferred the wording “irrespective of post-code”.

Statements where no consensus was reached

One statement was categorised as a weak consensus statement:

- Whilst we support the use of spacers in all eligible patients, our consensus opinion is that if resource constraints exist, patients receiving ultra-hypofractionated or hypofractionated radiotherapy should be prioritised for access to a spacer.

Four experts (57%) fully agreed with the statement. The remaining three (43%) partially agreed but had additional comments. One expert expressed that individual risk factors should be considered, rather than the RT modality. The second expert agreed on the need to identify a group at higher risk of rectal toxicity, and suggested combination of RT modality considerations and patient characteristics (e.g., age) and comorbidities. The third respondent only agreed that patients receiving ultra-hypofractionated RT should be prioritised.

For the following two statements, no consensus was reached.

- Our consensus opinion is that for patients with anticipated short overall survival but who will receive radical radiotherapy, use of a spacer should only be considered after careful evaluation of potential benefit.

Three experts (43%) fully agreed. Four (57%) partially agreed but had additional comments. Two experts made the point that it is unlikely that patients with short anticipated overall survival would be indicated for radical radiotherapy. Two experts expressed uncertainty with the wording “overall survival”. One of them suggested a rewording that some carefully selected patients with short expected survival who are offered radical radiotherapy may benefit from spacer use after careful consideration. The second expressed that the statement was too unclear. Additionally, in subsequent discussions, the experts agreed that the term “anticipated shorter life expectancy” would have been preferred over “anticipated short overall survival”,

so as not to imply that the use of hydrogel spacers affects survival. Upon subsequent discussion, experts agreed that the statement would have been improved by adding "and side effects" to the end of the statement.

- Our consensus opinion is that there are a limited number of patients with risk factors, or combination of risk factors, in which use of a spacer should only be considered after careful evaluation of potential benefits.

Four experts (57%) fully agreed, two (29%) partially agreed, and one (14%) disagreed. Those who partially agreed expressed that an addition should be made to the statement, that the majority of patients who receive radical RT would also be suitable for a spacer, noting that patients who are not fit enough for a spacer, likely are also not fit for RT. The second partially agreeing expert wanted to add a recommendation to discuss such cases with a mentor with extensive experience in spacer insertion. Upon subsequent discussion, experts agreed that the statement would have been improved by adding "and side effects" to the end of the statement.

DISCUSSION

Statement of principal findings

There was strong consensus that rectal toxicity is a considerable issue, and that minimizing the risk of radiation side effects is an important treatment aim. Rectal hydrogel spacers can reduce the toxicity burden and benefit patients undergoing radical RT for the treatment of prostate cancer in the UK. Currently, the NHS does not routinely fund hydrogel spacers. Limited funding leads to limited resources, and therefore limited access. Experts estimated that on average, 83% of their patients that could benefit from a spacer are not currently getting access. There was moderate consensus that a higher benefit is expected in patients on anticoagulation, patients with diabetes, and patients with inflammatory bowel disease (Ulcerative colitis or Crohn's disease). However, experts expected the majority of patients to benefit from use of a spacer, and it was not possible to reach consensus on those patients

with lower expected benefit. Key takeaways from discussions around statements where no consensus was reached are that individual patient characteristics are more important for informing the decision on whether to prioritise the use a spacer than the RT regimen selected. However, a higher level of benefit from spacer use is expected with ultra-hypofractionated RT compared with standard RT, a conclusion in line with current clinical evidence.[27]

Meaning of the study: possible explanations and implications for clinicians and policy makers

Currently, patient selection is driven by limitations in the healthcare system rather than patient needs. This highlights the importance of developing guidance on spacer use, to ensure fair and equal access to healthcare. The COVID-19 pandemic has lengthened already substantial NHS waiting times, further exacerbating issues with access and underscoring the need for formal guidance. Additionally, practical issues (e.g., availability of trained staff, theatre capacity) need to be considered when preparing a clinic to start using hydrogel spacers. As is important for all techniques to be introduced, audit of practice and quality improvement is recommended.

Strengths and weaknesses

This study only included seven experts, who are all experienced users of hydrogel spacers Naturally, a broader selection of experts could have resulted in different answers. However, including non-users as panel experts would not have been feasible for the purposes of this study, as they would have not possessed the relevant experience required. Additionally, the RT modality used by panel members could influence their view on when to prioritise hydrogel spacer use. However, the diversity of the panel in terms of modalities used likely safeguarded the balance of the resulting consensus.

The main strengths of this study are the scientific rigour applied following a well-defined and proven Delphi methodology, and the experience and diversity of the panel. The Delphi method

allowed gathering insights from leading experts in the field from different UK countries utilising a mix of RT modalities, while reducing bias and separating the evaluation by tasking two independent researchers with analysis and scoring.

Comparison with other studies

To the best of our knowledge, no previous attempts have been done to establish consensus for rectal hydrogel spacer use in the UK. One study conducted secondary analyses of a single-blinded, phase III randomised trial, with the aim of identifying patients benefitting the least from hydrogel rectal spacer during prostate radiation therapy.[18] In line with this study, no subgroup without potential benefits of hydrogel spacers could be identified. The benefit of hydrogel spacers perceived by the experts is in line with current clinical evidence.[17]

Unanswered questions and future research

This study offers guidance to later adopters of rectal hydrogel spacers, building on the expertise of leading UK radiation oncologists and urologist. Future research should focus on implementing formal guidance on hydrogel spacer use and strive towards reaching a consensus on patient prioritisation. A larger follow-up consensus study would be of value, asking all UK domain experts their opinion on the consensus statements. With growing interest in hydrogel spacers, it is increasingly important to study the impact of the quality of the implant. There is an ongoing debate on what a good implant is, and how it is measured. Similarly, it would be valuable to reach an agreement on which toxicity data to generate and follow up through including hydrogel spacers in cancer treatment trials, or through the development of a quality registry. Finally, it is of utmost importance to investigate the availability and equality in access to spacers.

CONCLUSION

Rectal toxicity is a considerable issue, and focus should be on minimising side effects of curative treatment. There is a strong and general agreement that all prostate cancer patients

undergoing radical RT have the potential to benefit from hydrogel spacers. Currently, not all patients who could potentially benefit can access hydrogel spacers, and access is unequal. Implementation of the ten strong and moderate consensus recommendations would likely help prioritise and equalise access to rectal spacers for patients in the UK. In particular, prioritising access towards patients on anticoagulation, with diabetes, and/or patients with inflammatory bowel disease would, in our opinion, be a strong starting position.

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COMPETING INTERESTS

RS is the owner of Coreva Scientific, a health-economics and value-based healthcare consultancy that focuses on medical devices. AHH is an employee of Coreva Scientific. Coreva Scientific received consultancy fees from Boston Scientific for work related to this manuscript. The authors did not receive direct payment as a result of this work outside of their normal salary payments. EW is an employee of Boston Scientific.

AUTHOR CONTRIBUTIONS

EW conceptualised the idea. RS and AHH designed and ran the questionnaires and implemented data protection measures. EW reviewed the study design. AHH and RS analysed the responses. RS moderated the advisory boards. SJ, AT, AE, AB, PD, CP, and HP responded to the questionnaires, and participated in the advisory boards. AHH and RS drafted the manuscript, in collaboration with SJ, AT, AE, AB, PD, CP and HP. All authors critically reviewed the manuscript outline and manuscript drafts. All authors approved the final manuscript.

DATA SHARING STATEMENT

No additional data available.

LEAD AUTHOR TRANSPARENCY STATEMENT

I confirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

Prof. Heather Ann Payne

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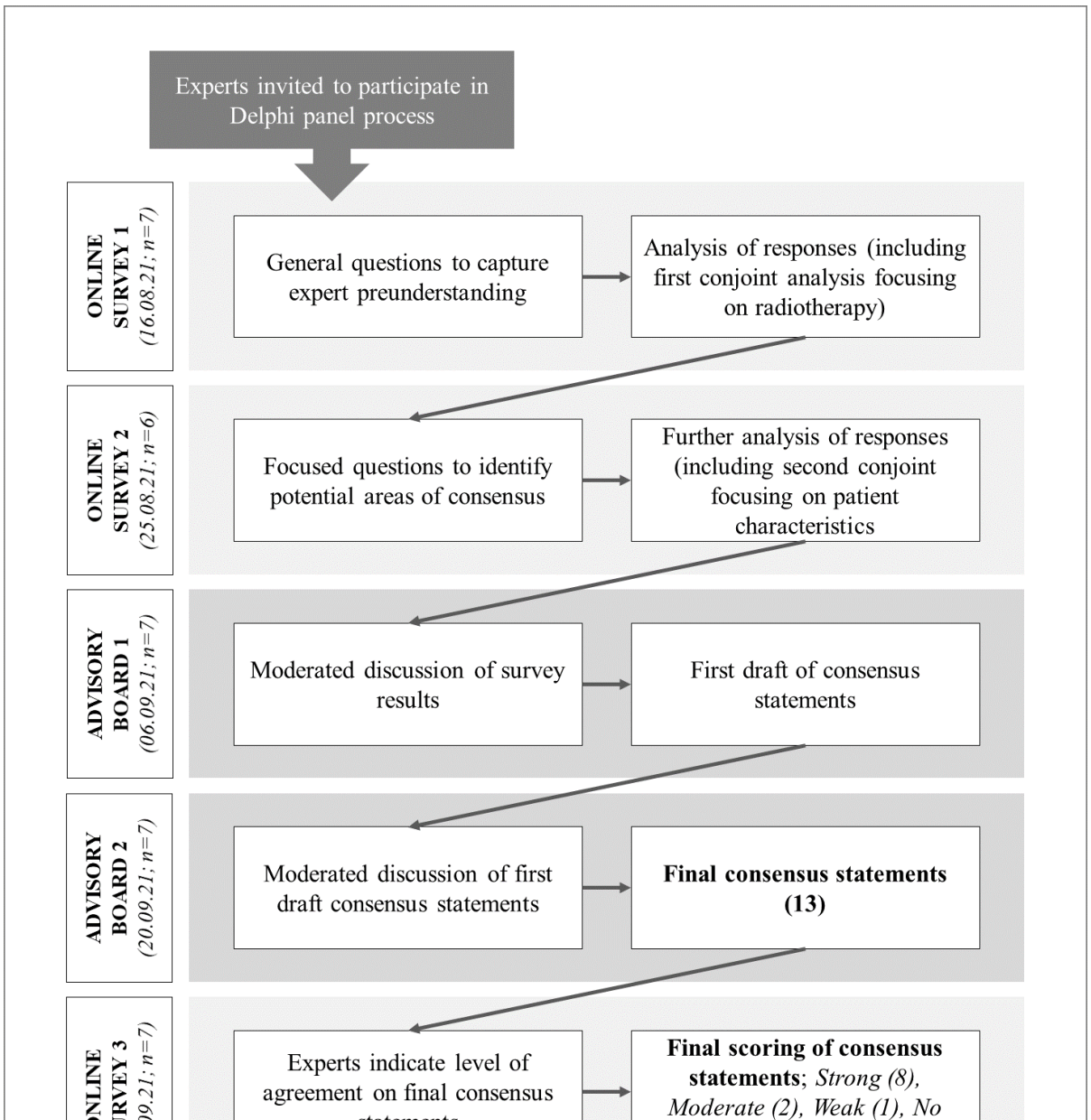
Figure legends

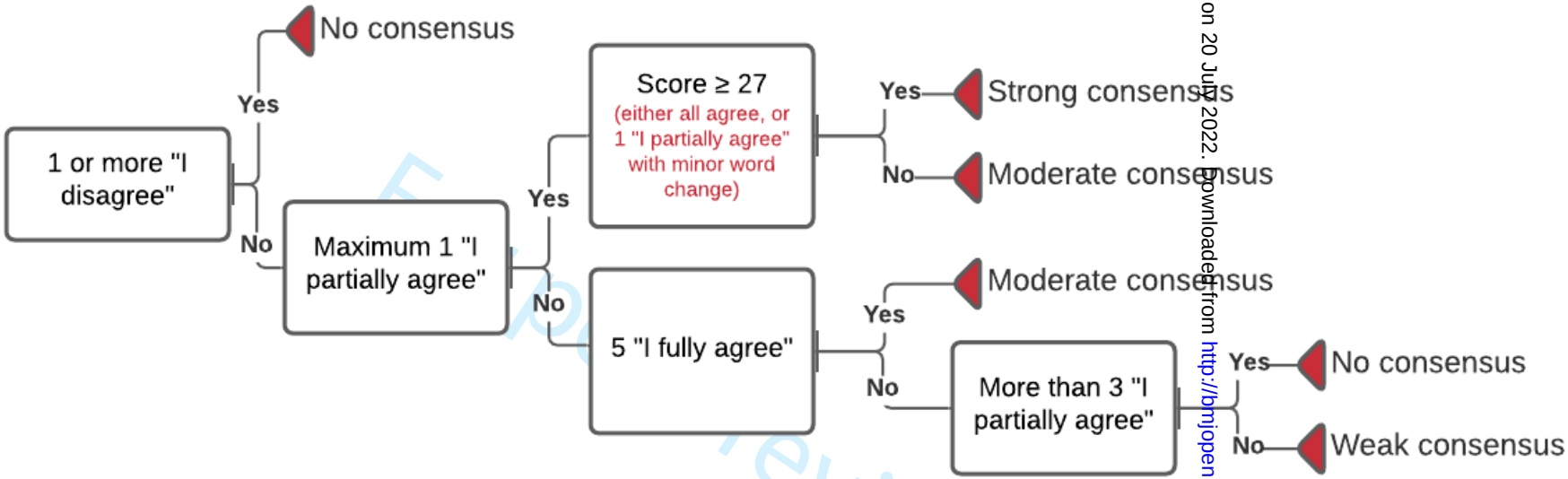
FIGURE 2:

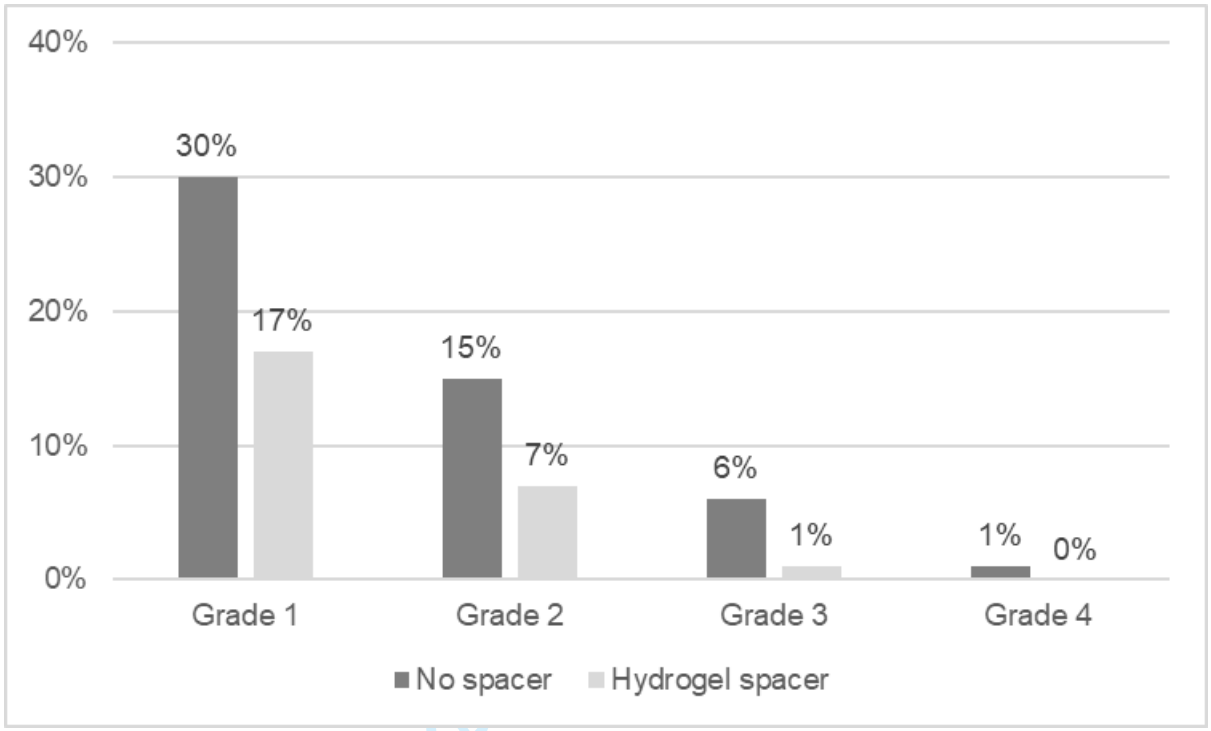
Strong consensus could only be reached if all experts indicated that they “Fully agree” or all except one “Fully agree”, with the last respondent “Partially agree” with only a minor word change (score ≥27). Moderate consensus could only be reached if at least five respondents “Fully agree”, and with no “Disagree”. Weak consensus was reached where a maximum of three respondents “Partially agree”, and with no “Disagree”. No consensus was indicated where at least one respondent “Disagree”, or if four or more respondents “Partially agree”.

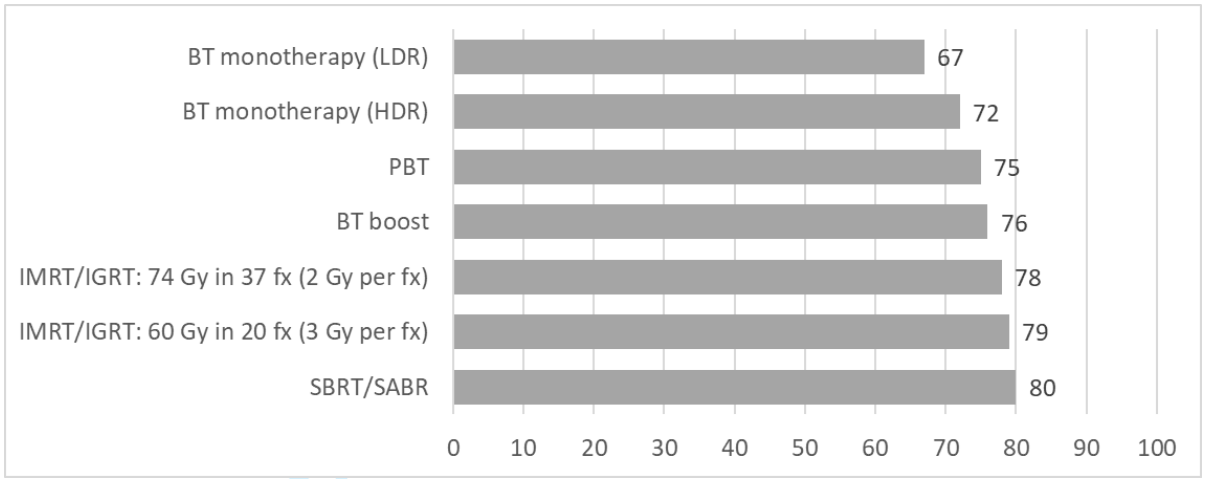
FIGURE 4:

Key: BT, brachytherapy; LDR, low dose rate; HDR, high dose rate; PBT, proton beam therapy, IMRT, intensity-modulated radiation therapy; IGRT, image guided radiation therapy, SBRT, stereotactic body radiation therapy; SABR, stereotactic ablative radiotherapy


Experts invited to participate in Delphi panel process
ONLINE SURVEY 1 (16.08.21; n=7)
General questions to capture expert preunderstanding
Analysis of responses (including first conjoint analysis focusing on radiotherapy)
ONLINE SURVEY 2 (25.08.21; n=6)
Focused questions to identify potential areas of consensus
Further analysis of responses (including second conjoint focusing on patient characteristics
ADVISORY BOARD 1 (06.09.21; n=7)
Moderated discussion of survey results
First draft of consensus statements
ADVISORY BOARD 2 (20.09.21; n=7)
Moderated discussion of first draft consensus statements
Final consensus statements (13)
ONLINE SURVEY 3 (29.09.21; n=7)
Experts indicate level of agreement on final consensus statements
Final scoring of consensus statements; Strong (8), Moderate (2), Weak (1), No consensus (2)







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Delphi study to identify consensus on patient selection for hydrogel rectal spacer use during radiation therapy for prostate cancer in the UK

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Primary Subject Heading:	Oncology
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Keywords:	Prostate disease < UROLOGY, Radiation oncology < RADIOLOGY & IMAGING, RADIOTHERAPY, Toxicity < THERAPEUTICS

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Title page

Delphi study to identify consensus on patient selection for hydrogel rectal spacer use during radiation therapy for prostate cancer in the UK.

Short title: Delphi study on hydrogel rectal spacer use (UK)

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Word count: 3,971

Delphi study to identify consensus on patient selection for hydrogel rectal spacer use during radiation therapy for prostate cancer in the UK.

Structured abstract *(Word count: 268, max 300)*

OBJECTIVES

To identify consensus on patient prioritisation for rectal hydrogel spacer use during radiation therapy for the treatment of prostate cancer in the United Kingdom.

DESIGN

Delphi study consisting of two rounds of online questionnaires, two virtual advisory board meetings and a final online questionnaire.

SETTING

Radical radiation therapy for localised and locally advanced prostate cancer in the United Kingdom.

PARTICIPANTS

Six leading clinical oncologists and one urologist from across the UK.

INTERVENTIONS

Rectal hydrogel spacer.

PRIMARY AND SECONDARY OUTCOME MEASURES

NR

RESULTS

The panel reached consensus on the importance of minimizing toxicity for treatments with curative intent, and that even low-grade toxicity-related adverse events can significantly

impact quality of life. There was agreement that despite meeting rectal dose constraints, too many patients experience rectal toxicity, and that rectal hydrogel spacers in eligible patients significantly reduces toxicity related adverse events. However, as a consequence of funding limitations, patients need to be prioritized for spacer use. A higher benefit of spacers can be expected in patients on anticoagulation, and in patients with diabetes or inflammatory bowel disease, but consensus could not be reached regarding patient groups expected to benefit less. While radiation therapy regimen is not a main factor determining prioritization, higher benefit is expected in ultra-hypofractionated regimens.

CONCLUSION

There is a strong and general agreement that all prostate cancer patients undergoing radical radiation therapy have the potential to benefit from hydrogel spacers. Currently, not all patients who could potentially benefit can access hydrogel spacers, and access is unequal. Implementation of the consensus recommendations would likely help prioritise and equalise access to rectal spacers for patients in the UK.

ARTICLE SUMMARY: STRENGTHS AND LIMITATIONS OF THIS STUDY

- The Delphi panel is a recognised method in developing NICE guidelines and is utilised here to gather insights from a diverse panel of UK radiation oncology and urology experts who are experienced users of hydrogel spacers.
- This study included seven panel experts and their experiences may not reflect all users of hydrogel spacers.
- To help reduce bias, answers and opinions were assessed by two researchers working independently.

INTRODUCTION

Prostate cancer burden

Prostate cancer is the second most common cancer in men globally,[1] and the most common in the UK.[2] More than 47,500 UK men are diagnosed with prostate cancer every year and over 400,000 men are living with and after prostate cancer.[3] The 5-year survival rate for localized prostate cancer in the UK is almost 100%,[4] with three quarters of men diagnosed at any stage expected to survive 10 years.[2] In England, 97%, 87% and 78% of men diagnosed with prostate cancer survive their disease for more than one, five and ten years, respectively.[2] Given the high likelihood of curative therapy, a key treatment goal is to prevent potential adverse events from impacting patient quality of life after treatment.

In addition to the patient burden, prostate cancer is a costly disease with the European costs of care for prostate cancer estimated at EUR 199 billion in 2018.[5]

Radiation therapy for prostate cancer

Choice of treatment for prostate cancer is complex and involves multi-factorial considerations including presenting cancer stage (localised, locally advanced or metastatic), risk stratification, life expectancy, comorbidities, and other patient-specific factors, such as lifestyle, patient preference and treatment goals.[6] For localised and locally advanced prostate cancer, treatment options include active surveillance, surgery, brachytherapy and radiation therapy (RT), with or without hormone treatment, as well as multimodality treatment combining surgery or RT with systemic therapy.[7-9] RT with radical intent is a first-line treatment for localised and locally advanced prostate cancer.[8] Intensity-modulated RT (IMRT) with image guidance (IGRT) is considered the gold-standard form of external beam RT (EBRT).[10] Of the circa 18,000 men identified as having received radical RT for prostate cancer in England and Wales between April 2018 and March 2019, over 90% were treated with IMRT.[11] Whilst stereotactic body RT (SBRT) is not currently routine practice in the UK, its use is increasing and it is now

delivered in several NHS centres.[12] Circa 95% of UK men with intermediate-risk disease receive a hypofractionated radiotherapy regimen.[11]

The success and clinical outcomes of RT depend on several factors, including radiation dose to the tumour and the extent of irradiation affecting nearby normal-tissue, particularly the rectum.[10] Dose-escalated EBRT is a highly effective curative treatment, with higher doses providing better biochemical control.[13] Higher doses can, however , increase radiation toxicity to nearby tissues. Despite substantial advancements in RT, acute and reversible, as well as rare but severe, long-term adverse effects of radiation toxicity such as urinary and bowel incontinence remain problematic. The National Prostate Cancer Audit (NPCA) reported that 11% of prostate cancer patients experienced ≥1 severe gastrointestinal complication within two years after radical RT. This outcome factor derived from hospital records data is defined as a confirmed diagnosis of radiation toxicity ≥ grade 2 according to National Cancer Institute Common Toxicity Criteria for Adverse Events [CTCAE] in addition to a documented procedure to the large bowel.[11 14] Late ≥ grade 2 gastrointestinal toxicity has been explored in numerous randomized clinical trials. The 2016 Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO) trial found an incidence of gastrointestinal toxicity at three years of 17.7% in standard fractionation and 21.9% in hypofractionation.[15] In 2017, results from the ASCENDE-RT trial showed a cumulative incidence of 5-year gastrointestinal side effects ranging from 20.2% (dose-escalated external beam radiation therapy) to 31.3% (low-dose-rate prostate brachytherapy).[16] Due to its proximity to the prostate, the anterior rectal wall is especially vulnerable to irradiation effects and the rectum is a dose-limiting organ at risk.[17]

Hydrogel spacers

One way of reducing the unwanted radiation dose to the rectum is by increasing the space between the prostate and the rectal wall. This can be achieved by use of a rectal spacer, with three currently indicated for use during RT for prostate cancer in the UK: biodegradable

balloons, hyaluronic acid gel, and polyethylene glycol (PEG) hydrogel.[18] In the UK, the use of biodegradable spacers to reduce rectal toxicity during RT for prostate cancer is accepted (IPG590) by NICE, based on safety and efficacy data on the use of PEG hydrogel spacers.[18] Use of rectal hydrogel spacers has been evaluated in a single-blind, phase III trial in image guided IMRT (N=222).[19] The spacer-placement success rate was 99%, and no device-related adverse events occurred.[19] Late (three to 15 months) rectal toxicity severity was significantly reduced in the spacer group.[19] At three years follow-up, decreased bowel toxicity and fewer declines in urinary and bowel quality of life were observed in the spacer group (41% men in the control group experienced a minimally important difference (MID) in decline in bowel quality of life vs 14% in the spacer group; P=0.002). The risk of large decline (twice the MID) was 21% (control) vs 5% (spacer; P=0.02) in bowel quality of life and 23% (control) vs 8% (spacer; P=0.02) in urinary quality of life respectively.[20]

Lack of routine reimbursement has led to restricted patient access to hydrogel spacers in the UK. Therefore, there is a requirement to prioritise patients for hydrogel spacer use in the UK, and attempts have been made to identify optimal usage. A secondary analysis of the hydrogel spacer trial data tried to identify the patient subgroups most and least likely to benefit from the intervention but found generally homogeneous results in bowel quality of life with benefits in all assessed subgroups.[21]

The aim of this study was to identify consensus on patient prioritisation for rectal hydrogel spacer use during RT for the treatment of prostate cancer in the UK.

METHODS

The Delphi technique and panel experts

The Delphi technique is a structured, iterative, multistage process using rounds of questionnaires to collect opinions and to stepwise develop consensus among a pre-defined panel of experts.[22] For this study, experts were approached and asked to participate in the panel based on being a UK radiation oncologist or urologist having experience with rectal

hydrogel spacers. To ensure a diverse panel, experts were sought to represent different geographies within the UK and use different types of RT modalities. There is no defined optimal panel size for a Delphi study,[23] but the selection of an odd number of experts ensured that a majority outcome could be reached.

Steps in the Delphi process

There is no fixed number of rounds in a Delphi survey.[23] As depicted in Figure 1, our study adopted a five-stage approach to elicit consensus, consisting of two pre-advisory board questionnaires administered through a web-based survey program, two virtual advisory board discussions, and a final concluding questionnaire.

The first questionnaire provided some background information on the experts, such as their most used RT modalities and open-ended questions to capture a broad understanding. The open-ended questions related to key treatment aims, which patient and treatment characteristics to consider when prioritising hydrogel spacer, factors typically deterring them from recommending hydrogel spacer use, and factors predictive for toxicity. Additionally, experts were asked to rank treatment modalities in order of how much patient benefit they would expect from hydrogel spacer use, on a scale from 0 (no patient benefit) to 100 (maximal patient benefit).

In the second questionnaire, the responses to the open-ended questions from the previous questionnaire were presented, and the experts asked to rank them by order of importance. In addition to follow-up questions, the second questionnaire included questions on perceived barriers to hydrogel spacer use.

Figure 1: Overview of Delphi panel process

Analysis and scoring

Qualitative content analysis was used to analyse responses to open-ended questions. Two researchers independently analysed responses and interpreted consensus. At the advisory

board meetings, results from the questionnaires were presented together with initial drafted consensus statements for discussion. Then followed moderated discussions which led to revisions of the consensus statements. In the final online questionnaire, the consensus statements were presented, and the experts asked to select a level of agreement: “I fully agree”, “I partially agree” or “I disagree”. Upon selecting “I partially agree”, experts were asked to give a comment and/or update the wording of the statement. The responses were linked to an agreement score, based on the answer selected, and the comment given if “I partially agree” was selected (Table 1).

Table 1: Consensus statement scoring key

Score	Answer selected	Description
4	"I fully agree"	
3	"I partially agree"	With minor word change
2	"I partially agree"	With minor change to statement interpretation/meaning
1	"I disagree"	

Consensus definitions vary between studies[24-28], with percent agreement being one of the more common approaches.[28] Based on the results of our final online survey, statements were categorised into four levels of consensus (strong, moderate, low, and no consensus). This study scored the level of consensus in terms of percent agreement, and additionally that consensus could not be reached in case any expert disagreed with a statement. Figure 2 depicts the consensus statement scoring for this study. Only statements grouped as either **Strong** or **Moderate** are considered statements where consensus was reached. **Weak** or **No** consensus mean that there was still substantial discussion or divergence of opinion among the experts.

Figure 2: Consensus statement scoring, decision tree

Consent, privacy, and data security

The panel experts were informed about and consented to the full Delphi process, including length and time of surveys and details on the data collected, stored, and deleted. The retention periods of collected data were pre-defined. Questionnaire responses were anonymised and securely stored on the survey software provider’s server in Germany. Audio recordings were

stored for 60 days on the conference provider's EU based server. All experts were contracted for this study and reimbursed at fair, local market rates for their time commitment during the Delphi process. The study was approved by an independent review board (HML IRB Review #952SCGC21).

Patient and public involvement

No patients involved.

RESULTS

Panel expert characteristics

All approached experts agreed to participate (N=7). Details on the panel experts' treatment practices are presented in Table 2. The majority of the panel (N=6) exclusively use rectal hydrogel spacers in their practices. One uses rectal hydrogel spacers as well as biodegradable balloons. Participation rates were high, with only one dropout (one expert did not complete the second questionnaire but participated in all other steps).

Table 2: Panel experts treatment practice

Geographical setting, N (%)	
England	5 (57)
Northern Ireland	1 (14)
Wales	1 (14)
Public or private setting, N (%)	
Public only	1 (14)
Private only	0 (0)
Both	6 (86)
Most frequently used RT modalities, % of patients (N experts using modality)	
IMRT	25–95 (6)
EBRT (not specified)	90 (1)
IMRT and HDR BT boost	15–30 (2)
SBRT	45 (1)
BT monotherapy (LDR)	10–20 (2)
PBT	10 (1)

Key: *IMRT, intensity-modulated radiation therapy; EBRT, external beam radiation therapy; HDR, high dose rate; BT, brachytherapy; SBRT, stereotactic body radiation therapy; LDR, low dose rate; PBT, proton beam therapy.*

Key treatment aims, besides curing or controlling cancer and increasing overall survival, were to minimise the risk of side effects and toxicity.

Questionnaire outcomes shaping the consensus statement discussion

Questionnaire outcomes showed that the panel estimated considerably less toxicity in patients with hydrogel spacer, as compared to those without (Figure 3). All experts agreed that hydrogel spacers reduce grade 1 and 2 late rectal toxicity, 86% agreed that it reduces grade 3 toxicity and 71% grade 4 toxicity.

Figure 3: Expected level of late (after 3 months) rectal toxicity in patients with and without hydrogel spacer

The panel considered toxicity a considerable issue, and underlined that also low-grade toxicity-related adverse events may significantly worsen patient's lives:

> *'I ask them [my patients], when you're out and about, is the first thing you think of where the toilet is?... And a remarkable number of patients say yes to that question, and it is affecting their quality of life.'*

In the first questionnaire, the panel estimated that an average of 83% (SD: 13%) patients who could potentially benefit from a hydrogel spacer were denied access. Throughout the discussions, patient access in general and equal access in particular were central themes. The panel voiced their concern, for example regarding differences between NHS and private practice:

> *'In my private practice, every patient gets it [hydrogel spacer] unless there is a reason why they should not get it. Whereas in my NHS practice, unfortunately no patient gets it, unless there is a reason why they should get it.'*

The main barrier to hydrogel spacer use was funding and resource constraints, followed by lack of trained staff.

'The ideal way to go would be to offer it to every eligible patient. But given that this is not currently feasible in our centre, there has to be some kind of categorisation.'

As seen in Figure 4, a trend towards hypo-fractionated external-beam regimens, with potential increased bowel dose and toxicity being associated with more potential benefit for spacers was apparent. This was also reflected in the outcome of the conjoint analysis. The absolute variation between expected benefit was, however, relatively low, ranging from 67 (BT monotherapy LDR) to 80 (SBRT/SABR) on average. This was reflected in later discussions, where experts agreed that RT modality is not the main consideration when prioritising patients for hydrogel spacer use.

Figure 4: Expected patient benefit from hydrogel spacer use, by treatment modality

When asked about patient characteristics to consider when deciding whether to recommend using hydrogel spacer the experts gave a wide range of suggestions, including comorbidities (age, diabetes, high bleeding risk, hip prothesis, inflammatory bowel disease and rectal and bowel problems, normal erectile function), cancer stage, localisation, and heavy smoking. This was narrowed down in subsequent discussion, with general agreement that patients with certain comorbidities (diabetes, inflammatory bowel disease) or on anticoagulation may have higher benefit from hydrogel spacers.

Consensus statements

Upon being shown the results of the questionnaires, two rounds of moderated discussion followed, resulting in 13 consensus statements. These statements were subsequently voted on in a final questionnaire, and a final scoring was assigned as described in the method section.

The following eight statements reached strong consensus:

- Our consensus opinion is that for treatments with curative intent, focus should be on minimising toxicity and the risk of side effects.

- Our consensus opinion is that use of spacers in eligible patients significantly reduces radiation dose to the rectum and toxicity-related adverse events.
- Our consensus opinion is that despite meeting rectal dose constraints, too many patients continue to experience rectal toxicity.
- Our consensus opinion is that certain grade 1 toxicity-related adverse events[1] can still have a significant impact on patient quality of life.
- Our consensus opinion is that any toxicity grading system in use should be complemented by patient-reported outcomes.
- Our consensus opinion is that patients receiving long-term anticoagulation therapy with medications such as direct oral anticoagulants (DOACs)[2] should be considered for spacer use if their anticoagulation can be safely paused.
- Our consensus opinion is that spacers are useful in eligible patients with T1-T2 disease. Spacer use in patients with T2+ disease should not be excluded but should be assessed on an individual basis by a team proficient in inserting spacers.
- Our consensus opinion is that patients should have the opportunity to take part in the discussion regarding the use of a spacer.[29]

For the following two statements, moderate consensus was reached. Each statement is followed by an explanation on why strong consensus was not reached.

- Our consensus opinion is that a higher benefit of spacers is expected in eligible patients with certain comorbidities[3] and/or longer expected overall survival.

[1] Bowel frequency and urgency, diarrhoea, flatulence, radiation cystitis, radiation proctitis, rectal bleeding, rectal mucus.
[2] The reason for prescribing the DOAC, rather than the medication itself, is more important for the decision. All patients on DOACs, except for cardiac stent and prosthetic valve replacement patients may be able to safely pause their anticoagulation.
[3] Anticoagulation, diabetes, inflammatory bowel disease (ulcerative colitis and Crohn's disease)

Six experts (86%) fully agreed with the statement. One expert (14%) only partially agreed and suggested removing “and/or longer expected overall survival”. This was deemed a change to the statement interpretation.

- All eligible radiotherapy patients should have equal opportunity to access spacers, independent of socio-economic factors.

Five experts (71%) fully agreed with the statement. While there was an overall agreement that lack of equality in access to spacers is currently an important issue, two experts (29%) had rewording suggestions that would have impacted the statement interpretation. One proposed to add more detail on eligibility, and to add that patients suitable for a spacer implant should have access, irrespective of whether they can afford it. The other expert expressed some uncertainty regarding the term “socio-economic factors” and would have preferred the wording “irrespective of post-code”.

Statements where no consensus was reached

One statement was categorised as a weak consensus statement:

- Whilst we support the use of spacers in all eligible patients, our consensus opinion is that if resource constraints exist, patients receiving ultra-hypofractionated or hypofractionated radiotherapy should be prioritised for access to a spacer.

Four experts (57%) fully agreed with the statement. The remaining three (43%) partially agreed but had additional comments. One expert expressed that individual risk factors should be considered, rather than the RT modality. The second expert agreed on the need to identify a group at higher risk of rectal toxicity, and suggested combination of RT modality considerations and patient characteristics (e.g., age) and comorbidities. The third respondent only agreed that patients receiving ultra-hypofractionated RT should be prioritised.

For the following two statements, no consensus was reached.

- Our consensus opinion is that for patients with anticipated short overall survival but who will receive radical radiotherapy, use of a spacer should only be considered after careful evaluation of potential benefit.

Three experts (43%) fully agreed. Four (57%) partially agreed but had additional comments. Two experts made the point that it is unlikely that patients with short anticipated overall survival would be indicated for radical radiotherapy. Two experts expressed uncertainty with the wording “overall survival”. One of them suggested a rewording that some carefully selected patients with short expected survival who are offered radical radiotherapy may benefit from spacer use after careful consideration. The second expressed that the statement was too unclear. Additionally, in subsequent discussions, the experts agreed that the term “anticipated shorter life expectancy” would have been preferred over “anticipated short overall survival”, so as not to imply that the use of hydrogel spacers affects survival. Upon subsequent discussion, experts agreed that the statement would have been improved by adding “and side effects” to the end of the statement.

- Our consensus opinion is that there are a limited number of patients with risk factors, or combination of risk factors, in which use of a spacer should only be considered after careful evaluation of potential benefits.

Four experts (57%) fully agreed, two (29%) partially agreed, and one (14%) disagreed. Those who partially agreed expressed that an addition should be made to the statement, that the majority of patients who receive radical RT would also be suitable for a spacer, noting that patients who are not fit enough for a spacer, likely are also not fit for RT. The second partially agreeing expert wanted to add a recommendation to discuss such cases with a mentor with extensive experience in spacer insertion. Upon subsequent discussion, experts agreed that the statement would have been improved by adding “and side effects” to the end of the statement.

DISCUSSION

Statement of principal findings

There was strong consensus that rectal toxicity is a considerable issue, and that minimizing the risk of radiation side effects is an important treatment aim. Rectal hydrogel spacers can reduce the toxicity burden and benefit patients undergoing radical RT for the treatment of prostate cancer in the UK. Currently, the NHS does not routinely fund hydrogel spacers. Limited funding leads to limited resources, and therefore limited access. Experts estimated that on average, 83% of their patients that could benefit from a spacer are not currently getting access. There was moderate consensus that a higher benefit is expected in patients on anticoagulation, patients with diabetes, and patients with inflammatory bowel disease (Ulcerative colitis or Crohn's disease). However, experts expected the majority of patients to benefit from use of a spacer, and it was not possible to reach consensus on those patients with lower expected benefit. Key takeaways from discussions around statements where no consensus was reached are that individual patient characteristics are more important for informing the decision on whether to prioritise the use a spacer than the RT regimen selected. However, a higher level of benefit from spacer use is expected with ultra-hypofractionated RT compared with standard RT, a conclusion in line with current clinical evidence.[30]

Meaning of the study: possible explanations and implications for clinicians and policy makers

Currently, patient selection is driven by limitations in the healthcare system rather than patient needs. This highlights the importance of developing guidance on spacer use, to ensure fair and equal access to healthcare. The COVID-19 pandemic has lengthened already substantial NHS waiting times, further exacerbating issues with access and underscoring the need for formal guidance. Additionally, practical issues (e.g., availability of trained staff, theatre capacity) need to be considered when preparing a clinic to start using hydrogel spacers. As is

important for all techniques to be introduced, audit of practice and quality improvement is recommended.

Strengths and weaknesses

This study only included seven experts, who are all experienced users of hydrogel spacers Naturally, a broader selection of experts could have resulted in different answers. However, including non-users as panel experts would not have been feasible for the purposes of this study, as they would have not possessed the relevant experience required. Additionally, the RT modality used by panel members could influence their view on when to prioritise hydrogel spacer use. However, the diversity of the panel in terms of modalities used likely safeguarded the balance of the resulting consensus.

The main strengths of this study are the scientific rigour applied following a well-defined and proven Delphi methodology, and the experience and diversity of the panel. The Delphi method allowed gathering insights from leading experts in the field from different UK countries utilising a mix of RT modalities, while reducing bias and separating the evaluation by tasking two independent researchers with analysis and scoring.

Comparison with other studies

To the best of our knowledge, no previous attempts have been done to establish consensus for rectal hydrogel spacer use in the UK. A study published in 2016 used a model-based approach to identify patients expected to benefit the most from implantable rectum spacers among 26 patients with localized prostate cancer treated at a German hospital. The clinical risk factors found relevant were anticoagulant use, hormonal therapy, antihypertensive use, diabetes, haemorrhoids, pelvic nodal RT, and prior abdominal surgery.[31] Single-centre studies of rectal spacers in Crohn's and ulcerative colitis patients suggest benefit of spacers.[32 33] One study conducted secondary analyses of a single-blinded, phase III randomised trial, with the aim of identifying patients benefitting the least from hydrogel rectal spacer during prostate

radiation therapy.[21] In line with this study, no subgroup without potential benefits of hydrogel spacers could be identified. The benefit of hydrogel spacers perceived by the experts is in line with current clinical evidence.[20]

Unanswered questions and future research

This study offers guidance to later adopters of rectal hydrogel spacers, building on the expertise of leading UK radiation oncologists and urologist. Future research should focus on implementing formal guidance on hydrogel spacer use and strive towards reaching a consensus on patient prioritisation. A larger follow-up consensus study would be of value, asking all UK domain experts their opinion on the consensus statements. With growing interest in hydrogel spacers, it is increasingly important to study the impact of the quality of the implant. There is an ongoing debate on what a good implant is, and how it is measured. Similarly, it would be valuable to reach an agreement on which toxicity data to generate and follow up through including hydrogel spacers in cancer treatment trials, or through the development of a quality registry. Finally, it is of utmost importance to investigate the availability and equality in access to spacers. For this aim to be reached, further cost-effectiveness research and a continued discussion on willingness to pay should be undertaken. Analyses of spacers in prostate cancers have shown cost-effectiveness in certain radiation modalities in US[34 35] and Dutch[36] contexts.

CONCLUSION

Rectal toxicity is a considerable issue, and focus should be on minimising side effects of curative treatment. There is a strong and general agreement that all prostate cancer patients undergoing radical RT have the potential to benefit from hydrogel spacers. Currently, not all patients who could potentially benefit can access hydrogel spacers, and access is unequal. Implementation of the ten strong and moderate consensus recommendations would likely help prioritise and equalise access to rectal spacers for patients in the UK. In particular, prioritising

access towards patients on anticoagulation, with diabetes, and/or patients with inflammatory bowel disease would, in our opinion, be a strong starting position.

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COMPETING INTERESTS

RS is the owner of Coreva Scientific, a health-economics and value-based healthcare consultancy that focuses on medical devices. AHH is an employee of Coreva Scientific. Coreva Scientific received consultancy fees from Boston Scientific for work related to this manuscript. The authors did not receive direct payment as a result of this work outside of their normal salary payments. EW is an employee of Boston Scientific.

AUTHOR CONTRIBUTIONS

EW conceptualised the idea. RS and AHH designed and ran the questionnaires and implemented data protection measures. EW reviewed the study design. AHH and RS analysed the responses. RS moderated the advisory boards. SJ, AT, AE, AB, PD, CP, and HP responded to the questionnaires, and participated in the advisory boards. AHH and RS drafted the manuscript, in collaboration with SJ, AT, AE, AB, PD, CP and HP. All authors critically reviewed the manuscript outline and manuscript drafts. All authors approved the final manuscript.

ETHICS APPROVAL STATEMENT

The study was approved by an independent review board (HML IRB Review #952SCGC21). All participants gave informed consent before taking part.

DATA SHARING STATEMENT

No additional data available.

LEAD AUTHOR TRANSPARENCY STATEMENT

I confirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

Prof. Heather Ann Payne

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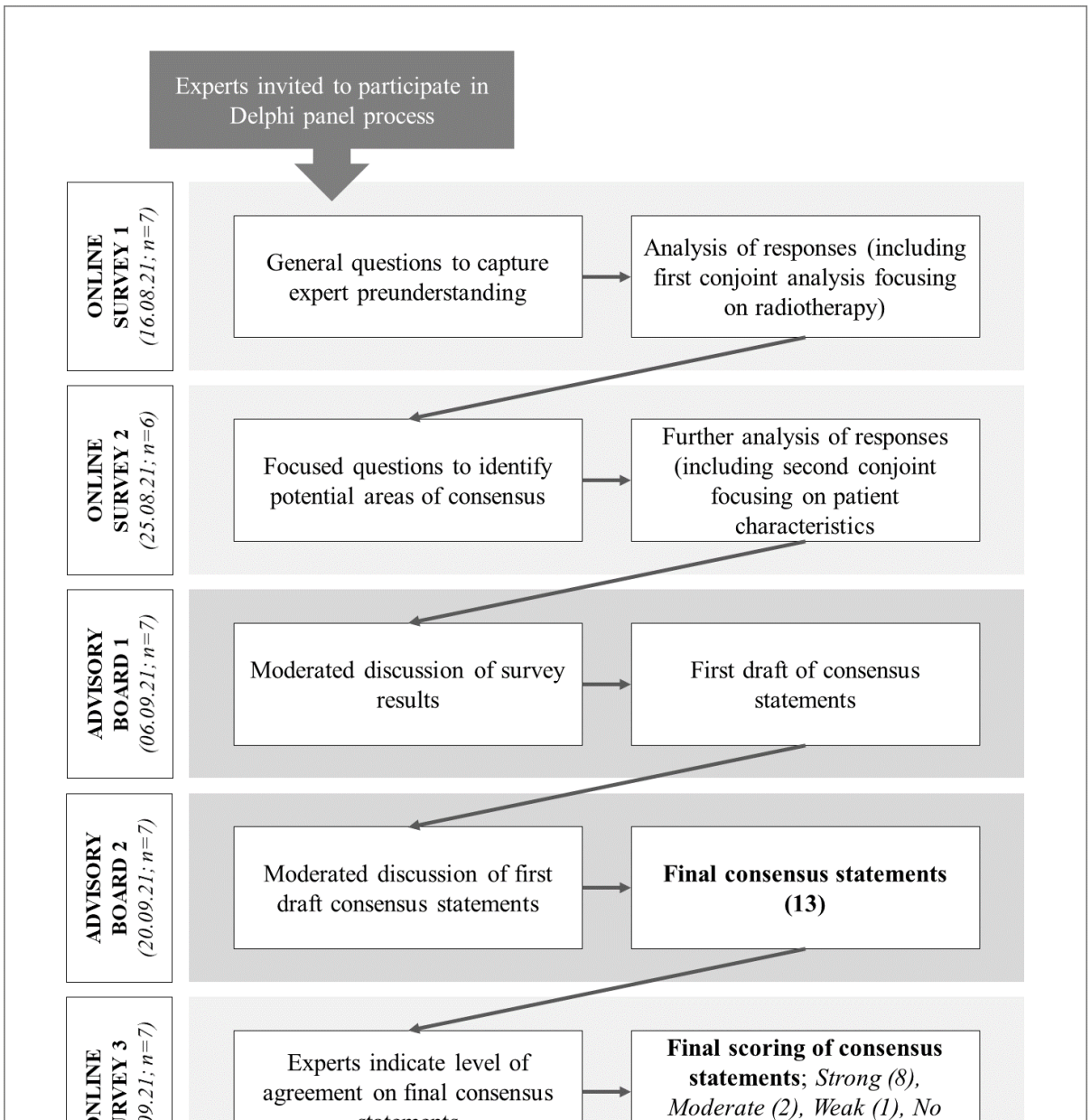
Figure legends

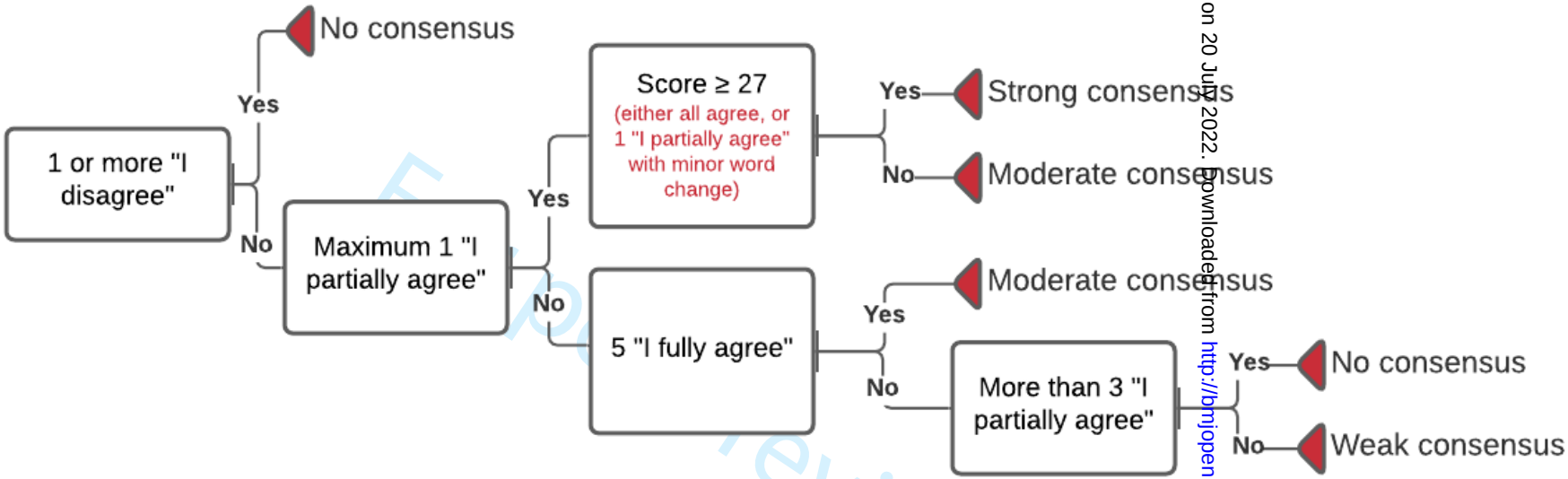
FIGURE 2:

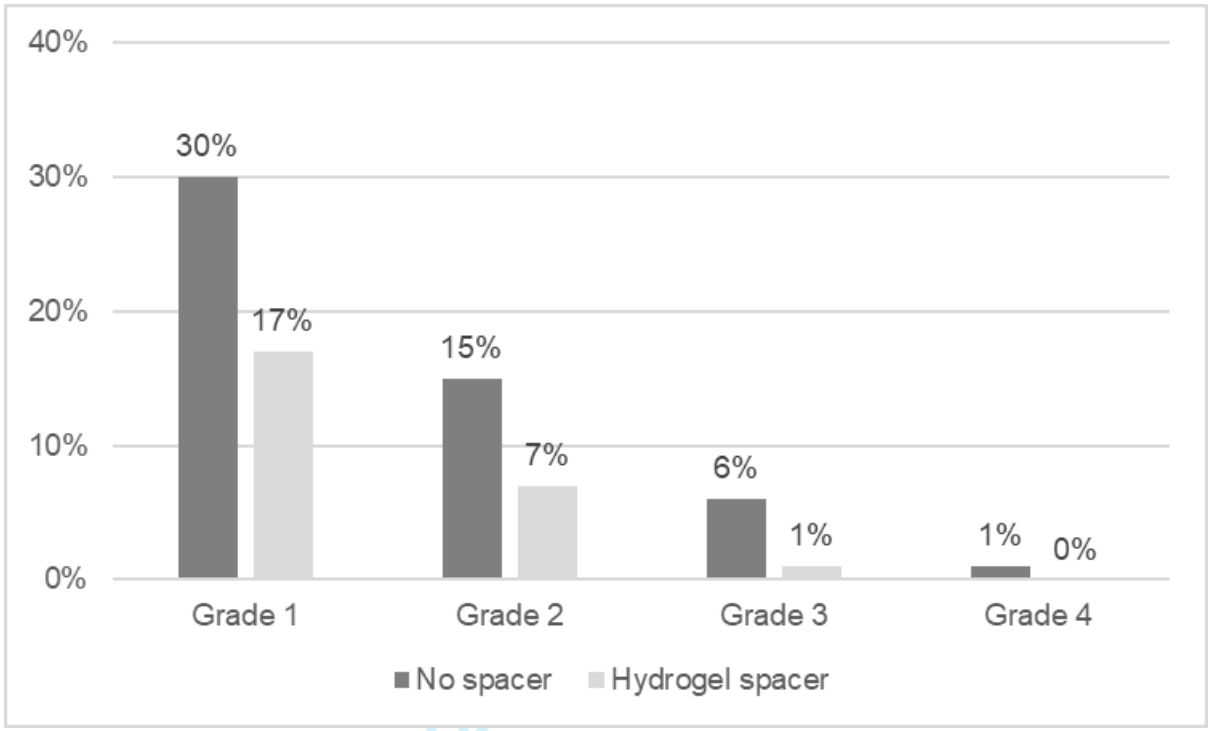
Strong consensus could only be reached if all experts indicated that they “Fully agree” or all except one “Fully agree”, with the last respondent “Partially agree” with only a minor word change (score ≥27). Moderate consensus could only be reached if at least five respondents “Fully agree”, and with no “Disagree”. Weak consensus was reached where a maximum of three respondents “Partially agree”, and with no “Disagree”. No consensus was indicated where at least one respondent “Disagree”, or if four or more respondents “Partially agree”.

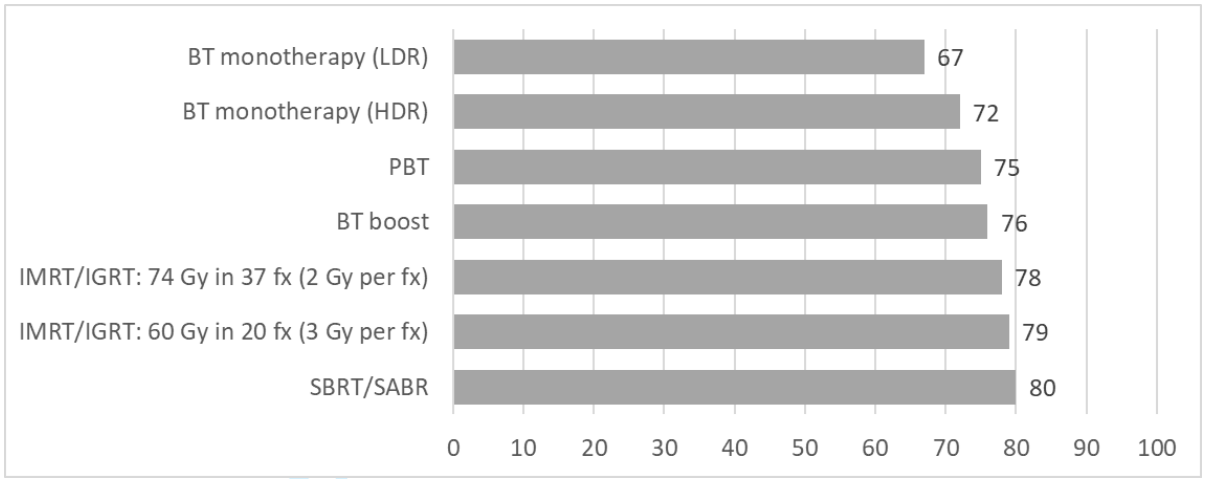
FIGURE 4:

Key: BT, brachytherapy; LDR, low dose rate; HDR, high dose rate; PBT, proton beam therapy, IMRT, intensity-modulated radiation therapy; IGRT, image guided radiation therapy, SBRT, stereotactic body radiation therapy; SABR, stereotactic ablative radiotherapy


Experts invited to participate in Delphi panel process
ONLINE SURVEY 1 (16.08.21; n=7)
General questions to capture expert preunderstanding
Analysis of responses (including first conjoint analysis focusing on radiotherapy)
ONLINE SURVEY 2 (25.08.21; n=6)
Focused questions to identify potential areas of consensus
Further analysis of responses (including second conjoint focusing on patient characteristics
ADVISORY BOARD 1 (06.09.21; n=7)
Moderated discussion of survey results
First draft of consensus statements
ADVISORY BOARD 2 (20.09.21; n=7)
Moderated discussion of first draft consensus statements
Final consensus statements (13)
ONLINE SURVEY 3 (29.09.21; n=7)
Experts indicate level of agreement on final consensus statements
Final scoring of consensus statements; Strong (8), Moderate (2), Weak (1), No consensus (2)







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This PowerPoint document contains the images that you requested.

Standards for Reporting Qualitative Research (SRQR)a

Table 1

No.	Topic	Item
	Title and abstract	
S1	Title	Concise description of the nature and topic of the study identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended
S2	Abstract	Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions
	Introduction	
S3	Problem formulation	Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement
S4	Purpose or research question	Purpose of the study and specific objectives or questions
	Methods	
S5	Qualitative approach and research paradigm	Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/interpretivist) is also recommended; rationale[b]
S6	Researcher characteristics and reflexivity	Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability
S7	Context	Setting/site and salient contextual factors; rationale[b]
S8	Sampling strategy	How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale[b]
S9	Ethical issues pertaining to human subjects	Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues
S10	Data collection methods	Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale[b]
S11	Data collection instruments and technologies	Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study
S12	Units of study	Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)
S13	Data processing	Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/deidentification of excerpts
S14	Data analysis	Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale [b]
S15	Techniques to enhance trustworthiness	Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale[b]
	Results/findings	
S16	Synthesis and interpretation	Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory
S17	Links to empirical data	Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings
	Discussion	
S18	Integration with prior work, implications, transferability, and contribution(s) to the field	Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/ generalizability; identification of unique contribution(s) to scholarship in a discipline or field
S19	Limitations	Trustworthiness and limitations of findings
	Other	
S20	Conflicts of interest	Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed
S21	Funding	Sources of funding and other support; role of funders in data collection, interpretation, and reporting

[a]The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.
[b]The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

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Standards for Reporting Qualitative Research: A Synthesis of Recommendations

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Academic Medicine 89(9):1245-1251, September 2014.

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Indication where relevant information can be found in manuscript

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Delphi study to identify consensus on patient selection for hydrogel rectal spacer use during radiation therapy for prostate cancer in the UK

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Secondary Subject Heading:	Radiology and imaging, Urology
Keywords:	Prostate disease < UROLOGY, Radiation oncology < RADIOLOGY & IMAGING, RADIOTHERAPY, Toxicity < THERAPEUTICS

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Title page

Delphi study to identify consensus on patient selection for hydrogel rectal spacer use during radiation therapy for prostate cancer in the UK.

Short title: Delphi study on hydrogel rectal spacer use (UK)

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Delphi study to identify consensus on patient selection for hydrogel rectal spacer use during radiation therapy for prostate cancer in the UK.

Structured abstract *(Word count: 268, max 300)*

OBJECTIVES

To identify consensus on patient prioritisation for rectal hydrogel spacer use during radiation therapy for the treatment of prostate cancer in the United Kingdom.

DESIGN

Delphi study consisting of two rounds of online questionnaires, two virtual advisory board meetings and a final online questionnaire.

SETTING

Radical radiation therapy for localised and locally advanced prostate cancer in the United Kingdom.

PARTICIPANTS

Six leading clinical oncologists and one urologist from across the UK.

INTERVENTIONS

Rectal hydrogel spacer.

PRIMARY AND SECONDARY OUTCOME MEASURES

NR

RESULTS

The panel reached consensus on the importance of minimizing toxicity for treatments with curative intent, and that even low-grade toxicity-related adverse events can significantly

impact quality of life. There was agreement that despite meeting rectal dose constraints, too many patients experience rectal toxicity, and that rectal hydrogel spacers in eligible patients significantly reduces toxicity related adverse events. However, as a consequence of funding limitations, patients need to be prioritized for spacer use. A higher benefit of spacers can be expected in patients on anticoagulation, and in patients with diabetes or inflammatory bowel disease, but consensus could not be reached regarding patient groups expected to benefit less. While radiation therapy regimen is not a main factor determining prioritization, higher benefit is expected in ultra-hypofractionated regimens.

CONCLUSION

There is a strong and general agreement that all prostate cancer patients undergoing radical radiation therapy have the potential to benefit from hydrogel spacers. Currently, not all patients who could potentially benefit can access hydrogel spacers, and access is unequal. Implementation of the consensus recommendations would likely help prioritise and equalise access to rectal spacers for patients in the UK.

ARTICLE SUMMARY: STRENGTHS AND LIMITATIONS OF THIS STUDY

- The Delphi panel is a recognised method in developing NICE guidelines and is utilised here to gather insights from a diverse panel of UK radiation oncology and urology experts who are experienced users of hydrogel spacers.
- This study included seven panel experts and their experiences may not reflect all users of hydrogel spacers.
- To help reduce bias, answers and opinions were assessed by two researchers working independently.

INTRODUCTION

Prostate cancer burden

Prostate cancer is the second most common cancer in men globally,[1] and the most common in the UK.[2] More than 47,500 UK men are diagnosed with prostate cancer every year and over 400,000 men are living with and after prostate cancer.[3] The 5-year survival rate for localized prostate cancer in the UK is almost 100%,[4] with three quarters of men diagnosed at any stage expected to survive 10 years.[2] In England, 97%, 87% and 78% of men diagnosed with prostate cancer survive their disease for more than one, five and ten years, respectively.[2] Given the high likelihood of curative therapy, a key treatment goal is to prevent potential adverse events from impacting patient quality of life after treatment.

In addition to the patient burden, prostate cancer is a costly disease with the European costs of care for prostate cancer estimated at EUR 199 billion in 2018.[5]

Radiation therapy for prostate cancer

Choice of treatment for prostate cancer is complex and involves multi-factorial considerations including presenting cancer stage (localised, locally advanced or metastatic), risk stratification, life expectancy, comorbidities, and other patient-specific factors, such as lifestyle, patient preference and treatment goals.[6] For localised and locally advanced prostate cancer, treatment options include active surveillance, surgery, brachytherapy and radiation therapy (RT), with or without hormone treatment, as well as multimodality treatment combining surgery or RT with systemic therapy.[7-9] RT with radical intent is a first-line treatment for localised and locally advanced prostate cancer.[8] Intensity-modulated RT (IMRT) with image guidance (IGRT) is considered the gold-standard form of external beam RT (EBRT).[10] Of the circa 18,000 men identified as having received radical RT for prostate cancer in England and Wales between April 2018 and March 2019, over 90% were treated with IMRT.[11] Whilst stereotactic body RT (SBRT) is not currently routine practice in the UK, its use is increasing and it is now

delivered in several NHS centres.[12] Circa 95% of UK men with intermediate-risk disease receive a hypofractionated radiotherapy regimen.[11]

The success and clinical outcomes of RT depend on several factors, including radiation dose to the tumour and the extent of irradiation affecting nearby normal-tissue, particularly the rectum.[10] Dose-escalated EBRT is a highly effective curative treatment, with higher doses providing better biochemical control.[13] Higher doses can, however , increase radiation toxicity to nearby tissues. Despite substantial advancements in RT, acute and reversible, as well as rare but severe, long-term adverse effects of radiation toxicity such as urinary and bowel incontinence remain problematic. The National Prostate Cancer Audit (NPCA) reported that 11% of prostate cancer patients experienced ≥1 severe gastrointestinal complication within two years after radical RT. This outcome factor derived from hospital records data is defined as a confirmed diagnosis of radiation toxicity ≥ grade 2 according to National Cancer Institute Common Toxicity Criteria for Adverse Events [CTCAE] in addition to a documented procedure to the large bowel.[11 14] Late ≥ grade 2 gastrointestinal toxicity has been explored in numerous randomized clinical trials. The 2016 Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO) trial found an incidence of gastrointestinal toxicity at three years of 17.7% in standard fractionation and 21.9% in hypofractionation.[15] In 2017, results from the ASCENDE-RT trial showed a cumulative incidence of 5-year gastrointestinal side effects ranging from 20.2% (dose-escalated external beam radiation therapy) to 31.3% (low-dose-rate prostate brachytherapy).[16] Due to its proximity to the prostate, the anterior rectal wall is especially vulnerable to irradiation effects and the rectum is a dose-limiting organ at risk.[17]

Hydrogel spacers

One way of reducing the unwanted radiation dose to the rectum is by increasing the space between the prostate and the rectal wall. This can be achieved by use of a rectal spacer, with three currently indicated for use during RT for prostate cancer in the UK: biodegradable

balloons, hyaluronic acid gel, and polyethylene glycol (PEG) hydrogel.[18] In the UK, the use of biodegradable spacers to reduce rectal toxicity during RT for prostate cancer is accepted (IPG590) by NICE, based on safety and efficacy data on the use of PEG hydrogel spacers.[18] Use of rectal hydrogel spacers has been evaluated in a single-blind, phase III trial in image guided IMRT (N=222).[19] The spacer-placement success rate was 99%, and no device-related adverse events occurred.[19] Late (three to 15 months) rectal toxicity severity was significantly reduced in the spacer group.[19] At three years follow-up, decreased bowel toxicity and fewer declines in urinary and bowel quality of life were observed in the spacer group (41% men in the control group experienced a minimally important difference (MID) in decline in bowel quality of life vs 14% in the spacer group; P=0.002). The risk of large decline (twice the MID) was 21% (control) vs 5% (spacer; P=0.02) in bowel quality of life and 23% (control) vs 8% (spacer; P=0.02) in urinary quality of life respectively.[20]

Lack of routine reimbursement has led to restricted patient access to hydrogel spacers in the UK. Therefore, there is a requirement to prioritise patients for hydrogel spacer use in the UK, and attempts have been made to identify optimal usage. A secondary analysis of the hydrogel spacer trial data tried to identify the patient subgroups most and least likely to benefit from the intervention but found generally homogeneous results in bowel quality of life with benefits in all assessed subgroups.[21]

The aim of this study was to identify consensus on patient prioritisation for rectal hydrogel spacer use during RT for the treatment of prostate cancer in the UK.

METHODS

The Delphi technique and panel experts

The Delphi technique is a structured, iterative, multistage process using rounds of questionnaires to collect opinions and to stepwise develop consensus among a pre-defined panel of experts.[22] For this study, experts were approached and asked to participate in the panel based on being a UK radiation oncologist or urologist having experience with rectal

hydrogel spacers. To ensure a diverse panel, experts were sought to represent different geographies within the UK and use different types of RT modalities. There is no defined optimal panel size for a Delphi study,[23] but the selection of an odd number of experts ensured that a majority outcome could be reached.

Steps in the Delphi process

There is no fixed number of rounds in a Delphi survey.[23] As depicted in Figure 1, our study adopted a five-stage approach to elicit consensus, consisting of two pre-advisory board questionnaires administered through a web-based survey program, two virtual advisory board discussions, and a final concluding questionnaire.

The first questionnaire provided some background information on the experts, such as their most used RT modalities and open-ended questions to capture a broad understanding. The open-ended questions related to key treatment aims, which patient and treatment characteristics to consider when prioritising hydrogel spacer, factors typically deterring them from recommending hydrogel spacer use, and factors predictive for toxicity. Additionally, experts were asked to rank treatment modalities in order of how much patient benefit they would expect from hydrogel spacer use, on a scale from 0 (no patient benefit) to 100 (maximal patient benefit).

In the second questionnaire, the responses to the open-ended questions from the previous questionnaire were presented, and the experts asked to rank them by order of importance. In addition to follow-up questions, the second questionnaire included questions on perceived barriers to hydrogel spacer use.

Figure 1: Overview of Delphi panel process

Analysis and scoring

Qualitative content analysis was used to analyse responses to open-ended questions. Two researchers independently analysed responses and interpreted consensus. At the advisory

board meetings, results from the questionnaires were presented together with initial drafted consensus statements for discussion. Then followed moderated discussions which led to revisions of the consensus statements. In the final online questionnaire, the consensus statements were presented, and the experts asked to select a level of agreement: “I fully agree”, “I partially agree” or “I disagree”. Upon selecting “I partially agree”, experts were asked to give a comment and/or update the wording of the statement. The responses were linked to an agreement score, based on the answer selected, and the comment given if “I partially agree” was selected (Table 1).

Table 1: Consensus statement scoring key

Score	Answer selected	Description
4	"I fully agree"	
3	"I partially agree"	With minor word change
2	"I partially agree"	With minor change to statement interpretation/meaning
1	"I disagree"	

Consensus definitions vary between studies[24-28], with percent agreement being one of the more common approaches.[28] Based on the results of our final online survey, statements were categorised into four levels of consensus (strong, moderate, low, and no consensus). This study scored the level of consensus in terms of percent agreement, and additionally that consensus could not be reached in case any expert disagreed with a statement. Figure 2 depicts the consensus statement scoring for this study. Only statements grouped as either **Strong** or **Moderate** are considered statements where consensus was reached. **Weak** or **No** consensus mean that there was still substantial discussion or divergence of opinion among the experts.

Figure 2: Consensus statement scoring, decision tree

Consent, privacy, and data security

The panel experts were informed about and consented to the full Delphi process, including length and time of surveys and details on the data collected, stored, and deleted. The retention periods of collected data were pre-defined. Questionnaire responses were anonymised and securely stored on the survey software provider’s server in Germany. Audio recordings were

stored for 60 days on the conference provider's EU based server. All experts were contracted for this study and reimbursed at fair, local market rates for their time commitment during the Delphi process. The study was approved by an independent review board (HML IRB Review #952SCGC21).

Patient and public involvement

No patients involved.

RESULTS

Panel expert characteristics

All approached experts agreed to participate (N=7). Details on the panel experts' treatment practices are presented in Table 2. The majority of the panel (N=6) exclusively use rectal hydrogel spacers in their practices. One uses rectal hydrogel spacers as well as biodegradable balloons. Participation rates were high, with only one dropout (one expert did not complete the second questionnaire but participated in all other steps).

Table 2: Panel experts treatment practice

Geographical setting, N (%)	
England	5 (57)
Northern Ireland	1 (14)
Wales	1 (14)
Public or private setting, N (%)	
Public only	1 (14)
Private only	0 (0)
Both	6 (86)
Most frequently used RT modalities, % of patients (N experts using modality)	
IMRT	25–95 (6)
EBRT (not specified)	90 (1)
IMRT and HDR BT boost	15–30 (2)
SBRT	45 (1)
BT monotherapy (LDR)	10–20 (2)
PBT	10 (1)

Key: *IMRT, intensity-modulated radiation therapy; EBRT, external beam radiation therapy; HDR, high dose rate; BT, brachytherapy; SBRT, stereotactic body radiation therapy; LDR, low dose rate; PBT, proton beam therapy.*

Key treatment aims, besides curing or controlling cancer and increasing overall survival, were to minimise the risk of side effects and toxicity.

Questionnaire outcomes shaping the consensus statement discussion

Questionnaire outcomes showed that the panel estimated considerably less toxicity in patients with hydrogel spacer, as compared to those without (Figure 3). All experts agreed that hydrogel spacers reduce grade 1 and 2 late rectal toxicity, 86% agreed that it reduces grade 3 toxicity and 71% grade 4 toxicity.

Figure 3: Expected level of late (after 3 months) rectal toxicity in patients with and without hydrogel spacer

The panel considered toxicity a considerable issue, and underlined that also low-grade toxicity-related adverse events may significantly worsen patient's lives:

> *'I ask them [my patients], when you're out and about, is the first thing you think of where the toilet is?... And a remarkable number of patients say yes to that question, and it is affecting their quality of life.'*

In the first questionnaire, the panel estimated that an average of 83% (SD: 13%) patients who could potentially benefit from a hydrogel spacer were denied access. Throughout the discussions, patient access in general and equal access in particular were central themes. The panel voiced their concern, for example regarding differences between NHS and private practice:

> *'In my private practice, every patient gets it [hydrogel spacer] unless there is a reason why they should not get it. Whereas in my NHS practice, unfortunately no patient gets it, unless there is a reason why they should get it.'*

The main barrier to hydrogel spacer use was funding and resource constraints, followed by lack of trained staff.

'The ideal way to go would be to offer it to every eligible patient. But given that this is not currently feasible in our centre, there has to be some kind of categorisation.'

As seen in Figure 4, a trend towards hypo-fractionated external-beam regimens, with potential increased bowel dose and toxicity being associated with more potential benefit for spacers was apparent. This was also reflected in the outcome of the conjoint analysis. The absolute variation between expected benefit was, however, relatively low, ranging from 67 (BT monotherapy LDR) to 80 (SBRT/SABR) on average. This was reflected in later discussions, where experts agreed that RT modality is not the main consideration when prioritising patients for hydrogel spacer use.

Figure 4: Expected patient benefit from hydrogel spacer use, by treatment modality

When asked about patient characteristics to consider when deciding whether to recommend using hydrogel spacer the experts gave a wide range of suggestions, including comorbidities (age, diabetes, high bleeding risk, hip prothesis, inflammatory bowel disease and rectal and bowel problems, normal erectile function), cancer stage, localisation, and heavy smoking. This was narrowed down in subsequent discussion, with general agreement that patients with certain comorbidities (diabetes, inflammatory bowel disease) or on anticoagulation may have higher benefit from hydrogel spacers.

Consensus statements

Upon being shown the results of the questionnaires, two rounds of moderated discussion followed, resulting in 13 consensus statements. These statements were subsequently voted on in a final questionnaire, and a final scoring was assigned as described in the method section.

The following eight statements reached strong consensus:

- Our consensus opinion is that for treatments with curative intent, focus should be on minimising toxicity and the risk of side effects.

- Our consensus opinion is that use of spacers in eligible patients significantly reduces radiation dose to the rectum and toxicity-related adverse events.
- Our consensus opinion is that despite meeting rectal dose constraints, too many patients continue to experience rectal toxicity.
- Our consensus opinion is that certain grade 1 toxicity-related adverse events[1] can still have a significant impact on patient quality of life.
- Our consensus opinion is that any toxicity grading system in use should be complemented by patient-reported outcomes.
- Our consensus opinion is that patients receiving long-term anticoagulation therapy with medications such as direct oral anticoagulants (DOACs)[2] should be considered for spacer use if their anticoagulation can be safely paused.
- Our consensus opinion is that spacers are useful in eligible patients with T1-T2 disease. Spacer use in patients with T2+ disease should not be excluded but should be assessed on an individual basis by a team proficient in inserting spacers.
- Our consensus opinion is that patients should have the opportunity to take part in the discussion regarding the use of a spacer.[29]

For the following two statements, moderate consensus was reached. Each statement is followed by an explanation on why strong consensus was not reached.

- Our consensus opinion is that a higher benefit of spacers is expected in eligible patients with certain comorbidities[3] and/or longer expected overall survival.

[1] Bowel frequency and urgency, diarrhoea, flatulence, radiation cystitis, radiation proctitis, rectal bleeding, rectal mucus.
[2] The reason for prescribing the DOAC, rather than the medication itself, is more important for the decision. All patients on DOACs, except for cardiac stent and prosthetic valve replacement patients may be able to safely pause their anticoagulation.
[3] Anticoagulation, diabetes, inflammatory bowel disease (ulcerative colitis and Crohn's disease)

Six experts (86%) fully agreed with the statement. One expert (14%) only partially agreed and suggested removing “and/or longer expected overall survival”. This was deemed a change to the statement interpretation.

- All eligible radiotherapy patients should have equal opportunity to access spacers, independent of socio-economic factors.

Five experts (71%) fully agreed with the statement. While there was an overall agreement that lack of equality in access to spacers is currently an important issue, two experts (29%) had rewording suggestions that would have impacted the statement interpretation. One proposed to add more detail on eligibility, and to add that patients suitable for a spacer implant should have access, irrespective of whether they can afford it. The other expert expressed some uncertainty regarding the term “socio-economic factors” and would have preferred the wording “irrespective of post-code”.

Statements where no consensus was reached

One statement was categorised as a weak consensus statement:

- Whilst we support the use of spacers in all eligible patients, our consensus opinion is that if resource constraints exist, patients receiving ultra-hypofractionated or hypofractionated radiotherapy should be prioritised for access to a spacer.

Four experts (57%) fully agreed with the statement. The remaining three (43%) partially agreed but had additional comments. One expert expressed that individual risk factors should be considered, rather than the RT modality. The second expert agreed on the need to identify a group at higher risk of rectal toxicity, and suggested combination of RT modality considerations and patient characteristics (e.g., age) and comorbidities. The third respondent only agreed that patients receiving ultra-hypofractionated RT should be prioritised.

For the following two statements, no consensus was reached.

- Our consensus opinion is that for patients with anticipated short overall survival but who will receive radical radiotherapy, use of a spacer should only be considered after careful evaluation of potential benefit.

Three experts (43%) fully agreed. Four (57%) partially agreed but had additional comments. Two experts made the point that it is unlikely that patients with short anticipated overall survival would be indicated for radical radiotherapy. Two experts expressed uncertainty with the wording “overall survival”. One of them suggested a rewording that some carefully selected patients with short expected survival who are offered radical radiotherapy may benefit from spacer use after careful consideration. The second expressed that the statement was too unclear. Additionally, in subsequent discussions, the experts agreed that the term “anticipated shorter life expectancy” would have been preferred over “anticipated short overall survival”, so as not to imply that the use of hydrogel spacers affects survival. Upon subsequent discussion, experts agreed that the statement would have been improved by adding “and side effects” to the end of the statement.

- Our consensus opinion is that there are a limited number of patients with risk factors, or combination of risk factors, in which use of a spacer should only be considered after careful evaluation of potential benefits.

Four experts (57%) fully agreed, two (29%) partially agreed, and one (14%) disagreed. Those who partially agreed expressed that an addition should be made to the statement, that the majority of patients who receive radical RT would also be suitable for a spacer, noting that patients who are not fit enough for a spacer, likely are also not fit for RT. The second partially agreeing expert wanted to add a recommendation to discuss such cases with a mentor with extensive experience in spacer insertion. Upon subsequent discussion, experts agreed that the statement would have been improved by adding “and side effects” to the end of the statement.

DISCUSSION

Statement of principal findings

There was strong consensus that rectal toxicity is a considerable issue, and that minimizing the risk of radiation side effects is an important treatment aim. Rectal hydrogel spacers can reduce the toxicity burden and benefit patients undergoing radical RT for the treatment of prostate cancer in the UK. Currently, the NHS does not routinely fund hydrogel spacers. Limited funding leads to limited resources, and therefore limited access. Experts estimated that on average, 83% of their patients that could benefit from a spacer are not currently getting access. There was moderate consensus that a higher benefit is expected in patients on anticoagulation, patients with diabetes, and patients with inflammatory bowel disease (Ulcerative colitis or Crohn's disease). However, experts expected the majority of patients to benefit from use of a spacer, and it was not possible to reach consensus on those patients with lower expected benefit. Key takeaways from discussions around statements where no consensus was reached are that individual patient characteristics are more important for informing the decision on whether to prioritise the use a spacer than the RT regimen selected. However, a higher level of benefit from spacer use is expected with ultra-hypofractionated RT compared with standard RT, a conclusion in line with current clinical evidence.[30]

Meaning of the study: possible explanations and implications for clinicians and policy makers

Currently, patient selection is driven by limitations in the healthcare system rather than patient needs. This highlights the importance of developing guidance on spacer use, to ensure fair and equal access to healthcare. The COVID-19 pandemic has lengthened already substantial NHS waiting times, further exacerbating issues with access and underscoring the need for formal guidance. Additionally, practical issues (e.g., availability of trained staff, theatre capacity) need to be considered when preparing a clinic to start using hydrogel spacers. As is

important for all techniques to be introduced, audit of practice and quality improvement is recommended.

Strengths and weaknesses

This study only included seven experts, who are all experienced users of hydrogel spacers Naturally, a broader selection of experts could have resulted in different answers. However, including non-users as panel experts would not have been feasible for the purposes of this study, as they would have not possessed the relevant experience required. Additionally, the RT modality used by panel members could influence their view on when to prioritise hydrogel spacer use. However, the diversity of the panel in terms of modalities used likely safeguarded the balance of the resulting consensus.

The main strengths of this study are the scientific rigour applied following a well-defined and proven Delphi methodology, and the experience and diversity of the panel. The Delphi method allowed gathering insights from leading experts in the field from different UK countries utilising a mix of RT modalities, while reducing bias and separating the evaluation by tasking two independent researchers with analysis and scoring.

Comparison with other studies

To the best of our knowledge, no previous attempts have been done to establish consensus for rectal hydrogel spacer use in the UK. A study published in 2016 used a model-based approach to identify patients expected to benefit the most from implantable rectum spacers among 26 patients with localized prostate cancer treated at a German hospital. The clinical risk factors found relevant were anticoagulant use, hormonal therapy, antihypertensive use, diabetes, haemorrhoids, pelvic nodal RT, and prior abdominal surgery.[31] Single-centre studies of rectal spacers in Crohn's and ulcerative colitis patients suggest benefit of spacers.[32 33] One study conducted secondary analyses of a single-blinded, phase III randomised trial, with the aim of identifying patients benefitting the least from hydrogel rectal spacer during prostate

radiation therapy.[21] In line with this study, no subgroup without potential benefits of hydrogel spacers could be identified. The benefit of hydrogel spacers perceived by the experts is in line with current clinical evidence.[20]

Unanswered questions and future research

As well as hydrogel rectal spacers, other materials including hyaluronic acid, saline-filled balloon, and human collagen have been used to create space between the rectum and prostate. Readers should familiarize themselves with the available evidence on each product when considering between the different options. This study offers guidance to later adopters of rectal hydrogel spacers, building on the expertise of leading UK radiation oncologists and urologist. Future research should focus on implementing formal guidance on hydrogel spacer use and strive towards reaching a consensus on patient prioritisation. A larger follow-up consensus study would be of value, asking all UK domain experts their opinion on the consensus statements. With growing interest in hydrogel spacers, it is increasingly important to study the impact of the quality of the implant. There is an ongoing debate on what a good implant is, and how it is measured. Similarly, it would be valuable to reach an agreement on which toxicity data to generate and follow up through including hydrogel spacers in cancer treatment trials, or through the development of a quality registry. Finally, it is of utmost importance to investigate the availability and equality in access to spacers. For this aim to be reached, further cost-effectiveness research and a continued discussion on willingness to pay should be undertaken. Analyses of spacers in prostate cancers have shown cost-effectiveness in certain radiation modalities in US[34 35] and Dutch[36] contexts.

CONCLUSION

Rectal toxicity is a considerable issue, and focus should be on minimising side effects of curative treatment. There is a strong and general agreement that all prostate cancer patients undergoing radical RT have the potential to benefit from hydrogel spacers. Currently, not all patients who could potentially benefit can access hydrogel spacers, and access is unequal.

Implementation of the ten strong and moderate consensus recommendations would likely help prioritise and equalise access to rectal spacers for patients in the UK. In particular, prioritising access towards patients on anticoagulation, with diabetes, and/or patients with inflammatory bowel disease would, in our opinion, be a strong starting position.

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COMPETING INTERESTS

RS is the owner of Coreva Scientific, a health-economics and value-based healthcare consultancy that focuses on medical devices. AHH is an employee of Coreva Scientific. Coreva Scientific received consultancy fees from Boston Scientific for work related to this manuscript. The authors did not receive direct payment as a result of this work outside of their normal salary payments. EW is an employee of Boston Scientific.

AUTHOR CONTRIBUTIONS

EW conceptualised the idea. RS and AHH designed and ran the questionnaires and implemented data protection measures. EW reviewed the study design. AHH and RS analysed the responses. RS moderated the advisory boards. SJ, AT, AE, AB, PD, CP, and HP responded to the questionnaires, and participated in the advisory boards. AHH and RS drafted the manuscript, in collaboration with SJ, AT, AE, AB, PD, CP and HP. All authors critically reviewed the manuscript outline and manuscript drafts. All authors approved the final manuscript.

ETHICS APPROVAL STATEMENT

The study was approved by an independent review board (HML IRB Review #952SCGC21). All participants gave informed consent before taking part.

DATA SHARING STATEMENT

No additional data available.

LEAD AUTHOR TRANSPARENCY STATEMENT

I confirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

Prof. Heather Ann Payne

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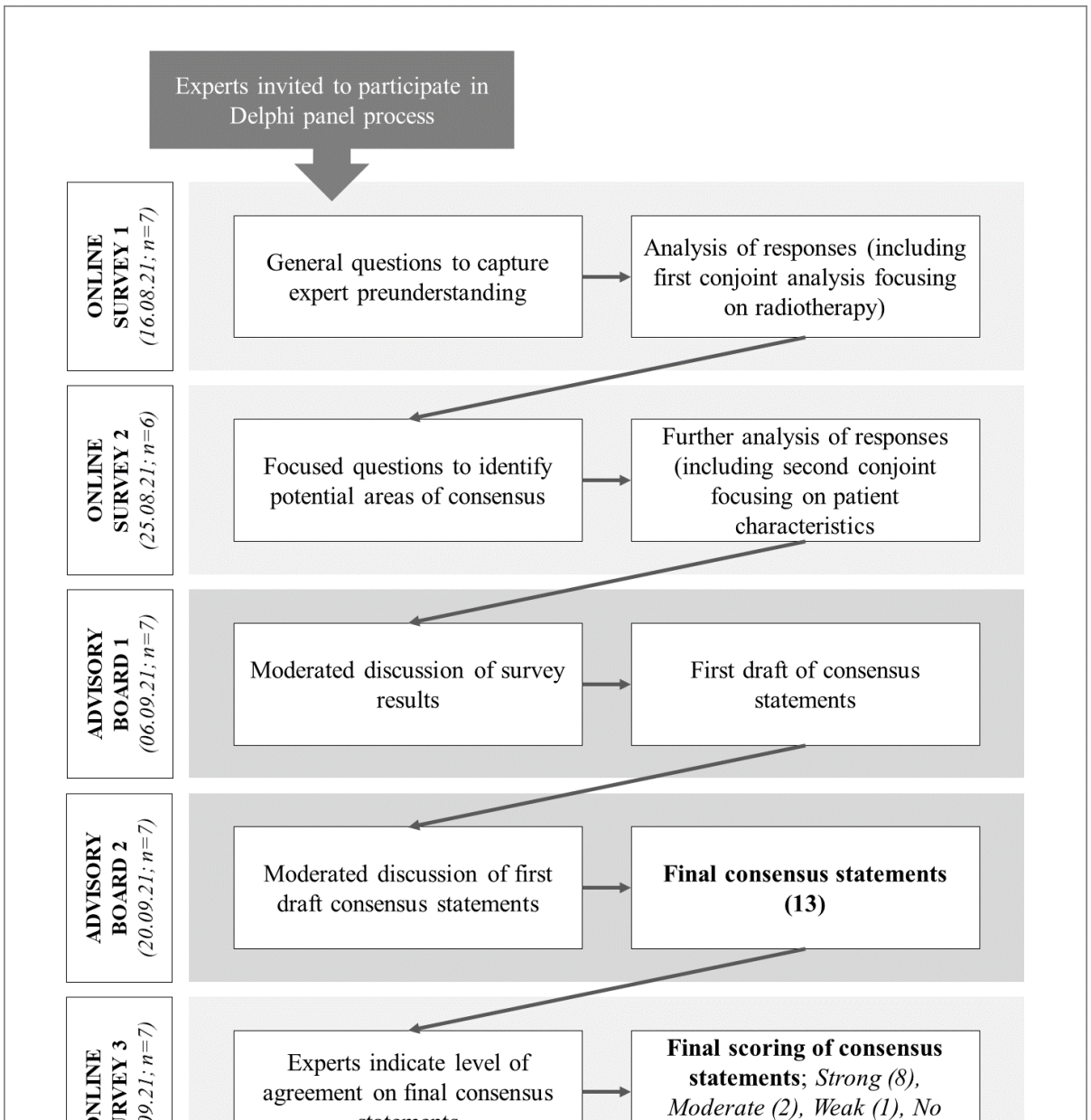
Figure legends

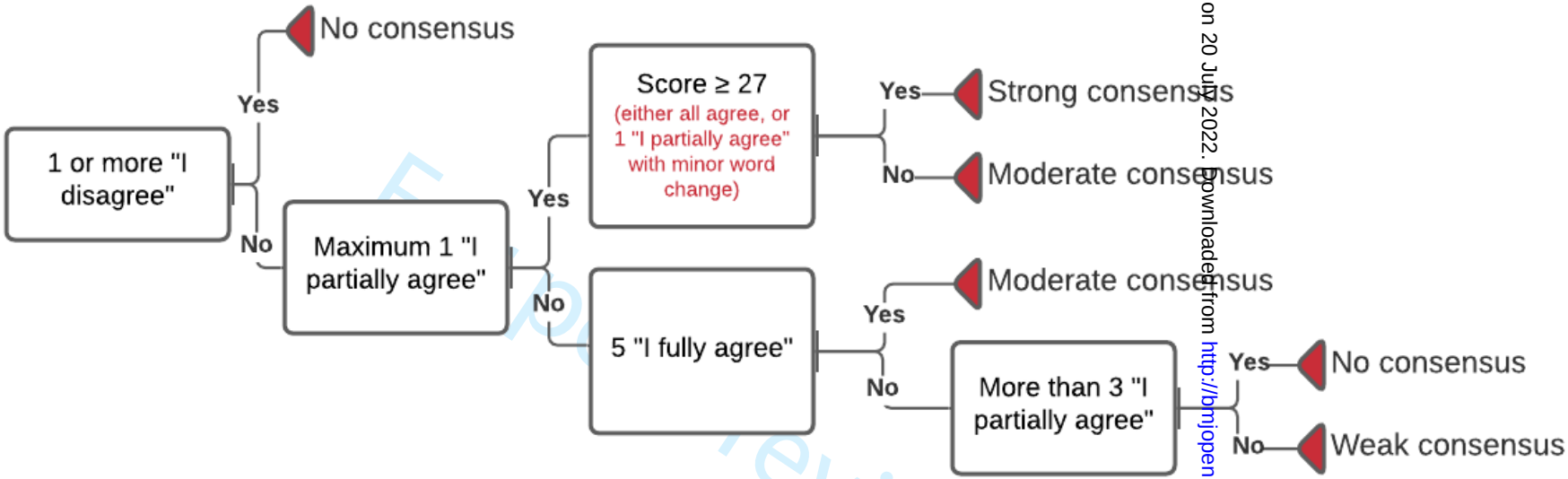
FIGURE 2:

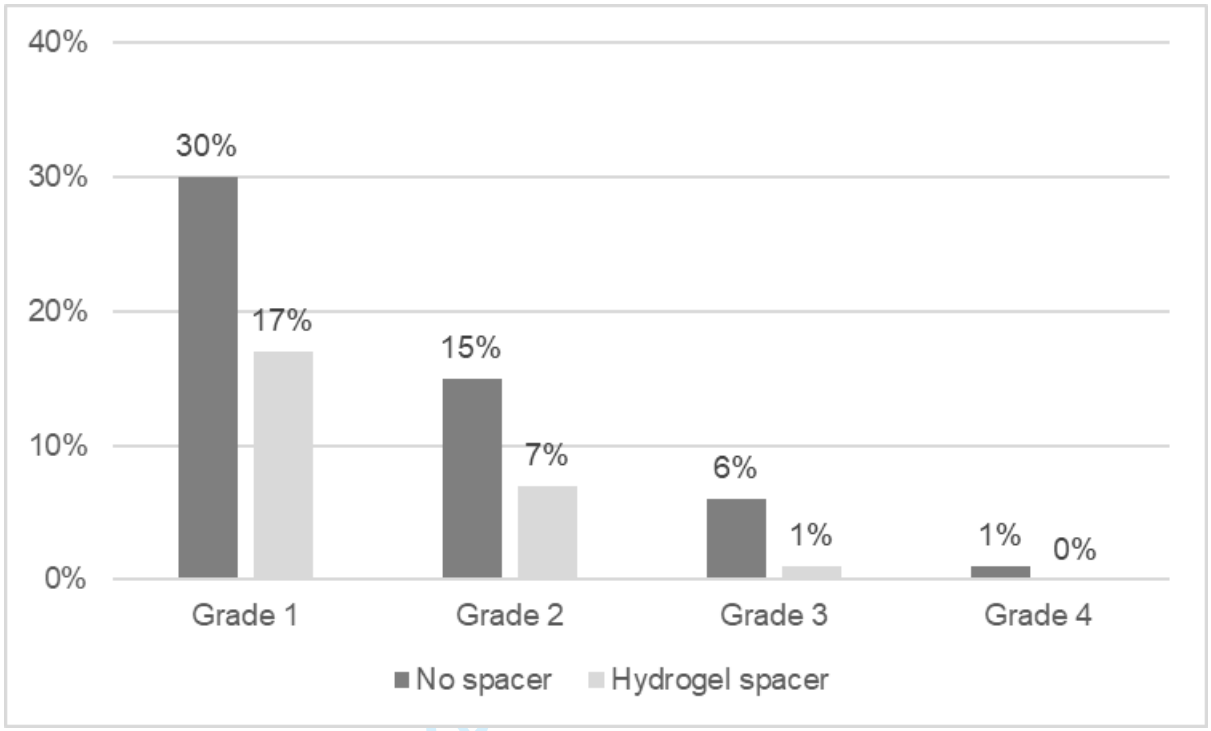
Strong consensus could only be reached if all experts indicated that they “Fully agree” or all except one “Fully agree”, with the last respondent “Partially agree” with only a minor word change (score ≥27). Moderate consensus could only be reached if at least five respondents “Fully agree”, and with no “Disagree”. Weak consensus was reached where a maximum of three respondents “Partially agree”, and with no “Disagree”. No consensus was indicated where at least one respondent “Disagree”, or if four or more respondents “Partially agree”.

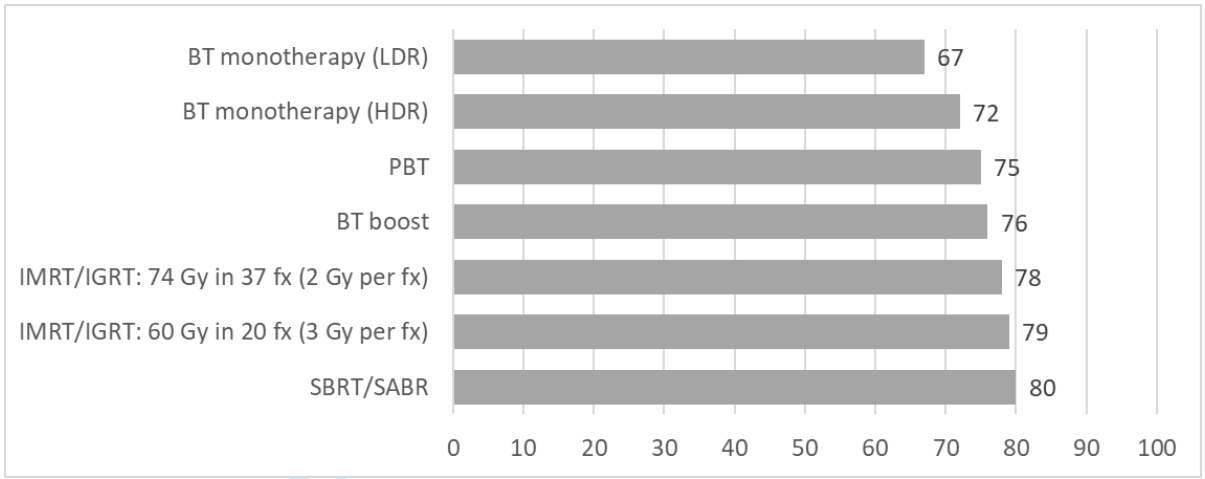
FIGURE 4:

Key: BT, brachytherapy; LDR, low dose rate; HDR, high dose rate; PBT, proton beam therapy, IMRT, intensity-modulated radiation therapy; IGRT, image guided radiation therapy, SBRT, stereotactic body radiation therapy; SABR, stereotactic ablative radiotherapy


Experts invited to participate in Delphi panel process
ONLINE SURVEY 1 (16.08.21; n=7)
General questions to capture expert preunderstanding
Analysis of responses (including first conjoint analysis focusing on radiotherapy)
ONLINE SURVEY 2 (25.08.21; n=6)
Focused questions to identify potential areas of consensus
Further analysis of responses (including second conjoint focusing on patient characteristics
ADVISORY BOARD 1 (06.09.21; n=7)
Moderated discussion of survey results
First draft of consensus statements
ADVISORY BOARD 2 (20.09.21; n=7)
Moderated discussion of first draft consensus statements
Final consensus statements (13)
ONLINE SURVEY 3 (29.09.21; n=7)
Experts indicate level of agreement on final consensus statements
Final scoring of consensus statements; Strong (8), Moderate (2), Weak (1), No consensus (2)







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Thank You

This PowerPoint document contains the images that you requested.

Standards for Reporting Qualitative Research (SRQR)a

Table 1

No.	Topic	Item
	Title and abstract	
S1	Title	Concise description of the nature and topic of the study identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended
S2	Abstract	Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions
	Introduction	
S3	Problem formulation	Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement
S4	Purpose or research question	Purpose of the study and specific objectives or questions
	Methods	
S5	Qualitative approach and research paradigm	Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/interpretivist) is also recommended; rationale[b]
S6	Researcher characteristics and reflexivity	Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability
S7	Context	Setting/site and salient contextual factors; rationale[b]
S8	Sampling strategy	How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale[b]
S9	Ethical issues pertaining to human subjects	Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues
S10	Data collection methods	Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale[b]
S11	Data collection instruments and technologies	Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study
S12	Units of study	Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)
S13	Data processing	Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/deidentification of excerpts
S14	Data analysis	Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale [b]
S15	Techniques to enhance trustworthiness	Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale[b]
	Results/findings	
S16	Synthesis and interpretation	Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory
S17	Links to empirical data	Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings
	Discussion	
S18	Integration with prior work, implications, transferability, and contribution(s) to the field	Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/ generalizability; identification of unique contribution(s) to scholarship in a discipline or field
S19	Limitations	Trustworthiness and limitations of findings
	Other	
S20	Conflicts of interest	Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed
S21	Funding	Sources of funding and other support; role of funders in data collection, interpretation, and reporting

[a]The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.
[b]The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

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Standards for Reporting Qualitative Research: A Synthesis of Recommendations

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Indication where relevant information can be found in manuscript

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