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HEALTH TECHNOLOGY ASSESSMENT:
Hydrogel rectal spacer SpaceOAR™ in prostate cancer radiation therapy - Health economic evaluation

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Key messages

The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway ("Nye Metoder") commissioned the Norwegian Institute of Public Health to perform a health technology assessment of SpaceOAR™ hydrogel for prevention of radiation-induced side effects following treatment for prostate cancer. Efficacy and safety of the intervention are addressed in a recent EUnetHTA report published in July 2020 (1). This report assesses the technology in light of the Norwegian priority setting criteria (health benefits, resource use and disease severity). Health benefits and disease severity are expressed in quality adjusted life years (QALYs).

Key findings:

- Absolute shortfall for patients suffering from radiation-induced adverse events is 1.85 QALYs.
- The cost-utility analysis indicated that SpaceOAR™ in combination with radiation therapy was more costly (incremental costs: 15,330 NOK) and slightly more effective (incremental effects: 0.008 QALYs) than radiation therapy alone.
- The health benefit of the intervention is very uncertain. Our analysis indicates that the intervention only has a 59% likelihood of generating a net health benefit as measured in QALYs.
- The incremental cost-effectiveness ratio (ICER) is NOK 2,006,985 per QALY.
- The results of sensitivity analysis indicated that the price of the spacer, the quality of life weights and the efficacy of the treatment have the greatest impact on the results.
- The budget impact analysis indicated that costs of the intervention would be approximately 15 million NOK per year.

Title:
Hydrogel rectal spacer SpaceOAR™ in prostate cancer radiation therapy - Health economic evaluation

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Type of publication:
Health technology Assessment
Health technology assessment (HTA) is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the development of safe, effective health policies that are patient focused and that seek to achieve best value.

Doesn't answer everything:
The analysis should be updated when new studies on the effectiveness of rectal spacers become available

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Publisher:
Norwegian Institute of Public Health

Internal peer reviewer:
Arna Desser,
Health economist,
Norwegian Institute of Public Health

Executive summary (English)

Background

Radiation therapy is the most common treatment for prostate cancer. Dose-escalated external beam radiation provides better disease control, but also increases the chances for developing radiation-induced gastrointestinal and genitourinary toxicities. Hydrogel rectal spacer SpaceOAR™ is a medical device intended to reduce harm from the radiation therapy by increasing the space between the rectum and the prostate.

Decisions to introduce new technologies within the Norwegian Specialist Health Services are informed by three primary criteria for setting health care priorities in Norway: the benefit criterion, the resource criterion, and the severity criterion (2). The benefit criterion refers to a technology's expected health effects: increased longevity and/or improved health-related quality of life, measured in quality adjusted life years (QALY). According to the benefit criterion, priority increases with the size of the expected benefit of the intervention. According to the resource criterion, priority increases, as fewer resources are needed for the intervention. According to the severity criterion, priority increases with expected future health loss resulting from the disease. Severity of disease is measured as "absolute shortfall", defined as the expected loss of future health (QALYs) associated with a specified diagnosis. For treatment of a diagnosed disease, severity is the average expected absolute shortfall for the relevant patient group given the current standard treatment.

In practice, the three priority setting criteria are taken into account by weighing costs against benefits in a cost-effectiveness analysis of the technology of interest relative to a comparator. The result is reported as a cost-effectiveness ratio in which the numerator captures incremental resource use, measured in monetary terms, while the denominator reflects the incremental health effect measured in QALYs. Different levels of disease severity and associated threshold values for cost-effectiveness is outlined in health policy

documents (report from the Magnussen group, https://www.regjeringen.no/no/dokumenter/pa-ramme-alvor/id2460080/), although an official cost-effectiveness threshold does not currently exist in Norway.

Objective

The objective of this report is to assess the cost-effectiveness and budget impact of the hydrogel rectal spacer SpaceOAR™ for the prevention of radiation induced harm in patients with prostate cancer in Norway.

Method

In order to evaluate the cost-effectiveness of SpaceOAR™, we developed a health economic model consisting of a decision tree and a state-transition Markov model. We calculated the severity of disease, measured as absolute shortfall, by subtracting the model predicted prognosis of patients receiving current treatment from the age adjusted number of remaining quality adjusted life years, as recommended for priority setting in Norway. The cost-effectiveness analysis compares the incremental costs expressed in 2020 Norwegian kroner (NOK) and health effects as measured in quality adjusted life years (QALYs) of the device in combination with the radiation therapy with radiation therapy alone. The analysis applies a ten-year time horizon and a broad healthcare perspective on costs, as recommended in Norwegian guidelines. Data on the efficacy and safety of SpaceOAR™ were collected from a 2020 EUnetHTA report (1). A Norwegian summary of this EUnetHTA report is included in the appendix 14. We discounted costs and health effects using an annual discount rate of 4%. The results were expressed as incremental cost-effectiveness ratio (ICER), i.e. expected incremental costs (NOK) per unit of health gain (QALY). We performed on-way sensitivity analyses and a probabilistic sensitivity analysis. To estimate the financial consequences of implementing the device in health care practice, we conducted a budget impact analysis.

Results

The estimated absolute shortfall for patients suffering from the radiation-induced adverse events was 1.85 QALYs, which places it in the least severe of the six classes suggested by the Magnussen group (https://www.regjeringen.no/no/dokumenter/pa-ramme-alvor/id2460080/). We find SpaceOAR™ to be more costly (incremental costs: 15,330 NOK) and slightly more effective (incremental effects: 0.008 QALYs) than radiation therapy alone. The resulting incremental cost-effectiveness ratio (ICER) is 2,006,985 NOK/QALY. Note that the high ICER is a result of the very modest health gain achieved by the intervention. The results of sensitivity analysis illustrated that the price

of the spacer, the quality of life weights and the efficacy of the intervention had the greatest impact on the results.

The probabilistic sensitivity analysis indicates that the health benefit of the intervention is very uncertain, with only 59% of simulations resulting in a net health gain as measured in QALYs. There is however 100% certainty that the spacer will increase costs. The budget impact analysis indicated that adoption of hydrogel rectal spacer would increase spending by approximately 15 million NOK per year.

Discussion

EUnetHTA's relative effectiveness assessment included two studies: one RCT on SpaceOAR™ with companion studies (3–6) and one non-RCT (7).

Further research may change the conclusion of this analysis. Notably, the documentation on the efficacy of hydrogel rectal spacer is uncertain, the cost-effectiveness analysis should be updated if or when more documentation becomes available. In addition, the cost effectiveness analysis would benefit from more studies on the natural history of the disease, i.e. duration of radiation induced toxicities, the incidence rate of such toxicities and the percentage of patients who would experience a resolution of their symptoms.

Bases on current evidence, it seems unlikely that SpaceOAR™ will be considered a high priority technology for adoption in routine public financing. The analysis would need to be updated if or when new evidence becomes available and the conclusions may thus change.

Conclusion

This report has assessed to what degree the technology meets the Norwegian priority setting criteria (health benefits, resource use and disease severity). The absolute shortfall is 1.85 QALY, placing the disease in the lowest priority setting group following the approach suggested by the Magnussen group (https://www.regjeringen.no/no/dokumenter/pa-ramme-alvor/id2460080/). The health benefit of the intervention is small (0.008 QALYs) and very uncertain.

Hovedfunn (norsk)

Bestillerforum RHF i Nye Metoder ga Folkehelseinstituttet (FHI) i oppdrag å utføre en nasjonal metodevurdering på bruk av nedbrytbar beskytter SpaceOAR™ for forebygging av toksisiteter ved strålebehandling av prostatakreft. Effekt og sikkerhet av denne intervensjonen er beskrevet i en rapport fra EUnetHTA publisert i juli 2020 (1). Denne rapporten belyser i hvilken grad den foreslåtte teknologien oppfyller de norske prioriteringskriteriene (sykdommens alvorlighet, nytte og kostnad). Sykdommens alvorlighet og nytte av behandlingen er uttrykt i kvalitetsjusterte leveår (QALYs).

De viktigste funnene er:

- Sykdommens alvorlighet beregnet som absolutt prognosetap for pasienter med stråleskader er 1,85 QALY.
- Den helseøkonomiske evalueringen indikerer at SpaceOAR™ sammen med strålebehandling er dyrere (inkrementelle kostnader: 15 330 NOK) og noe mer effektiv (inkrementelle effekter: 0,008 QALYs) enn strålebehandling alene.
- Det inkrementelle kostnadseffektivitets ratioen (ICER) er 2 006 985 NOK/QALY.
- Sensitivitetsanalysen indikerer at prisen på beskytter, livskvalitetsvektene og effekten av intervensjonen hadde størst innvirkning på resultatet.
- Nytten av intervensjonen er veldig usikker, resultatene våre indikerer at intervensjonen kun har en 59% sannsynlighet for å generere en positiv helsegevinst målt i livskvalitetsjusterte leveår (QALYs).
- Budsjettvirkningen av å inkludere SpaceOAR™ i offentlig finansiering er ca. 15 millioner kroner ekstra per år.

Tittel:
Nedbrytbar beskytter SpaceOAR™ ved strålebehandling av prostatakreft - Helseøkonomisk evaluering

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Publikasjonstype:
Fullstendig metodevurdering
En metodevurdering er resultatet av å
- innhente
- kritisk vurdere og
- sammenfatte

relevante forskningsresultater ved hjelp av forhåndsdefinerte og eksplisitte metoder.

Minst ett av følgende tillegg er også med:
helseøkonomisk evaluering, vurdering av konsekvenser for etikk, jus, organisasjon eller sosiale forhold

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Svarer ikke på alt:
Analysen bør oppdaters når det publiseres nye studier på effekten av nedbrytbar beskytter

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Hvem står bak denne publikasjonen?
Folkehelseinstituttet har gjennomført oppdraget etter forespørsel fra Nye Metoder

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Intern fagfelle:
Arna Desser, helseøkonom, Folkehelseinstituttet

Sammendrag

Bakgrunn

Strålebehandling er en av de vanligste behandlingstypene for pasienter med prostatakreft. Dose-eskalert utvendig strålebehandling gir bedre sykdomskontroll, men øker imidlertid også sjansene for å utvikle stråleinduserte skader på de tilstøtende organene i form av rektal- og urinveistoksisitet. Nedbrytbar beskytter SpaceOAR™ er et medisinsk utstyr som tar sikte på å redusere bivirkninger av strålebehandling ved å øke avstanden mellom endetarm og prostata.

Det er tre primære kriterier for prioritering i norsk helsevesen: nyttekriteriet, ressurskriteriet og alvorlighetskriteriet (2). Nyttekriteriet refererer til en teknologis forventede helseeffekter: økt levetid og / eller forbedret helserelatert livskvalitet, målt i kvalitetsjusterte leveår (QALY). I samsvar med nyttekriteriet øker prioriteten med størrelsen på den forventede helsegevinsten av intervensjonen. Ifølge ressurskriteriet øker prioriteten, jo færre ressurser intervensjonen legger beslag på. I henhold til alvorlighetskriteriet, øker prioriteten med forventet fremtidig helsetap som følge av sykdommen. Alvorlighetsgraden av sykdommen måles som absolutt prognosetap, definert som forventet tap av fremtidig helse (QALYs) med en spesifisert diagnose. For behandling av en diagnostisert sykdom, er alvorlighetsgraden det gjennomsnittlige forventede absolutte helsetapet for den aktuelle pasientgruppen gitt dagens behandling.

I praksis blir de tre prioriteringskriteriene tatt i betraktning ved å avveie kostnader mot helseeffekter i en kostnadseffektivitetsanalyse. Ressursbruk, målt som monetære kostnader, inngår telleren av kostnadseffektivitetsratioen, mens helseeffekten kommer inn i nevneren. Et av forarbeidene til prioriteringsmeldingen (rapport fra Magnussen-gruppen, https://www.regjeringen.no/no/dokumenter/pa-ramme-alvor/id2460080/) skisserer forskjellige nivåer av alvorlighetsgrad og tilhørende terskelverdier for kostnadseffektivitet. En offisiell grense for kostnadseffektivitet finnes imidlertid ikke i Norge i dag.

Problemstilling

Formålet med denne rapporten er å vurdere kostnadseffektiviteten og budsjettkonsekvenser av SpaceOAR™ ved strålebehandling av prostatakreft i Norge.

Metode

For å evaluere kostnadseffektiviteten til SpaceOAR™, utviklet vi en helseøkonomisk modell bestående av et beslutningstre og en Markov-komponent. Alvorlighetsgraden av sykdommen, målt som absolutt prognosetap, ble beregnet ved å trekke den modellberegnede prognosen for pasienter på dagens behandling fra aldersjustert antall gjenværende kvalitetsjusterte leveår, som anbefalt for prioritering i Norge.

Kostnadseffektivitetsanalysen sammenligner forventede kostnader uttrykt i norske 2020 kroner (NOK) og helseeffekter målt i kvalitetsjusterte leveår (QALYs) av SpaceOAR™ i tillegg til strålebehandling med strålebehandling alene. Analysen er utført med et tiårs tidsperspektiv og har et bredt helseperspektiv på kostnader, som anbefalt i norske retningslinjer. Data på effekt og sikkerhet av SpaceOAR™ er basert på en EUnetHTA rapport publisert 2020 (1). Et norsk sammendrag av denne rapporten ligger i vedlegg 14.Både helseeffekter og kostnader ble diskontert med en rate på 4%. Resultatene ble uttrykt som inkrementell kostnadseffektivitetsratio (ICER), dvs. forventede kostnader (NOK) per enhet av helsegevinst (QALY). Vi utførte enveis-sensitivitetsanalyser og en probabilistisk sensitivitetsanalyse. For å estimere de økonomiske konsekvensene av å implementere enheten i praksis, gjennomførte vi en budsjettkonsekvensanalyse.

Resultater

Det absolutte prognosetapet for pasienter som led av de strålingsinduserte bivirkninger var lik 1,85 QALYs, og sykdommen ble dermed plassert i den minst alvorlige av de seks prioriteringsklassene som ble foreslått av Magnussen-gruppen (https://www.regjeringen.no/no/dokumenter/pa-ramme-alvor/id2460080/). Vi finner at SpaceOAR™ er mer kostnadskrevende (inkrementelle kostnader: 15 330 NOK) og gir litt mer helse (inkrementelle effekter: 0,008 QALYs) enn strålebehandling alene. Det resulterende inkrementelle kostnadseffektivitetsratioen (ICER) er 2 006 985 NOK /QALY. Merk at den høye ICERen i dette tilfellet er et resultat av den svært beskjedne helsegevinsten oppnådd med intervensjonen. Resultatene av sensitivitetsanalyse illustrerte at prisen på nedbrytbar beskytter, livskvalitetsvektene og effekten av intervensjonen hadde størst innvirkning på resultatene. Den probabilistiske sensitivitetsanalysen viser at helsegevinsten ved intervensjonen er svært usikker, kun 59% av simuleringene resulterer i en netto helsegevinst målt i QALYs. Det er imidlertid 100% sikkerhet for at avstandsstykket vil øke kostnadene. Forutsatt en alvorlighetsjustert terskel som anbefalt av Magnussen-gruppen (https://www.regjeringen.no/no/dokumenter/pa-ramme-alvor/id2460080/

), er det 6% sannsynlig at SpaceOAR™ er et kostnadseffektivt behandlingsalternativ. Budsjettkonsekvensanalysen indikerte at adopsjon av nedbrytbar beskytter ville øke kostnadene med cirka 15 millioner kroner per år.

Diskusjon

EUnetHTAs relative effektivitetsvurdering inkluderte to studier: en RCT på SpaceOAR ™ med tilleggsstudier (3–6) og en ikke-RCT (7). Dataene fra ikke-RCT ble ikke innlemmet i kostnadseffektivitetsanalysen på grunn av rapportert svært lav kvalitet på dokumentasjonen.

Videre forskning kan endre konklusjonen i denne analysen. Spesielt er dokumentasjonen på den kliniske effekten av SpaceOAR™ usikker, og kostnadseffektivitetsanalysen bør oppdateres hvis eller når mer dokumentasjon blir tilgjengelig. I tillegg vil kostnadseffektivitetsanalysen ha nytte av flere studier av sykdommens naturlige forløp og prognose, eksempelvis studier på varigheten av strålingsindusert toksisitet, forekomsten av slike toksisiteter og prosentandelen pasienter som vil oppleve en spontan forbedring av symptomene.

Basert på dagens kunnskapsgrunnlag, virker det lite sannsynlig at SpaceOAR™ vil bli prioritert for opptak på rutinemessig offentlig finansiering. Analysen må oppdateres når nye data blir tilgjengelige, og konklusjonen kan da endre seg.

Konklusjon

Vi har i denne rapporten vurdert i hvilken grad nedbrytbar beskytter oppfyller de norske prioriteringskriteriene (helsegevinst, ressursbruk og sykdoms alvorlighetsgrad).

Det estimerte absolutte prognosetapet er 1,85 QALY, hvilket plasserer sykdommen i den lavest prioriterte gruppen etter tilnærmingen foreslått av Magnussenutvalget (https://www.regjeringen.no/no/dokumenter/pa-ramme-alvor/id2460080/). Helsegevinsten ved intervensjonen er liten (0,008 QALYs) og veldig usikker.

Preface

The Division for Health Services in the Norwegian Institute of Public Health was commissioned by the National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway to conduct a health technology assessment of hydrogel rectal spacer SpaceOAR™ together with prostate cancer radiation therapy compared to the radiation therapy alone.

The efficacy and safety of the intervention is addressed in a EUnetHTA report published in July 2020 (1). The aim of this health economic evaluation was to assess the cost-effectiveness of hydrogel rectal spacer SpaceOAR™ in adjunct to the radiation therapy compared to the radiotherapy alone for patients with prostate cancer.

The project group consisted of:
Kateryna Porkhun (M.Phil., Health economist)
Gunhild Hagen (M.Phil., PhD, Researcher Health Economics)

Clinical experts:
Karol Axcrona (MD, PhD, Senior consultant in urology at Akerhus University Hospital)
Wolfgang Lilleby (MD, PhD, Senior consultant in oncology at Oslo University Hospital)

The study has used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

Norwegian Institute of Public Health assumes final responsibility for the content of this report. The aim of this report is to support well-informed decisions in health care that lead to improved quality of services. The evidence should be considered together with other relevant issues, such as clinical experience and patient preference.

LOGG	
Suggestion submitted for STA	15.05.2018
STA report commissioned	27.08.2018
Commissioning changed to an MTA	27.01.2020
Clinical experts contacted first time	15.04.2020
Report sent to internal reviewer	09.11.2020
Report sent to New Methods	28.01.2021
Number of days from STA commission to MTA project start	622
Number of days from MTA commission to delivery	367

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Introduction

In this report we evaluate the degree to which hydrogel rectal spacer SpaceOAR™ used in combination with radiation therapy meets the Norwegian priority setting criteria (health benefits, resource use and disease severity).

Introduction to disease and treatment

Prostate cancer is the most diagnosed cancer in men in Norway with approximately 5,000 new cases diagnosed each year and over 54,000 men living with disease (8). Improved diagnostics and treatment options have contributed to a slight decline in prostate cancer mortality. Treatment options depend on the risk classification assigned by the clinician based on the pathological and clinical results of the PSA level, Gleason score and the tumour node metastasis (TNM) classification. Risk classification details are described in the Prostate cancer annual report (8).

Radiation therapy is one of the main treatment options for prostate cancer patients. It destroys cancer cells with high-energy x-rays or other particles. When radiation therapy is delivered internally (also called brachytherapy) radioactive material is placed into the cancer or surrounding tissues either permanently or temporarily. External-beam radiation therapy, the most common type of radiation therapy, delivers radiation from the machine (linear accelerator) located outside of the body.

Delivering higher doses of radiation is associated with better disease control, but can cause radiation damage to the adjacent organs, such as rectum, urinary bladder, and blood vessels involved in penile erection. Common side effects of the prostate cancer radiation therapy are gastrointestinal and genitourinary toxicities, which can give the following symptoms: rectal bleeding, hematuria, dysuria, radiation cystitis, urinary and/or bowel obstruction, diarrhoea, fistula formation, rectal and urinary leakage and erectile dysfunction.

To ensure safer treatment and promote better quality of life, several biodegradable rectum spacers were developed. Insertion of biodegradable rectum spacer into the perirectal space (space between the prostate and the rectum) increases the distance between the rectum and the prostate, in an attempt to reduce irradiation of the rectum and thereby lower the risk of side effects.

The efficacy and safety of SpaceOAR™ has been investigated through a randomised controlled trial (RCT) by Mariados and colleagues (3). In addition, several companion studies (4–6,9) have been published. EUnetHTA has recently published an assessment of the current evidence base for rectal spacers, one of which is SpaceOAR™, manufactured by Boston Scientific (1). This health economic evaluation is based on the efficacy and safety estimates in the EUnetHTA report . Should new evidence become available, this health economic evaluation would need to be updated.

Priority setting criteria

There are three primary criteria for setting priorities in the Norwegian health care sector: the benefit criterion, the resource criterion, and the severity criterion (2).

Benefit

According to the benefit criterion, priority increases with the size of the expected benefit of the intervention. The benefit criterion primarily refers to a technology's expected health effects: increased longevity and/or improved health-related quality of life. By combining these two types of health gains into a single outcome measure, the quality-adjusted life-year (QALY), it is possible to compare treatment outcomes across different diseases, patient groups and types of treatments.

Resources

According to the resource criterion, priority increases, as fewer resources are needed for the intervention.

The resource criterion focuses on how the health sector uses its limited resources. Introducing a new technology creates demands for personnel, equipment, facilities, etc. that could be used to provide treatments for other patients – a reality that is referred to as the "opportunity cost" of the new technology. The larger the quantity of resources allocated to a technology for one patient group, the fewer the resources available for treating others.

In addition to resource use within the health sector, a technology may also engender costs for other parties.

Severity of Disease

According to the severity criterion, priority increases with expected future health loss resulting from the disease. Severity of disease is measured as "absolute shortfall", defined as the expected loss of future health (QALYs) associated with a specified diagnosis. For treatment of a diagnosed disease, severity is the average expected absolute shortfall for the relevant patient group given the current standard treatment. Generally, the greater the absolute shortfall associated with a disease, the more resources per QALY gained the authorities may be willing to allocate.

Cost-effectiveness

In practice, the three priority setting criteria are taken into account by weighing costs against benefits in a cost-effectiveness analysis of the technology of interest. Resource use, measured in monetary terms, enters into the numerator of the cost-effectiveness ratio (see further description below), while the health effect enters in the denominator.

Norwegian policy documents indicate that weighting of resource use against health benefits should be based on the opportunity cost principle, and that priority should be further increased according to disease severity (absolute shortfall).

Introduction to Economic Evaluation of Health Care Programmes

The aim of a health economic evaluation is to compare the health effects and costs of the alternatives under consideration in an incremental analysis — one in which the differences in health effects are compared with differences in costs. Results of economic evaluations can be expressed as an incremental cost-effectiveness ratio (ICER), which is defined by the following equation:

$$ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}.$$

The health care sector, as the society in general, is restricted by limited resources and budget constraints. Therefore, economic evaluations are important tools for decision makers facing questions about how to prioritize treatments and maximize health benefits,

given resource scarcity. For an economic evaluation to be meaningful in a decision-making process, the ICER must be judged relative to a threshold value for cost-effectiveness, which is the willingness-to-pay threshold (WTP) λ. The threshold value for cost-effectiveness should reflect the opportunity cost of resources in health sector, which is the maximum willingness-to-pay for an extra QALY. The decision rule for an economic evaluation can therefore be expressed as:

$$\frac{\Delta C}{\Delta E} < \lambda ,$$

where λ equals the threshold value (opportunity cost) and indicates that if the ICER of an intervention is below the ceiling ratio, introducing the intervention represents good value for money. Because the ICER has poor statistical properties, ICERs are often rearranged to express either incremental net monetary benefit (INMB) or incremental net health benefit (INHB), which yields the following decision rules related to INMB or INHB:

INMB: $\lambda \bullet \Delta E - \Delta C > 0$,

INHB: $\Delta E - (\Delta C/\lambda) > 0$.

In other words, an intervention can be considered cost-effective if it yields a positive INHB or INMB.

Economic evaluations are often based on decision models (such as decision trees or Markov models) that calculate results based on various input parameters in the model. Because there are always uncertainties related to the values of these parameters, sensitivity analysis is an important feature of any economic evaluation based on a decision model framework. In short, sensitivity analysis illustrates how much the results vary when model parameters are changed.

Probabilistic sensitivity analysis (PSA) is a type of sensitivity analysis. The advantage of PSA is that it makes it possible to take the uncertainties of all model parameters into account simultaneously. The basic approach in PSA is to assign appropriate probability distributions to the model parameters, which makes it possible to replace the "fixed" values of each parameter with values generated by random draws from the statistical distribution around the mean. Doing this repeatedly, with a specified number of iterations, makes it possible to estimate the probabilities that alternative interventions are cost-effective

subject to different ceiling values of WTP. The calculation is based on the alternative that has the highest values of NMB or NHB. Results from PSAs are often presented as scatter plots, which show point estimates of the ICER for all iterations in the cost-effectiveness plane, and also as cost-effectiveness acceptability curves (CEACs), which show the probability of the alternatives being cost-effective subject to changing values of threshold value.

Review of published economic evaluations of SpaceOAR™

Several studies have evaluated the cost-effectiveness of the hydrogel rectal spacer SpaceOAR™ in comparison to radiation therapy alone (Table 1).

Vanneste and colleagues (10), compare the costs and utilities of intensity modulated radiation therapy with and without spacer in the Netherlands. The analysis applies a five-year time horizon, using a Markov model. They estimate an ICER of €55,880 per QALY gained. In this analysis, costs were discounted by 4% and effects by 1.5%. Assuming a willingness-to-pay threshold of €80,000, the intervention has a probability of 77% of being cost-effective.

In 2018, McGill University Health Centre in Canada preformed a cost-effectiveness and budget impact analysis of SpaceOAR™ as a part of health technology assessment report (11). The costs of treating 70 patients with and without hydrogel rectal spacer were CAD $388,015 and CAD $189,901 respectively (CAD $5,543 vs. CAD $2,712 per patient), costs estimates included costs of device, procedure, and treatment of complications. This resulted in additional costs for hydrogel rectal spacer application of CAD $198,114. The ICER for avoiding one additional case of rectal toxicity grade≥2 was CAD $191,230.

A cost-effectiveness analysis conducted by Levy and colleagues (12) compared the costs and effects of external beam radiation therapy with hydrogel rectal spacer and without hydrogel rectal spacer in the U.S., using a Markov model with a five-year time horizon. Three possible settings were considered: ambulatory surgery centre, physician office and hospital outpatient department. Subgroup analysis was performed for patients having good or bad erectile function at baseline. Data for costs and utilities were taken from the literature and discounted at an annual rate of 3%, while data on toxicity rates and erectile dysfunction were taken from the published RCTs on the hydrogel rectal spacer. Incremental costs were $3,879 and incremental effects were 0.011 QALYs. This resulted in an ICER of $341,068 per QALY for patient, much higher than the assumed willingness-to-pay threshold of $100,000 per QALY.

Table 1: Economic evaluations for the SpaceOAR™.

Study	Year	Time horizon	Perspective	Health effects hydrogel rectal spacer	Health effects of comparator	Δ effects	Costs of hydrogel rectal spacer	Costs of comparator	Δ costs	ICER
(10)	2015	5 years	Provider	3.570	3.542	0.028	€ 3,144	€ 1,604	€ 1,540	€ 55,880
(11)*	2018	15 months	Provider	X	X	X	C$ 388,015	C$ 189,901	C$ 198,114	C$ 191,230
(12)	2019	5 years	Provider	X	X	0.011	X	X	$3,879	$341,068

**Costs of treating 70 patients with or without SpaceOAR™ and ICER is defined as the ratio of the incremental cost to the incremental number of the cases of Grade≥2 rectal toxicity avoided.*

Objective

The objective of this analysis was to assess the cost-effectiveness and budget impact of the hydrogel rectal spacer SpaceOAR™ (Augmenix, Inc., Waltham, MA) in reducing gastrointestinal and genitourinary toxicities for patients undergoing prostate cancer radiation therapy with curative intent in a Norwegian setting.

Methods

Calculation of disease severity

In order to quantify the disease severity, we calculated the absolute shortfall related to radiation induced toxicities based on the guidelines of the Norwegian Medicines Agency (13). The expected loss of future healthy life years resulting from the disease in question, is estimated as the absolute shortfall (AS) as measured in QALYs lost compared to the average number of remaining healthy life years for patients receiving the standard treatment. The formula is as follows:

$$Absolute\ shortfall = QALYs_{age} - P_{age},$$

where $QALYs_{age}$ = number of expected remaining QALYs at the relevant age and P_{age} = number of expected QALYs for a person with the disease in question. P_{age} is an output calculated in the health economic model described below and is fully dependent on all assumptions and data inputs in this model, while $QALYS_{age}$ is estimated based on life expectancy information from Statistics Norway and average age-related quality of life weights, based on the EQ-5D methodology from the two studies of the Swedish population (14,15).

Analytical overview

Population

The patient population consists of 73-year-old males diagnosed with intermediate risk, high-risk localized, and high-risk locally advanced prostate cancer, who will receive primary radiation therapy with curative intent. Patients with low risk and younger patients would usually not be treated with radiation therapy in Norway.

For patients diagnosed in 2017, the median age for patients receiving radiation therapy with curative purpose was 73 years (8). Hydrogel rectal spacer application is considered to be safe for patients with T1 and T2 stages of prostate cancer. If the tumor has advanced

in the opposite direction from the hydrogel rectal spacer insertion, it is possible to use hydrogel rectal spacer for patients with T3 stage disease. Hydrogel rectal spacer would not be used in cases of hydrodissection failure or in the presence of other exclusion criteria: active inflammation, previous treatment with radiation therapy, cryotherapy and high-intensity focused ultrasound, active bleeding disorders, infectious diseases in pelvic area, etc. For patients meeting the exclusion criteria and/or with T3 stage prostate cancer, the decision about hydrogel rectal spacer insertion would typically be left to the clinician's discretion.

Intervention

The intervention is insertion of the hydrogel rectal spacer SpaceOAR™ between Denonvilliers fascia and the anterior rectal wall (prostate and rectum) prior to prostate cancer radiation therapy. The procedure is done once and is often preformed simultaneously to placement of fiducial markers. After successful hydrodissection, liquid hydrogel rectal spacer is injected in the perirectal space, where it creates a 10 - 15 mm thick soft, biodegradable gel. The procedure requires some type of anaesthesia, as determined by the clinician based on characteristics of the individual patient. The mean overall time of the procedure is 16 minutes with SD of 7.8 minutes (16,17). The hydrogel rectal spacer remains stable and solid during the course of the radiation therapy. Eventually it is absorbed and discharged from the body via renal filtration. Absorption occurs approximately 6 months after insertion. After radiation therapy patients follow standard care guidelines.

Comparator

The comparator is standard care for prostate cancer patients receiving radiation therapy with curative intent. Standard care is described in the National action program, which includes guidelines for diagnostics, treatment, and follow-up of the prostate cancer (18) and describes the coordinated treatment path for prostate cancer (19). Prostate cancer radiation therapy in Norway is delivered during 38 sessions with a total dose of 78 Gy. Prior to radiation therapy patients have three ordinary planning meetings with a clinician and one complex planning meeting, where insertion of fiducial markers takes place. After the radiation therapy control follow-up out-patient visits are recommended after three and six months. Continued follow-up visits with the patient's GP begin at the twelfth month after the radiation therapy and repeats every sixth month up to the third year after the end of the treatment and thereafter annually.

Perspective

The current analysis adopts a broad healthcare perspective, which considers health outcomes experienced by the patient, direct medical costs associated with health care provision and patient's out-of-pocket expenses connected with treatment. Direct medical costs include those associated with consultations prior to radiation therapy, the hydrogel rectal spacer and insertion procedure, radiotherapy treatment, out-patient and GP follow-up visits, and potential treatment of gastrointestinal and genitourinary toxicities.

Time horizon

The recommended time horizon for a health-economic analysis is that it is long enough to capture all the future possible differences in terms of both costs and effects (20). This analysis assumes a ten-year time horizon.

Discounting

Both health outcomes and costs are discounted at an annual rate of 4% (13).

Half-cycle correction

Transitions between states in Markov model happen at the beginning or at the end of the cycle, however that might not truly reflect the reality where the true time of transition is unknown and most likely may occur in the middle of the cycle. Thus, depending on the time of transition, estimates for costs or effects might be either over- or underestimated. To avoid this, the half-cycle correction is applied by calculating the mean of the present and previous year.

Software

The current CUA was conducted in Excel 2016. Code for probabilistic sensitivity analysis was written in Visual Basic. Graphs were digitised with the help of WebPlotDigitizer v. 4.3 (https://automeris.io/WebPlotDigitizer/index.html).

Toxicity measurements

Studies investigating the influence of the radiation therapy of prostate on the gastrointestinal and genitourinary toxicities measure the severity of acute (up to 3 months after radiation therapy) and late (beyond 3 months after radiation therapy) toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) (21), or modified Radiation Therapy Oncology Group (RTOG) criteria (22) (see Appendix 1 for a more detailed

interpretation). Briefly, the grades of rectal and genitourinary toxicity can be interpreted as follows:

Grade 0: no symptoms or complications present;
Grade 1: presence of mild symptoms but no intervention required;
Grade 2: moderate symptoms affecting daily activities required intervention;
Grade 3: severe symptoms; intervention is required;
Grade 4: life-threatening condition; urgent intervention is required;
Grade5: death.

Model structure

To compare the cost-effectiveness of the hydrogel rectal spacer SpaceOAR™ combined with standard care to standard care alone we used a combination of a decision tree, to capture different patient groups and clinical pathways; and a Markov model, to reflect the treatments and their effect on results. The decision tree and the Markov model were inspired by consultations with clinical experts and the model from the study by Levy et al. (12).

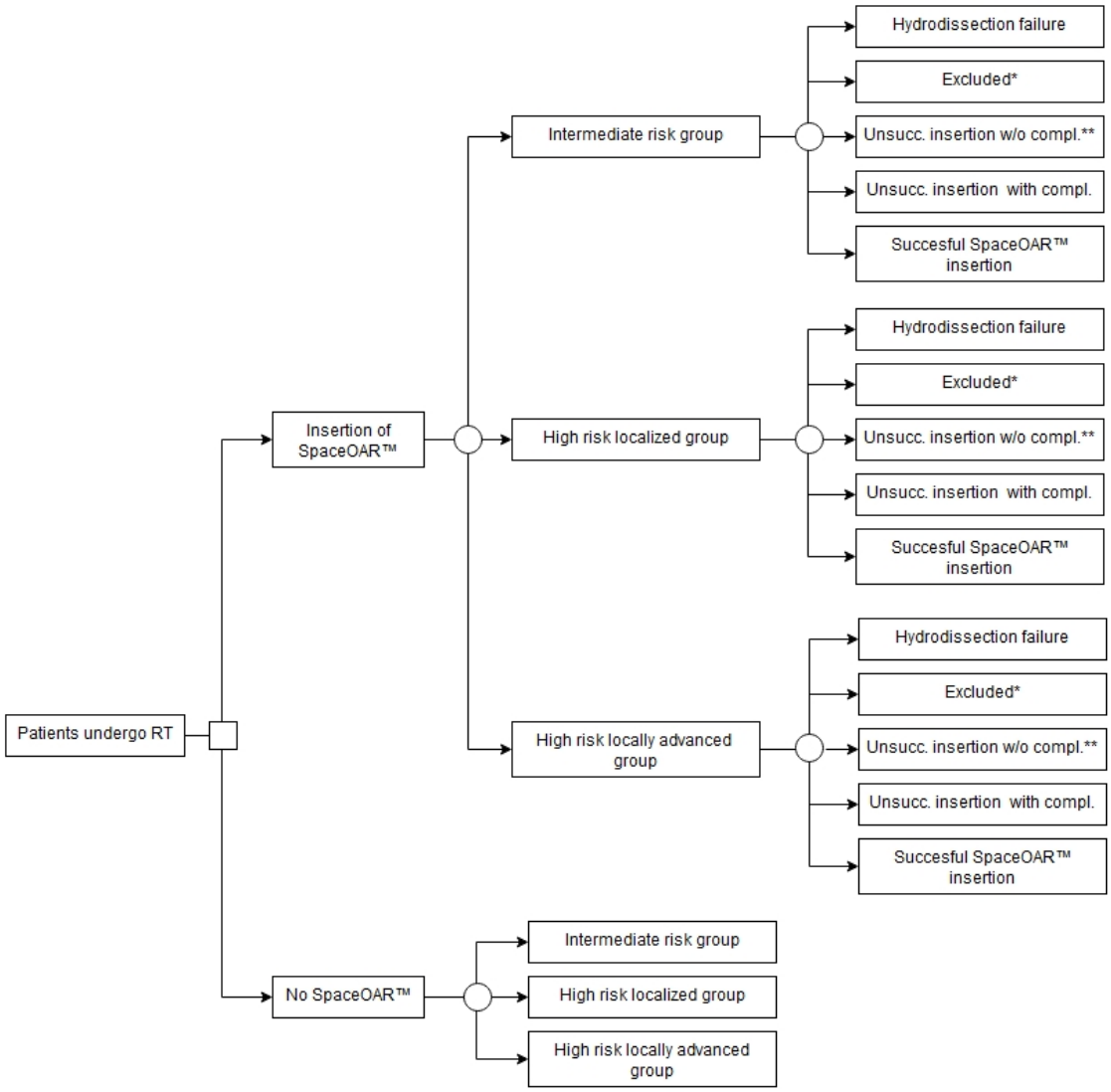
Decision tree

The decision tree is built to capture costs and benefits of two treatment alternatives during the initial phase of treatment, from the allocation to a treatment group to the through the outcome of the spacer insertion procedure. As well the decision tree determines the initial allocation of patients to states in the Markov model.

Figure 1. shows the various pathways in the model. Patients in each treatment group are divided into three risk groups accordingly to the risk classification from the Prostate cancer annual report (8): intermediate risk, high-risk localized, and high-risk locally advanced. This way of the categorizing the overall severity of the prostate cancer is based on the:

- PSA values (prostate specific antigen);
- TNM staging system, which describes stage of tumor (T), if the cancer has spread to the lymph nodes (N)and if the cancer has spread to a different part of the body (M);
- Gleason score, which describes how much the cancer cells look like normal cells.

Figure 1: Decision tree comparing standard care with hydrogel rectal spacer insertion in addition to standard care.



**This group also included patients who were ineligible for anaesthesia.*

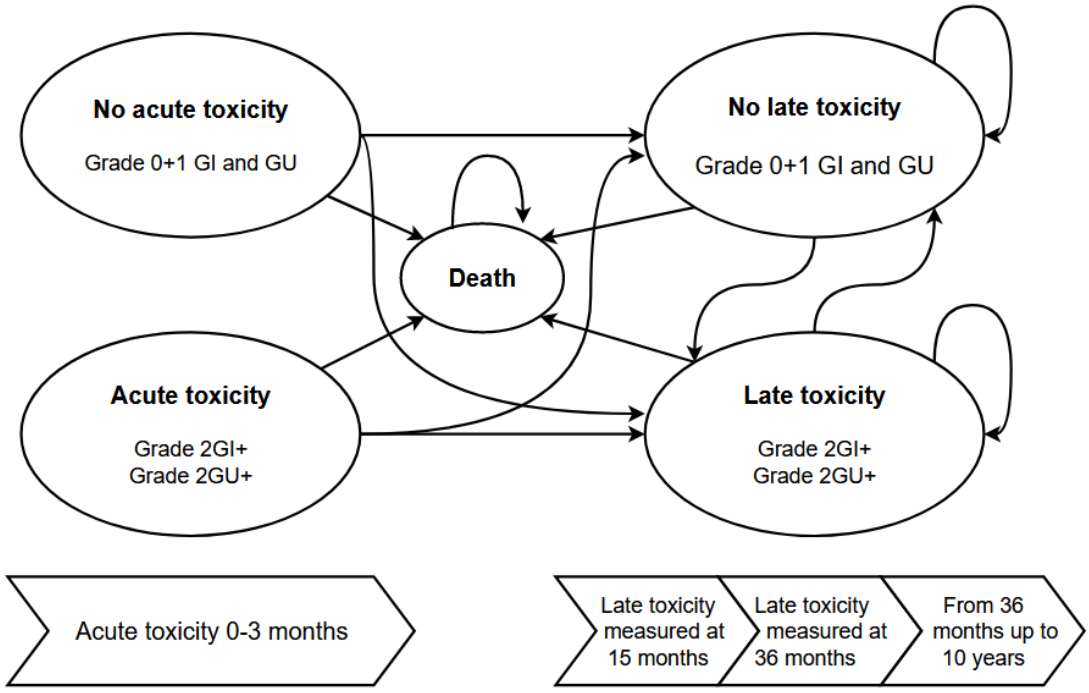
***Inserted hydrogel rectal spacer did not achieve the required thickness and improper polymer reconstruction.*

Patients in the intervention group, are further subdivided into five groups depending on the results of the insertion procedure. Patients may not receive the spacer at all, either because of *hydrodissection failure*, or because of being *excluded* based on the criteria for hydrogel rectal spacer insertion. Of those patients who receive the hydrogel rectal spacer insertion some experience *unsuccessful insertion with complications* (rectal wall or urinary bladder penetration, unpredicted complications, infections), while others experience *unsuccessful insertion without complications* (improper polymer reconstruction, low thickness of the hydrogel rectal spacer). *Successful hydrogel rectal spacer insertion* is achieved among the remaining patients.

Markov model

The Markov part of the model includes five mutually exclusive states, which each reflect a specific health condition that the patient can experience. Cycle length in the Markov model is three months and timeline in the model moves from left to right. The states are as follows: *Acute toxicity*, *No acute toxicity*, *Late toxicity*, *No late toxicity* and *Death*. *Acute toxicity* and *Late toxicity* are overarching states which include gastrointestinal toxicity Grade≥2 (*Grade 2GI+*) and genitourinary toxicity Grade≥2 (*Grade 2GU+*). We decided to treat gastrointestinal and genitourinary toxicities of Grades 0 and 1 as a single group in the health states *No acute toxicity* and *No late toxicity*, to reflect that there are little or no costs and discomfort for patients in these grades. *Death* is defined as an "absorbing state", as the probability of transition to another state is zero.

Figure 2: Markov state transition model. Circles represent states, lines represent transition between states.



Based on the decision tree outcome, patients enter either the *No acute toxicity* state or *Acute toxicity* state of the Markov model and transition through the model following three-month cycles. After the first three months (at the end of the first cycle) all patients transition to *Late toxicity* state, *No late toxicity* state or *Death*. Late toxicities occur usually in the time period from the third month and to the end of the third year after the radiation therapy. To describe this in the model patients from the *No late toxicity* state move to the *Late toxicity* state. Patients in *Late toxicity* can experience the resolution of toxicities and transition to *No late toxicity* state or *Death*.

Depending on the cycle number, the model was populated with relevant data on costs and effects. Patients can be only in one health state during the cycle. Probability of dying depends on the risk group and cycle number. The proportion of patients who experience toxicity in the RCT on SpaceOAR™ was measured at 3, 15 and 36 months. The health economic model assumes the same time points to estimate the proportion of people in each health state as were used in the trial. Relative risks were calculated and applied in the model according to the measurements in the trial.

Key assumptions

To construct a simplified model that captures the important aspects of treatment, we made the following assumptions about model inputs and structure:

- Patients are assigned to a specific risk group based on the data from the Prastate cancer annual report (8) and remain in the same risk group throughout the analysis.
- Patients remain in a single health state each cycle and transition to another health state once per cycle.
- Gastrointestinal and genitourinanry toxicities are modelled together assuming that a person will experience just one of the states. In reality the same person can experience both of them simultaniously.
- Patients, who enter the model, receive curative radiation therapy for prostate cancer as a primary treatment option, but not all patients in the intervention group ultimately receive the spacer.
- Age is not considered to be predictor for either gastrointestinal or genitourinanry toxicity; acute toxicity is however considered to be predictor of late toxicity.
- Acute toxicity effects costs and health for the first cycle, i.e. for the first 3 months.
- Patients with grade 0 or 1 gastrointestinal and genitourinanry toxicity are grouped in the single overarching state *No toxicity*. Patients with grade 2 or 3 gastrointestinal and genitourinary toxicities are included in a state *Grade 2+ GI* and *Grade 2+ GU* accordingly. We assumed that 95% of patients in the merged state would belong to the grade 2 and 5% to the grade 3.
- Effects of late gastrointestinal toxicity on costs and health last for 36 months from onset, later 91% of patients experience resolution of the symptoms (23,24) and transition to the *No late toxicity* state.
- Effects of late genitourinary toxisity on costs and health last for 12 months from onset, lates 81% of patients experience resolution of the symptoms (23) and transition to the *No late toxicity* state.

- Patients who remain in the *Late toxicity* state experience some improvement in symptoms after 36 months and 12 months, respectively, from onset of gastrointestinal and genitourinary toxicity. Symptoms become less bothersome. Therfore impact on quality of life declines and costs associated with these states decrease significantly.
- No new cases of late toxicity occur after 36 months.
- The effect of hydrogel rectal spacer on erectile function was not considered in this analysis, because almost all of the patients receive androgen depriviation therapy (ADT) in addition to the radiation therapy in Norway. ADT has a strong decremental effect on the erectile function.
- The benefit of hydrogel rectal spacer insertion on gastrointestinal and genitourinanry toxicities is possible only with succesful hydrogel rectal spacer insertion.

Model parameters

Probabilities

We performed two analysis: base case analysis and scenario analysis, considering different proportion of patients who would suffer from the adverse events of the radiation therapy. Natural history of disease probabilities for the base case analysis is based on the RCT by Michalski and colleagues (25). Data was extracted from the published figures using WebPlotDigitizer v. 4.3 (https://automeris.io/WebPlotDigitizer/index.html). The assumed proportion of men experiencing radiation induced gastrointestinal and genitourinary toxicities is based on the information from clinical experts. Transition probabilities for the scenario analysis and treatment effects for both models are based on the SpaceOAR™ randomised controlled trial (3,4), included in the EUnetHTA report (1). A Nowegian summary of the EUnetHTa report can be found in Appendix 14. Proportions of patients in each health state were adjusted by the probability of dying according to age and risk group and converted into the 3-months probabilities (Appendices 2 - 5).
Relative risks and standard errors for them were calculated following the instructions described by Briggs and colleagues (26).

Table 2: Probabilities and relative risks.

Parameters	Value	SE	Distribu-tion	Source
RR GI grade 2 +(measured at 3 months)	0.97	0.69	Log normal	(3)
RR GU grade 2 + (measured at 3 months)	0.851	0.169	Log normal	(3)
RR GI grade 2+(measured at 15 months)	0.161	0.108	Log normal	(3)
RR GU grade 2 +(measured at 15 months)	1.599	0.108	Log normal	(3)
RR GI grade 2 +(measured at 36 months)	0.071	1.501	Log normal	(4)
Failure of hydrodissection	0.045		Dirichlet	(27)
Exclusion criteria*	0.075		Dirichlet	(27) and expert opinion
Unsuccessful insertion without complications	0.083		Dirichlet	(28)
Unsuccessful insertion with complications	0.04		Dirichlet	expert opinion
Success insertion of hydrogel rectal spacer	0.85		Dirichlet	
Probability of being in intermediate risk group	0.349		Dirichlet	(8)
Probability of being in high localised risk group	0.373		Dirichlet	(8)
Probability of being in high locally advanced group	0.279		Dirichlet	(8)
Transitional probability of GI resolution	0.91	0.182	Beta**	(23,24)
Transitional probability of GU resolution	0.81	0.162	Beta**	(23)

**Exclusion criteria also includes patients ineligible for anaesthesia, assumed value was based on both literature and expert opinion.*
*** SE assumed to be 20% of the mean value.*

Statistical distributions were assigned to each parameter to capture the uncertainty in the point estimate. Costs were modelled with gamma distributions, relative risks with log-normal, utilities with beta, transition probabilities with Dirichlet or beta.

Mortality parameters

Mortality data for the risk group were provided by the Cancer Registry of Norway (27) (Appendix 6). Patient who received brachytherapy were included in the mortality data but were not modelled separately because of the small number of patients. All-cause mortality values are provided in Appendix 7. Beta distributions were applied to mortality parameters, with an assumed standard error of 20%. Probabilities of dying were adjusted to reflect 3-months cycles.

Utilities

Age-specific utility values measured with the EQ-5D instrument were taken from the study by Burström et al. (14) and Sun et al. (15). We used utility scores from the study by Shimizu et al. (28) to estimate decrements for gastrointestinal and genitourinary toxicities (Table 3).

We assumed that the utility value for unsuccessful insertion with complications equals the mean value of grade 2 genitourinary and grade 2 gastrointestinal toxicity for 73-year-old men. Based on consultation with clinical experts, we assumed that patients who did not experience resolution of their symptoms of grade 2 and higher after 36 months for gastrointestinal toxicities and 12 months for genitourinary toxicity would experience some improvement. These patients were assigned utility values of grade 2 toxicity accordingly to the toxicity type. Additionally, we assumed that for patients in the merged states, 95% had Grade 2 and 5% had Grade 3 toxicity. Beta distributions were assigned to all utility parameters, with an assumed standard error of 20% of the mean value. Age-dependant utility values are presented in the Appendix 8.

Table 3: Utility scores from the study by Shimizu et al.(28).

Covariates	Utility score
Bowel problem	
Grade 0+1 GI	0.94
Grade 2 GI	0.91
Grade 3 GI	0.84
Urinary function	
Grade 0+1 GU	0.94
Grade 2 GU	0.88
Grade 3 GU	0.84

Costs

Costs were estimated on the basis of the reviewed studies (11,29), Norwegian treatment guidelines for prostate cancer (18,19), and information from clinical experts.

Out-patient costs were calculated based on Norwegian DRG codes for somatic diseases, the unit price of a DRG in 2020 was 45,808 NOK (30). Costs of visits to a general practitioner (GP) and anaesthesiologist were estimated based on the relevant tariffs from the Norwegian Medical Association (NMA) (31,32). Price of hydrogel rectal spacer and costs associated with insertion procedure are presented in Table 4. The hydrogel rectal spacer insertion procedure does not currently have an assigned DRG weight but, based on information from clinical experts, we assumed that hydrogel rectal spacer would be similar to DRG code 912A. Costs of procedure related health states are presented in Table 5, while costs connected to health states are presented in Table 6, additional details can be found in Appendix 9-12.

Table 4: Cost of hydrogel rectal spacer insertion, NOK.

Cost components:	DRG code*/ Tariff**	DRG weight/Fee, NOK	Cost, NOK	Standard error*	Distribu-tion	Source
Price of hydrogel rectal spacer	X	X	16,000	4,800	Gamma	Estimated price from the distributor incl. VAT
Cost of procedure	912O*	0.033	1,512	453	Gamma	Expert opinion
Cost of anaesthesia	151aX2**+3abX2**	600X2+351X2	1,902	571	Gamma	Expert opinion
Cost of hydrogel rectal spacer insertion			**19,414**			

*(30).

**(32).

Table 5: Costs of states connected to the hydrogel rectal spacer insertion, NOK.

States	DRG code/Tariff*/Price, NOK	DRG weight/Fee, NOK**/Price, NOK	Cost, NOK	Standard error***	Distribution	Source
Failure of hydrodissection (cost of anaesthesia and procedure)	912O+151aX2* +3abX2*	0.033/600X2* +351X2*	3,414	1,024	Gamma	Expert opinion
Excluded* (no procedure costs, no spacer costs, no effects)	X	X	X		Gamma	Expert opinion
Unsuccessful insertion without complications**	912O+151aX2* +3abX2*+16,000	0.033/600X2* +351X2*/16,000	19,414	5,824	Gamma	Expert opinion
Unsuccessful insertion with complications	912OX2+151aX2* +3abX2*+16,000	0.033/600X2* +351X2*/16,000	20,925	6,278	Gamma	Expert opinion
Successful insertion	912O+151aX2* +3abX2*+16,000	0.033/600X2* +351X2*/16,000	19,414	5,824	Gamma	Expert opinion

*(31,32).

***Patients excluded due to exclusion criteria for hydrogel rectal spacer insertion or did not receive clearance for anaesthesia.*

**** Standard error assumed to be 30% of mean.*

Table 6: Cost estimates for health states with prices for 2020, NOK.

Cost parameters for health states	Cost per year	Cost per cycle	Standard error*	Distribu-tion
Acute gastrointestinal toxicity Grade 2+**	2,994	2,994	898	Gamma
Acute genitourinary Grade 2+**	4,587	4,587	1,376	Gamma
Acute gastrointestinal and genitourinary Grade 0+1	1,512	1,512	453	Gamma
Late gastrointestinal and genitourinary Grade 0+1, year 1	1,832	458	137	Gamma
Late gastrointestinal and genitourinary Grade 0+1, year 2	640	160	48	Gamma
Late gastrointestinal and genitourinary Grade 0+1, year 3	640	160	48	Gamma
Late gastrointestinal and genitourinary Grade 0+1, from year 3	320	80	24	Gamma
Late genitourinary Grade 2+, year 1**	6,417	1,604	481	Gamma
Late genitourinary Grade 2+, from year 1**	396	99	30	Gamma
Late gastrointestinal Grade 2+, year 1**	8,027	2,007	602	Gamma
Late gastrointestinal Grade 2+, year 2**	6,836	1,709	513	Gamma
Late gastrointestinal Grade 2+, year 3**	6,836	1,709	513	Gamma
Late gastrointestinal Grade 2+, from year 3**	422	105	32	Gamma

** Standard error is 30%.*

***Costs were estimated assuming that only 5% of patients had grade 3 toxicity.*

Sensitivity analyses

Tornado diagram

Deterministic sensitivity analysis captures changes in the model outcomes resulting from changes in one or several input parameters. One-way sensitivity analysis measures how sensitive an outcome is to changes in the input parameters. Selected parameters are changed manually within the pre-set plausible maximum and minimum. A tornado diagram combines several one-way sensitivity analyses and arranges them according to their influence on incremental net monetary benefit.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis captures the combined uncertainty of all parameters within the model and can be used to estimate the probability that an intervention is cost-effective at different willingness-to-pay threshold values. We conducted the analysis using a Monte Carlo simulation, in which each parameter in the model is assigned a probability distribution that captures the range of values the parameter may potentially take. Each

time the model is run, a value for every model parameter is randomly drawn from its probability distribution and used to estimate the model outcome values. We performed 10,000 runs of the model to quantify the decision uncertainty. The results are reported as a scatterplot, in the cost-effectiveness plane, of the 10,000 outcomes for incremental costs and incremental effects. In addition, results are presented as cost-effectiveness acceptability curves (CEAC), which indicate the probability of treatment alternative being cost-effective at the given level of WTP threshold. Cost-effectiveness acceptability curves are derived by varying the threshold value, i.e. the slope of the threshold line, in the cost-effectiveness plane and determining the proportion of outcomes that would be considered cost-effective at each threshold value.

Budget impact

Budget impact analysis assesses the financial consequences of adopting a new health intervention at the aggregate population level by comparing total incremental costs of introducing the intervention relative to current practice. The analysis was conducted according to the recommendations from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (33).

Results

Estimated disease severity

We analysed 73-year-old men, the median age for radiation therapy (8). $QALYs_{age\ 73}$ was calculated on the base on Norwegian lifetables and health related quality of life information from a Swedish population (14,15). At age 73 years, the quality adjusted life expectancy was 10.85 QALYs. The prognosis with the disease for the standard treatment patients was 9.62 QALYs for the base case analysis.

$Absolute\ shortfall_{base\ case} = 10.85 - 9.62 = 1.85$ QALYs.

According to the approach suggested by Magnussen and Norheim, incorporated into the White Paper on priority setting in Norway (2), threshold values for cost-effectiveness should be adjusted relative to the estimated severity of the disease.

Results of cost-effectiveness analyses

Results from the deterministic cost-effectiveness analyses for the base-case and scenario analyses are summarised in Table 7. The figures reflect total treatment costs and QALYs gained for treatment with the intervention compared to the standard care. The analysis included half-cycle correction and discount at a rate of 4% for all results.

Table 7: Expected total costs and effects for the alternative interventions for base case and scenario analyses.

Type of analysis	Intervention	Costs (NOK)	Incremental Costs (NOK)	Effects (QALY)	Incremental Effect (QALY)	ICER (NOK/QALY)
Base case analysis	Standard care	115,423		5.793		
	Standard care + hydrogel rectal spacer	130,753	15,330	5.801	0.008	2,006,985
Scenario analysis	Standard care	114,503		5.449		
	Standard care + hydrogel rectal spacer	130,843	16,339	5.453	0.004	4,136,716

In base case analysis standard care with hydrogel rectal spacer had an ICER of 2,006,985 NOK per QALY gained, indicating that adopting hydrogel rectal spacer resulted in additional expenses of approximately 2,006,985 NOK per QALY gained. Note that it is the very low QALY gain that drives the high ICER in this case. The ICER for the scenario analysis was 4,136,716 NOK per QALY gained. Incremental net monetary benefit for the base case analysis was -13,230 NOK at an assumed threshold value of 275,000 NOK/QALY.

Sensitivity analyses

One-way sensitivity analysis

We performed one-way sensitivity analysis on each uncertain variable in the base case model. Variables with the greatest impact on results are summarised in a tornado diagram, Figure 3. The complete analysis is available in Appendix 13. Each parameter is represented by a horizontal bar that illustrates uncertainty in the incremental net monetary benefit associated with uncertainty in the parameter of interest.

The one-way sensitivity analysis revealed six key parameters that had a large influence on incremental net monetary benefit: price of hydrogel rectal spacer, utilities for no late toxicity at age 75, utilities for GI toxicity grade 2+ at the age 75, utilities for GI toxicity grade 2+ at the age 74, relative risk measured at 36 month of having GI toxicity grade 2+, utilities for having no toxicity at the age of 74 and 73. Results indicate that the highest uncertainty in the model is associated with price of the hydrogel rectal spacer and utility values. Although the incremental net monetary benefit is in fact sensitive to changes in these parameters, none of these changes alter the conclusion about the cost-effectiveness of hydrogel rectal spacer.

One-way sensitivity analysis for the price of the hydrogel rectal spacer is illustrated in Figure 4, where it is assumed that the price would vary from 16,000 to 0 NOK. This analysis shows that hydrogel rectal spacer can become cost-effective, if heavily discounted.

Figure 3: Tornado diagram representing the results of the one-way sensitivity analyses for different parameters.

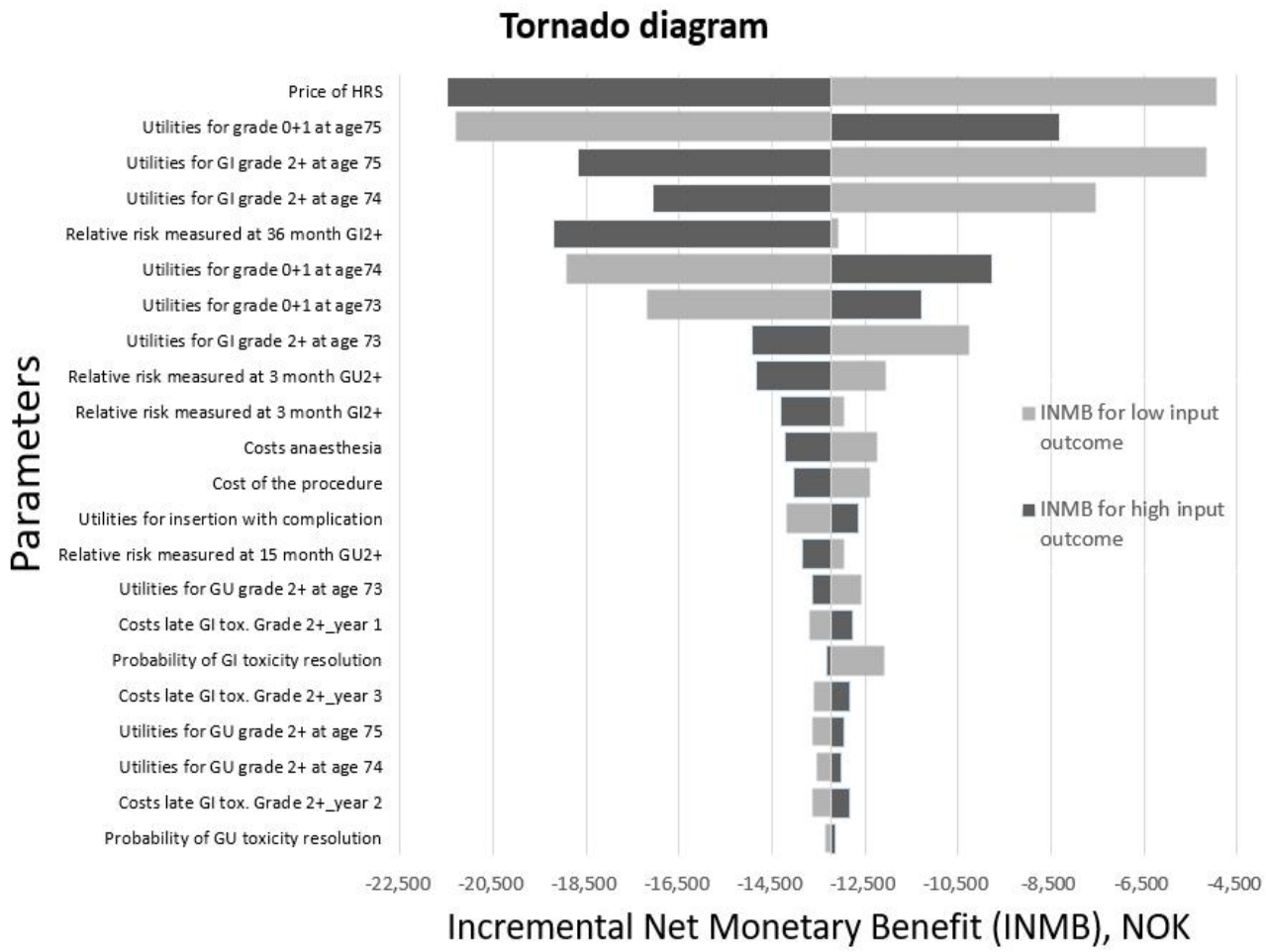
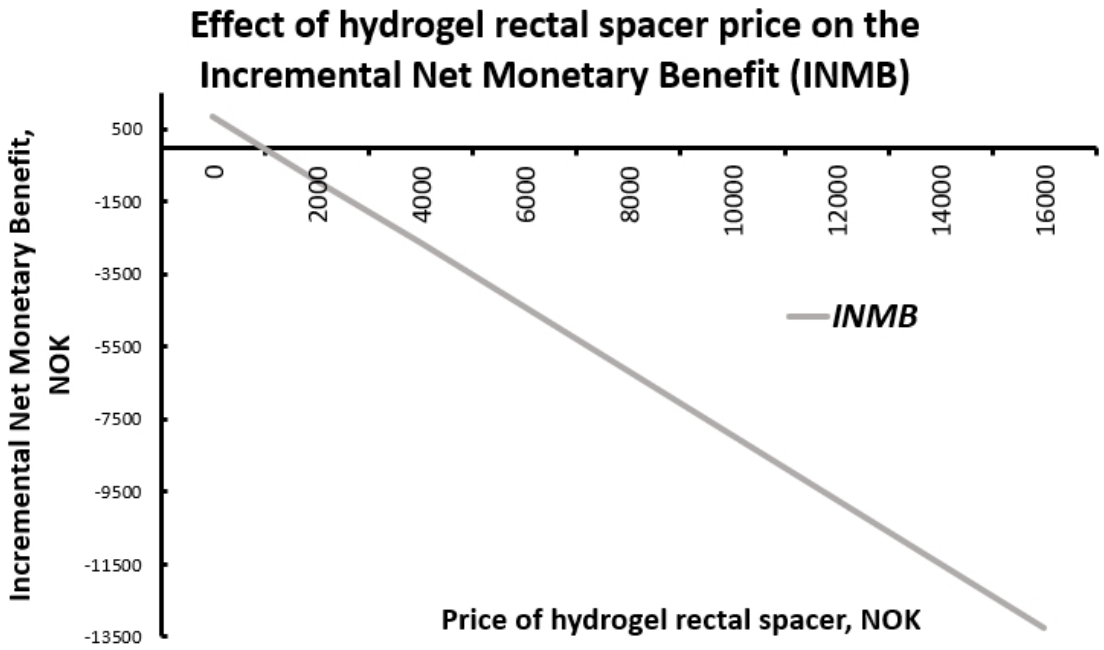


Figure 4: Effect of hydrogel rectal spacer price on incremental net monetary benefit.



Probabilistic sensitivity analysis

The cost-effectiveness plane for the base case analysis illustrates 10,000 Monte Carlo simulations of the ICER, the WTP threshold of 275,000 NOK per QALY (red line) and the deterministic ICER for the base case model. The ICERs on the cost-effectiveness plane are distributed across two quadrants, with majority of ICERs in the north-east quadrant, meaning that the intervention is both more effective and more costly than the comparator. The plane also shows that the expected health gain from hydrogel rectal spacer is very small and also very uncertain, in this simulation only 59% of simulations indicate that hydrogel rectal spacer will result in a net health gain, i.e. there is a 41% likelihood that hydrogel rectal spacer will, in fact, be harmful. The cost part of the equation has a high degree of certainty, with 100% of simulations indicating a net cost increase with adoption of hydrogel rectal spacer.

Figure 5: Cost-effectivenes plane for hydrogel rectal spacer SpaceOAR™ compared to standard care.

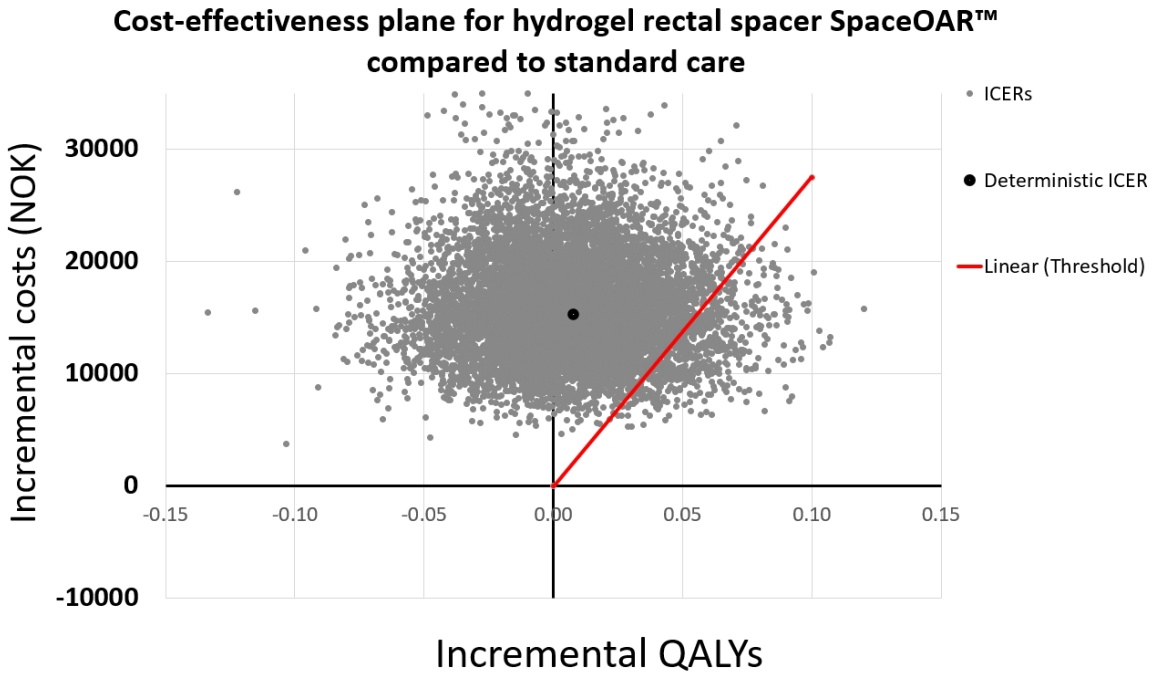
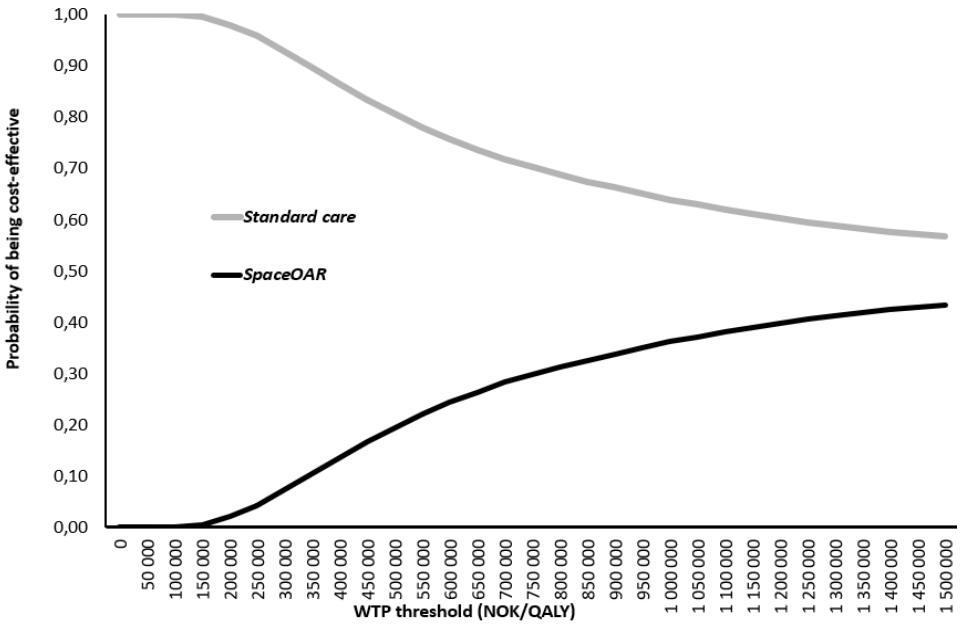


Figure 6: ***Cost-effectivenes acceptability curve for hydrogel rectal spacer SpaceOAR™ with standard care versus standard care alone.***



Cost-effectiveness acceptability curve

The results of the probabilistic sensitivity analysis are used in the net monetary benefit analysis and plotted on the cost-effectiveness acceptability curve (CEAC) to illustrate the likelihood of the intervention being cost-effective compared to standard care alone at a given WTP threshold value. CEAC results from the joint density of the incremental costs and incremental effects represented on the cost-effectiveness plane. At WTP threshold of

0 NOK/QALY gained probability of intervention of being cost-effective is 0. Increasing the threshold level increases the likelihood that the intervention will be cost-effective, reaching a maximum of 59%.

Budget impact

To assess financial consequences, affordability of the decision and secure effective resource allocation, budget impact analysis (BIA) was performed. BIA was carried out for the base case analysis over a five-year perspective. Increase in patient population was based on the prognosis of the future prostate cancer incidence by Johannesen T.B. from the Cancer Registry of Norway (34). The total number of patients were extracted from the published figure using WebPlotDigitizer v. 4.3 (https://automeris.io/WebPlotDigitizer/index.html). Assumptions about the proportion of patients who will receive radiation therapy were based on the Prostate cancer annual report (8) and was 20%. Proportion of patients who will get hydrogel rectal spacer insertion is based on assumptions for the model stated in the section on Probabilities and expert opinion on the proportion of patients with T3 stage who can be inserted with hydrogel rectal spacer. It was assumed that hydrogel rectal spacer can be injected in around 50% of T3 stage patients. Table 8 illustrates the expected number of patients.

The undiscounted costs detailed in the presentation of costs in the Methods section were used for the BIA and included direct medical costs of the prostate cancer radiation therapy, follow-up, price of hydrogel rectal spacer and insertion procedure, and treatment of gastrointestinal and genitourinary toxicities. The insertion procedure is assumed to be performed at the same time as the placement of fiducial markers and requires an extra anaesthesiologist in addition to one nurse and one clinician. The procedure does not require any additional equipment, but increases the total procedure duration by approximately 15-20 minutes for the clinician and nurse. An anaesthesiologist also would be needed for the procedure. To have an approximate estimate of these costs DRG code 912A from the "Innsatsstyrt finansiering 2020" (30) was used for the insertion of hydrogel rectal spacer. For anaesthesia we used tariff 151a and 3ab from the "Normaltariff for avtalespesialister 2019-2020"(32). Costs for educating clinicians were not included for as the producer provides educational services without charge.

The budget impact was calculated as the difference between costs of the intervention (standard care with hydrogel rectal spacer) and standard care alone, based on assump-

tions about the number of patients expected to be eligible for the new intervention. Results, presented in the Table 9, illustrate that including the intervention as a potential treatment in the Norwegian health care system would cost from 14.6 to 15 million NOK extra per year compared to the cost of current standard care. Costs of the toxicity's treatment were lower in the intervention group and costs of hydrogel rectal spacer and insertion procedure plays a major role in overall exceeding costs of intervention.

Table 8: Number of patients expected to be treated over the next five-year period if the hydrogel rectal spacer SpaceOAR™ is granted pre-approved reimbursement.

Years	Approximate number of patients expected to get PC	Approximate number of patients expected to get curative RT	Approximate number of patients expected to get SpaceOAR™
2021	5,920	1,184	781
2022	6,050	1,210	799
2023	6,190	1,238	817
2024	6,320	1,264	834
2025	6,465	1,293	853

Table 9: Budget impact analysis.

Treatment option	Costs (NOK) Year 1 n*=781	Year 2 n*=799	Year 3 n*=817	Year 4 n*=834	Year 5 n*=853
Standard Care with hydrogel rectal spacer					
Costs of RT and hydrogel rectal spacer	97,637,583	99,887,873	102,138,164	104,263,437	106,638,744
Costs of toxicities	3,020,857	3,932,850	4,951,579	5,497,029	5,897,012
Total	100,658,440	103,820,723	107,089,742	109,760,466	112,535,756
Standard Care alone					
Costs of RT	82,428,015	84,327,764	86,227,513	88,021,721	90,027,012
Costs of toxicities	3,254,901	4,561,539	6,159,079,00	7,177,839,00	7,874,413
Total	85,682,915	88,889,303	92,386,592	95,199,560	97,901,425
Expected additional costs	14,975,525	14,931,420	14,703,150	14,560,906	14,634,331

**Approximate number of patients expected to get hydrogel rectal spacer insertion estimated from publication by Johannesen T.B.*(34) *and Prostate cancer annual report* (8).

Discussion

Key findings

Based on the current evidence, SpaceOAR™ is unlikely to be a cost-effective in reducing radiation induced adverse events.

The health economic evaluation was designed specifically for the Norwegian context. We considered that a 10-year perspective was sufficient to capture all relevant differences between the treatment alternatives. According to the healthcare perspective, costs incurred outside of the health care system and costs related to productivity loses were not included.

The total costs and QALYs per person for standard care in the base case analysis were 115,422 NOK/5.7932 QALY versus 130,752 NOK/5.8008 QALY for standard care with hydrogel rectal spacer, which resulted in 15,330 NOK for incremental costs and 0.00764 for incremental QALYs. The estimated ICER was 2,006,985 NOK/QALY Note that the very high ICER reflects the very small estimated health gain associated with hydrogel rectal spacer based on current estimates of hydrogel rectal spacer efficacy in preventing radiation induced harm. If hydrogel rectal spacer is shown to be more efficacious in future trials or costs associated with the intervention declined, the cost-effectiveness would improve.

Uncertainty associated with the model was addressed by performing one-way sensitivity analysis and probabilistic sensitivity analysis. The one-way sensitivity analysis revealed that the model was most sensitive to changes in utility values, some relative risk values and the price of the hydrogel rectal spacer. The results of PSA support the conclusion that standard care is the preferred option at the WTP threshold of 275,000 NOK/QALY. CEAC illustrates that at the given WTP threshold standard care alone had 94% of being cost effective. The results of the budget impact analysis suggest that the financial consequences

for the National Insurance Scheme with additional costs in the case of adoption of hydrogel rectal spacer would vary from 14.6 to 15 million NOK.

For the base case analysis, we chose to use data on toxicities from the NRG Oncology RTOG 0126 Randomized Clinical Trial (25) to inform the natural history parameters, and the multicentre randomized controlled trial on SpaceOAR™ (3,4) to inform efficacy parameters.

Because the incidence of adverse events after prostate irradiation is generally quite low we chose to use toxicity data from the study with the larger population (25). This choice was supported by our clinical expert and several other studies (35–38). To investigate the impact of uncertainty associated with toxicity rates on our results, we conducted a scenario analysis using data taken solely from the randomized controlled trial of SpaceOAR™. The results of both analyses support the conclusion that hydrogel rectal spacer SpaceOAR™ is unlikely to be cost-effective, even assuming rates of radiation induced adverse events that are higher than those in the SpaceOAR™ trial.

Future research is needed on the safety and clinical effectiveness of the hydrogel rectal spacer in larger population groups. For the purposes of future cost-effectiveness analyses, further research on the duration of toxicities and proportion of people who would experience resolution of their symptoms would also be useful.

Comparison to published economic evaluations

We identified several studies investigating different health economic aspects of hydrogel rectal spacer, however, only two of these were health economic evaluations comparing both costs and QALYs of the intervention (Table 10).

Table 10. Published economic evaluations hydrogel rectal spacer.

Study	Time horison	Health effects of hydrogel rectal spacer	Health effects comparator	Δ effects	Costs of hydrogel rectal spacer	Costs of comparator	Δ costs	ICER
Vaneste et al. (10)	5 years	3.570	3.542	0.028	€ 3,144	€ 1,604	€ 1,540	€ 55,880
Levy et al. (12)	5 years	X	X	0.011	X	X	$3,879	$341,068

Like our analysis, these studies find hydrogel rectal spacer to generate health gains and increase costs. Both studies find health gains that are larger than the gains estimated in our analysis, 0.028 and 0.011 as compared to 0.008, but estimates by Levy and colleagues are reasonably similar to our own considering differences in model structures and choice of input. Vanneste and colleagues conclude that hydrogel rectal spacer is cost-effective, while both Levy and our study indicated that it is unlikely that SpaceOAR™ can be considered a cost-effective treatment alternative.

Several factors contribute to the diverging QALY gains and conclusions in our study from the study by Vanneste et al. (10). One important factor is differences in the choice of data for the baseline rate of events and the estimate of clinical efficacy, resulting in different transition probabilities. Another factor is diverging assumptions about the severity of toxicities, while Vanneste et al. (10) assumes that 25% of severe late rectal toxicity would be grade 3, we assumed only 5%. Since Vanneste assumes a poorer prognosis, the benefit of prevention is larger in the Vanneste study than in ours. The two studies also chose utility values from different sources. Additionally, in the Vanneste study utility values were not adjusted for age, possibly contributing to higher utility values in their study than in ours.

The study by Levy and colleagues (12) reports QALY gains that are more similar to our results (0.011 vs 0.008) than the Vanneste results. Their estimated costs are also not very different from ours. Levy et al. (12) bases the effect of the intervention on the SpaceOAR™ RCT, as do we, but Levy has chosen different sources for the utility estimates. Like the Vanneste study, Levy does not adjust QALY weights for age. Levy uses a weight of 0.63 for GI toxicity, 0.83 for GU toxicity and 0.81 for the remission, whereas we have assumed higher weights for GI toxicities (from 0.77 to 0.70 QALYs) and lower for GU toxicities (from 0.75 to 0.67 QALYs).

Strengths and weaknesses of the health economic evaluation

Our analysis has several limitations related to model assumptions, structure and uncertainty in input parameters.

Due to the narrow inclusion criteria reported in the published literature, small sample size and a small number of trials in addition to the evidence of the "low" or "very low" certainty EUnetHTA report indicated that the future research is likely to change the efficacy estimates, and thus also estimates of cost-effectiveness. The efficacy documentation for SpaceOAR™ was graded as "low quality" in the EUnetHTA report, indicating that new research is likely to change the efficacy estimates, and thus also estimates of cost-effectiveness.

Cost parameters used in the model are uncertain, as they were derived by inferring the likely treatments and their associated costs for each of a variety of symptoms associated with gastrointestinal and genitourinary toxicities. In addition, the time from onset of symptoms to resolution for both types of toxicities and the proportion of patients who would experience resolution of the symptoms are also uncertain. However, in addition to consulting with the clinical experts, we identified two studies that, respectively, examined the duration of toxicities and proportion of patients who would have their toxicities resolved (23,39).

We have made some simplifications in our analysis. First, we excluded the potential effects of hydrogel rectal spacer on erectile function, as most of Norwegian patients will undergo androgen deprivation therapy. Erectile dysfunction is a common complication of the androgen deprivation therapy. Additionally, the evidence base for the effect of hydrogel rectal spacer on erectile function was considered to be of very low quality. We also assumed that one person can be in only one health state at a time while, in reality, the same person may experience both toxicities simultaneously. This might potentially change the input utility point estimates for those patients who have both types of toxicities, as the utilities would have been calculated not separately for each health but as for the joint health states. However, based on the reviewed literature it was not possible to define this proportion of patients.

This study estimated the cost effectiveness of hydrogel rectal spacer with two potential rates of radiation induced toxicities. As well it was accounted for the consequences asso-

ciated with the insertion related complications for both costs and effects. Opinions of several clinical experts were accounted for while estimating costs and duration of toxicities, their rates and proportion of patients who would experience resolution.

Conclusion

This report has assessed to what degree the technology meets the Norwegian priority setting criteria (health benefits, resource use and disease severity). The absolute shortfall is 1.85 QALY, placing the disease in the lowest severity group based on the approach suggested by the Magnussen group. The health benefit of the intervention is small (0.008 QALYs) and very uncertain.

Based on current evidence, it seems unlikely that SpaceOAR™ will be considered a high priority technology for adoption in routine public financing. This analysis would need to be updated if or when new evidence becomes available and the conclusions may thus change.

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Appendices

Appendix 1: Comparison of RTOG/EORTC and CTCAE (21,22).

Toxicity type	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			RTOG			
GI	No symptoms or no changes	Mild diarrhoea, mild cramping, bowel movement 5 times daily, slight rectal discharge or bleeding	Moderate diarrhoea or colic, bowel movement > 5 times daily, excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis, perforation, or fistula	Death directly related to radiation effects
GU	No symptoms or no changes	Frequency of urination or nocturia twice pre-treatment habit / dysuria, urgency not requiring medication	Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anaesthetic (e.g. Pyridium)	Frequency with urgency and nocturia hourly or more frequently / dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic / gross haematuria	Haematuria requiring transfusion / acute bladder obstruction not secondary to clot passage, ulceration, or necrosis	Death directly related to radiation effects
			CTCAE			
GI	No symptoms or no changes	Mild Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Minimal, local or non-invasive Intervention indicated; limiting age appropriate daily life activities	Severe or medically significant but not immediately life-threatening Hospitalization indicated; disabling; limiting selfcare and daily life activities	Life-threatening consequences; urgent invasive intervention indicated	Death directly related to radiation effects
GU	No symptoms or no changes	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross haematuria; transfusion, IV medications, or hospitalization indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent invasive intervention indicated	Death directly related to radiation effects

Appendix 2: The proportion of people accordingly to the risk group, adjusted for the probability of dying for the base case analysis (25).

	Base case				Intermediate risk group			
	States				States			
Month	**G1+0**	**GI2+**	**GU2+**	**Death**	**G1+0**	**GI2+**	**GU2+**	**Death**
0	1	X	X	X	1	X	X	X
3	0.76	0.07	0.17	X	0.76	0.07	0.17	X
15	0.87	0.08	0.05	X	0.86	0.08	0.05	0.01
36	0.74	0.17	0.09	X	0.71	0.16	0.09	0.04
	High localised risk group				**High locally advanced risk group**			
0	1	X	X	X	1	X	X	X
3	0.76	0.07	0.17	0.00	0.76	0.07	0.17	0.00
15	0.85	0.08	0.05	0.02	0.85	0.08	0.05	0.03
36	0.69	0.16	0.08	0.06	0.69	0.16	0.08	0.07

Appendix 3: The proportion of people accordingly to the risk group, adjusted for the probability of dying for the sc analysis (3,4).

	Base case				Intermediate risk group			
	States				States			
Month	**G1+0**	**GI2+**	**GU2+**	**Death**	**G1+0**	**GI2+**	**GU2+**	**Death**
0	1.00	X	X	X	1.00	X	X	X
3	0.51	0.04	0.44	X	0.51	0.04	0.44	X
15	0.94	0.01	0.04	X	0.93	0.01	0.04	0.01
36	0.87	0.07	0.07	X	0.83	0.06	0.06	0.04
	High localizer risk group				**High-locally advanced risk group**			
0	1.00	X	X	X	1.00	X	X	X
3	0.51	0.04	0.44	0.00	0.51	0.04	0.44	0.00
15	0.92	0.01	0.04	0.02	0.92	0.01	0.04	0.03
36	0.82	0.06	0.06	0.06	0.81	0.06	0.06	0.07

Appendix 4: Transition probabilities for base-case model based on the RCT by Michalski et al.(25).

Transition probabilities from 0 to 3 month					
Intermediate risk group		**High-localised risk group**		**High locally advanced risk group**	
Transition probabilities	**Values**	**Transition probabilities**	**Values**	**Transition probabilities**	**Values**
from "No toxicity" to "No toxicity"	0.760	from "No toxicity" to "No toxicity"	0.759	from "No toxicity" to "No toxicity"	0.758
from "No toxicity" to "Grade 2+ GI"	0.070	from "No toxicity" to "Death"	0.001	from "No toxicity" to "Death"	0.003
from "No toxicity" to "Grade 2+ GU"	0.170	from "No toxicity" to "Grade 2+ GI"	0.070	from "No toxicity" to "Grade 2+ GI"	0.070
		from "No toxicity" to "Grade 2+ GU"	0.170	from "No toxicity" to "Grade 2+ GU"	0.169
Transition probabilities from 3 to 15 month					
Intermediate risk group		**High-localised risk group**		**High locally advanced risk group**	
Transition probabilities	**Values**	**Transition probabilities**	**Values**	**Transition probabilities**	**Values**
from "No toxicity" to "Stay in this state"*	0.404	from "No toxicity" to "Stay in this state"*	0.423	from "No toxicity" to "Stay in this state"*	0.431
from "No toxicity" to “No toxicity"	0.589	from "No toxicity" to “No toxicity"	0.569	from "No toxicity" to “No toxicity"	0.560
from "No toxicity" to "Death"	0.003	from "No toxicity" to "Death"	0.005	from "No toxicity" to "Death"	0.006
from "No toxicity" to "Grade 2+ GI"	0.004	from "No toxicity" to "Grade 2+ GI"	0.004	from "No toxicity" to "Grade 2+ GI"	0.004
from "Grade 2+ GI" to "Stay in this state"*	0.334	from "Grade 2+ GI" to "Stay in this state"	0.367	from "Grade 2+ GI" to "Stay in this state"	0.380
from "Grade 2+ GI" to "Death"	0.003	from "Grade 2+ GI" to "Death"	0.005	from "Grade 2+ GI" to "Death"	0.006
from "Grade 2+ GI" to "Grade 2+ GI"	0.662	from "Grade 2+ GI" to "Grade 2+ GI"	0.629	from "Grade 2+ GI" to "Grade 2+ GI"	0.615
from "Grade 2+ GU" to "Stay in this state"*	0.650	from "Grade 2+ GU" to "Stay in this state"*	0.652	from "Grade 2+ GU" to "Stay in this state"*	0.651
from "Grade 2+ GU" to "Grade 2+ GU"	0.082	from "Grade 2+ GU" to "Grade 2+ GU"	0.082	from "Grade 2+ GU" to "Grade 2+ GU"	0.081
from "Grade 2+ GU" to "Death"	0.003	from "Grade 2+ GU" to "Death"	0.005	from "Grade 2+ GU" to "Death"	0.006
from "Grade 2+GU" to "No toxicity"	0.264	from "Grade 2+GU" to "No toxicity"	0.262	from "Grade 2+GU" to "No toxicity"	0.262
Transition probabilities from 15 to 36 month					
Intermediate risk group		**High-localised risk group**		**High locally advanced risk group**	
Transition probabilities	**Values**	**Transition probabilities**	**Values**	**Transition probabilities**	**Values**
from "Grade 2+ GI" to "Stay in this state"*	0.603	from "Grade 2+ GI" to "Stay in this state"*	0.631	From “Grade 2+ GI” to “Stay in this state”*	0.634
from "Grade 2+ GI" to "Death"	0.004	from "Grade 2+ GI" to "Death"	0.006	from "Grade 2+ GI" to "Death"	0.006
from "Grade 2+ GI" to "Grade 2+ GI"	0.393	from "Grade 2+ GI" to "Grade 2+ GI"	0.362	from "Grade 2+ GI" to "Grade 2+ GI"	0.360
from "Grade 2+ GU" to "Stay in this state"*	0.603	from "Grade 2+ GU" to "Stay in this state"*	0.631	from "Grade 2+ GU" to "Stay in this state"*	0.634
from "Grade 2+ GU" to "Grade 2+ GU"	0.393	from "Grade 2+ GU" to "Grade 2+ GU"	0.362	from "Grade 2+ GU" to "Grade 2+ GU"	0.360
from "Grade 2+ GU" to "Death"	0.004	from "Grade 2+ GU" to "Death"	0.006	from "Grade 2+ GU" to "Death"	0.006
from "No toxicity" to "Stay in this state"*	0.752	from "No toxicity" to "Stay in this state"*	0.757	from "No toxicity" to "Stay in this state"*	0.757
from "No toxicity" to "Death"	0.004	from "No toxicity" to "Death"	0.006	from "No toxicity" to "Death"	0.006
from "No toxicity" to “No toxicity"	0.221	from "No toxicity" to “No toxicity"	0.215	from "No toxicity" to “No toxicity"	0.214
from "No toxicity" to "Grade 2+ GI"	0.015	from "No toxicity" to "Grade 2+ GI"	0.015	from "No toxicity" to "Grade 2+ GI"	0.015
from "No toxicity" to "Grade 2+ GU"	0.007	from "No toxicity" to "Grade 2+ GU"	0.007	from "No toxicity" to "Grade 2+ GU"	0.007

**"Stay in this state" is a tunnel substate, patients leave it when their time there is over.*

Appendix 5: Transition probabilities for scenario analysis based on the RCTs on SpaceOAR™(3,4).

Transition probabilities from 0 to 3 month					
Intermediate risk group		**High-localised risk group**		**High locally advanced risk group**	
Transition probabilities	**Values**	**Transition probabilities**	**Values**	**Transition probabilities**	**Values**
from "No toxicity" to "No toxicity"	0.514	from "No toxicity" to "No toxicity"	0.513	from "No toxicity" to "No toxicity"	0.512
from "No toxicity" to "Grade 2+ GI"	0.042	from "No toxicity" to "Death"	0.001	from "No toxicity" to "Death"	0.003
from "No toxicity" to "Grade 2+ GU"	0.444	from "No toxicity" to "Grade 2+ GI"	0.042	from "No toxicity" to "Grade 2+ GI"	0.042
		from "No toxicity" to "Grade 2+ GU"	0.444	from "No toxicity" to "Grade 2+ GU"	0.443

Transition probabilities from 3 to 15 month					
Intermediate risk group		**High-localised risk group**		**High locally advanced risk group**	
Transition probabilities	**Values**	**Transition probabilities**	**Values**	**Transition probabilities**	**Values**
from "Grade 2+ GI" to "Stay in this state"*	0.668	from "Grade 2+ GI" to "Stay in this state"*	0.669	from "Grade 2+ GI" to "Stay in this state"*	0.662
from "Grade 2+GI" to "No toxicity"	0.233	from "Grade 2+GI" to "No toxicity"	0.231	from "Grade 2+GI" to "No toxicity"	0.237
from "Grade 2+ GI" to "Death"	0.003	from "Grade 2+ GI" to "Death"	0.005	from "Grade 2+ GI" to "Death"	0.006
from "Grade 2+ GI" to "Grade 2+ GI"	0.096	from "Grade 2+ GI" to "Grade 2+ GI"	0.096	from "Grade 2+ GI" to "Grade 2+ GI"	0.095
from "No toxicity" to "Stay in this state"*	0.334	from "No toxicity" to "Stay in this state"*	0.367	from "No toxicity" to "Stay in this state"*	0.38
from "No toxicity" to "No toxicity"	0.662	from "No toxicity" to "No toxicity"	0.629	from "No toxicity" to "No toxicity"	0.615
from "No toxicity" to "Death"	0.003	from "No toxicity" to "Death"	0.005	from "No toxicity" to "Death"	0.006
from "Grade 2+ GU" to "Stay in this state"*	0.531	from "Grade 2+ GU" to "Stay in this state"*	0.527	from "Grade 2+ GU" to "Stay in this state"*	0.528
from "Grade 2+ GU" to "Grade 2+ GU"	0.024	from "Grade 2+ GU" to "Grade 2+ GU"	0.024	from "Grade 2+ GU" to "Grade 2+ GU"	0.024
from "Grade 2+ GU" to "Death"	0.003	from "Grade 2+ GU" to "Death"	0.005	from "Grade 2+ GU" to "Death"	0.006
from "Grade 2+GU" to "No toxicity"	0.441	from "Grade 2+GU" to "No toxicity"	0.444	from "Grade 2+GU" to "No toxicity"	0.442

Transition probabilities from 15 to 36 month					
Intermediate risk group		**High-localised risk group**		**High locally-advanced risk group**	
Transition probabilities	**Values**	**Transition probabilities**	**Values**	**Transition probabilities**	**Values**
from "Grade 2+ GI" to "Stay in this state"*	0.603	from "Grade 2+ GI" to "Stay in this state"*	0.631	from "Grade 2+ GI" to "Stay in this state"*	0.634
from "Grade 2+ GI" to "Death"	0.004	from "Grade 2+ GI" to "Death"	0.006	from "Grade 2+ GI" to "Death"	0.006
from "Grade 2+ GI" to "Grade 2+ GI"	0.393	from "Grade 2+ GI" to "Grade 2+ GI"	0.362	from "Grade 2+ GI" to "Grade 2+ GI"	0.36
from "Grade 2+ GU" to "Stay in this state"*	0.603	from "Grade 2+ GU" to "Stay in this state"*	0.631	from "Grade 2+ GU" to "Stay in this state"*	0.634
from "Grade 2+ GU" to "Grade 2+ GU"	0.393	from "Grade 2+ GU" to "Grade 2+ GU"	0.362	from "Grade 2+ GU" to "Grade 2+ GU"	0.36
from "Grade 2+ GU" to "Death"	0.004	from "Grade 2+ GU" to "Death"	0.006	from "Grade 2+ GU" to "Death"	0.006
from "No toxicity" to "Stay in this state"*	0.711	from "No toxicity" to "Stay in this state"*	0.719	from "No toxicity" to "Stay in this state"*	0.719
from "No toxicity" to "Death"	0.004	from "No toxicity" to "Death"	0.006	from "No toxicity" to "Death"	0.006
from "No toxicity" to "No toxicity"	0.273	from "No toxicity" to "No toxicity"	0.263	from "No toxicity" to "No toxicity"	0.264
from "No toxicity" to "Grade 2+ GI"	0.008	from "No toxicity" to "Grade 2+ GI"	0.008	from "No toxicity" to "Grade 2+ GI"	0.008
from "No toxicity" to "Grade 2+ GU"	0.003	from "No toxicity" to "Grade 2+ GU"	0.004	from "No toxicity" to "Grade 2+ GU"	0.004

**"Stay in this state" is a tunnel substate, patients leave it when their time there is over.*

Appendix 6: All-cause mortality after the start of curative prostate cancer radiation therapy, %*.

Years since RT	Intermediate risk group Death from all causes (%)	High localized risk group Death from all causes (%)	High locally advanced risk group Death from all causes (%)
1	1.0	1.6	2.2
2	2.5	3.8	4.3
3	4.3	6.2	6.8
4	7.0	9.4	9.4
5	9.1	11.7	13.6
6	12.8	15.3	17.4
7	16.2	19.3	21.6
8	20.0	22.7	25.4
9	23.1	27.6	29.4
10	28.1	32.5	34.6
11	31.1	37.0	39.1
12	34.7	41.8	44.6
13	40.5	44.0	50.3

**Data was provided by the Cancer Registry of Norway with observation from 2004 to 2017, 2019. The Cancer Registry of Norway is not responsible for the presentation o pretation of the numbers. Inclusion criteria were 69-year-old men at the start of curative radiation therapy for prostate cancer.*

Appendix 7: Age-specific all-cause mortality for the general population**.

Age, years	Probability of dying/year, %	Rate	Cycle probability	SE*	Probability
85	7	0.019	0.019	0.004	Beta
86	8	0.022	0.022	0.004	Beta
87	10	0.026	0.025	0.005	Beta
88	11	0.030	0.030	0.006	Beta
89	12	0.031	0.031	0.006	Beta
90	14	0.038	0.037	0.007	Beta
91	16	0.045	0.044	0.009	Beta
92	18	0.049	0.048	0.010	Beta
93	19	0.054	0.053	0.011	Beta
94	21	0.060	0.058	0.012	Beta
95	23	0.066	0.064	0.013	Beta
96	27	0.077	0.074	0.015	Beta
97	31	0.091	0.087	0.017	Beta
98	30	0.090	0.086	0.017	Beta
99	32	0.097	0.093	0.019	Beta
100	39	0.123	0.116	0.023	Beta
101	37	0.116	0.109	0.022	Beta
102	37	0.114	0.108	0.022	Beta
103	29	0.087	0.083	0.017	Beta
104	44	0.146	0.136	0.027	Beta
105	42	0.137	0.128	0.026	Beta
106	n/a	n/a	n/a	n/a	n/a

** SE is 20%.*

*** Statistics Norway, data for 2019, available from: https://www.ssb.no/dode.*

Appendix 8: Age-dependent utility values measured with EQ-5D.

Age of the patient	Grade 0+1	GI toxicity			GU toxicity		
		Grade 2	Grade 3	Grade 2+*	Grade 2	Grade 3	Grade 2+*
73	0.80	0.77	0.71	0.77	0.75	0.71	0.75
74	0.76	0.74	0.68	0.73	0.71	0.68	0.71
75	0.76	0.74	0.68	0.73	0.71	0.68	0.71
76	0.76	0.74	0.68	0.73	0.71	0.68	0.71
77	0.76	0.74	0.68	0.73	0.71	0.68	0.71
78	0.76	0.74	0.68	0.73	0.71	0.68	0.71
79	0.76	0.74	0.68	0.73	0.71	0.68	0.71
80	0.76	0.74	0.68	0.73	0.71	0.68	0.71
81	0.76	0.74	0.68	0.73	0.71	0.68	0.71
82	0.76	0.74	0.68	0.73	0.71	0.68	0.71
83	0.76	0.74	0.68	0.73	0.71	0.68	0.71
84	0.76	0.74	0.68	0.73	0.71	0.68	0.71
85	0.76	0.74	0.68	0.73	0.71	0.68	0.71
86	0.76	0.74	0.68	0.73	0.71	0.68	0.71
87	0.76	0.74	0.68	0.73	0.71	0.68	0.71
88	0.76	0.74	0.68	0.73	0.71	0.68	0.71
89	0.72	0.70	0.65	0.70	0.68	0.65	0.67
90	0.72	0.70	0.65	0.70	0.68	0.65	0.67
91	0.72	0.70	0.65	0.70	0.68	0.65	0.67
92	0.72	0.70	0.65	0.70	0.68	0.65	0.67
93	0.72	0.70	0.65	0.70	0.68	0.65	0.67
94	0.72	0.70	0.65	0.70	0.68	0.65	0.67
95	0.72	0.70	0.65	0.70	0.68	0.65	0.67
96	0.72	0.70	0.65	0.70	0.68	0.65	0.67
97	0.72	0.70	0.65	0.70	0.68	0.65	0.67
98	0.72	0.70	0.65	0.70	0.68	0.65	0.67
99	0.72	0.70	0.65	0.70	0.68	0.65	0.67
100	0.72	0.70	0.65	0.70	0.68	0.65	0.67
101	0.72	0.70	0.65	0.70	0.68	0.65	0.67
102	0.72	0.70	0.65	0.70	0.68	0.65	0.67
103	0.72	0.70	0.65	0.70	0.68	0.65	0.67
104	0.72	0.70	0.65	0.70	0.68	0.65	0.67
105	0.72	0.70	0.65	0.70	0.68	0.65	0.67

Appendix 9: Costs of radiation therapy with prices for 2020, NOK.

Cost of radiation therapy	Times/year	DRG code*	DRG weight	Cost per 1 visit	Total cost for procedure	Source	Comment
Radiation therapy	38	851N	0.037	1,695	64,406	Expert opinion	Total of 78Gy
Polyclinical contact for planning RT	1	850A	0.453	20,751	20,751	Expert opinion	Patient visits 3 times but it is calculated as one DRG value
Polyclinical contact for complex planning RT	1	850B	0.445	20,385	20,385	Expert opinion	When the fiducial markers and hydrogel rectal spacer are placed
Total cost for radiation therapy					**105,542**		

*(30).

Appendix 1: Cost components for late toxicities with values given for 2020, NOK.

Procedure/ State	DRG code	DRG weight/ cost	Costs for year 1/state		Costs for year 2/state		Costs for year 3/state		Cost/year after year 3, NOK	
			Times/state	Cost/procedure-s, NOK	Times/state	Cost/procedure-s, NOK	Times/state	Cost/procedure-s, NOK	Times/state	Cost/procedure-s, NOK
Late gastrointestinal toxicity										
Late gastrointestinal toxicity Grade 0+1										
Out-patient visit (just once at 6 months)*	912A	0.033	1	1,512	X		X		X	X
GP visit*	honorarX2	320	1	320	2	640	2	640	1	320
Total cost per state				**1,832**		**640**		**640**		**320**
Late gastrointestinal toxicity Grade 2										
Out-patient visit (just once at 6 months) *	912A	0.033	1	1,512	X		X		X	X
GP visit*	honorarX2	320	1	320	2	640	2	640	1	320
Out-patient visit (Radiologist)**	912A	0.033	2	3,023	2	3,023	2	3,023	X	X
Total cost per state				**4,855**		**3,663**		**3,663**		**320**
Late gastrointestinal toxicity Grade 3										
Out-patient visit (just once at 6 months) *	912A	0.033	1	1,512	X	X	X	X	X	X
GP visit*	honorarX2	320	1	320	2	640	2	640	1	320
Out-patient visit**	912A	0.033	2	3,023	2	3,023	2	3,023	1	1,512
Colonoscopy from year 1 to 3 (1-3years/1 a year) **	710O	0	1	3,161	1	3,161	1	3,161	X	X
Colonoscopy after year 3 (1/10 years) **	710O	0.069	X	X	X	X	X	X	0.1	316
Argon plasma coagulation from year 1 to 3(1-3years/1 a year) **	806P	0	1	2,107	1	2,107	1	2,107	X	X
Argon plasma coagulation after 3rd year 1/10 years**	806P	0.046	X	X	X	X	X	X	0.1	211
Hyperbaric oxygen therapy (30 times once per case) **	823U	0.055	10	25,194	10	25,194	10	25,194	X	X
ER visit	453B	0.601	1	27,531	1	27,531	1	27,531	X	X
Blood transfusion	816R	0	1	3,939	1	3,939	1	3,939	X	X
Gastroenterologist from year 1 to year 3 (1-3 years/1 time/year) **	912A	0.033	1	1,512	1	1,512	1	1,512	X	X
Total cost per state				**68,299**		**67,107**		**67,107**		**2,358**
Late genitourinary toxicity										
Late genitourinary toxicity Grade 0+1										
X	X	X	X	X	X	X	X	X	X	X
Late genitourinary toxicity Grade 2										
GP visit**	honorarX2	320	1	320	1	320	1	320	1	320
Out-patient visit**	912A	0	2	3,023	2	3,023	2	3,023	X	X
Total cost per state				**3,343**		**3,343**		**3,343**		**320**
Late genitourinary toxicity Grade 3										
GP visit**	honorarX2	320	1	320	1	320	1	320	1	320
Out-patient visit (Urologist/Radiothera-pist) **	912A	0.033	4	6,047	4	6,047	4	6,047	1	1,512
ER visit**	453B	0.601	1	27,531	1	27,531	1	27,531	X	X
Cystoscopy**	718O	0.039	1	1,787	1	1,787	1	1,787	X	X
Blood transfusion**	816R	0.086	1	3,939	1	3,939	1	3,939	X	X
Hyperbaric oxygen therapy (30 times once per case) **	823U	0.055	10	25,194	10	25,194	10	25,194	X	X
Total cost per state				**64,818**		**64,818**		**64,818**		**1,832**

**Follow-up visit as a part of coordinated treatment path; first 2 times - out-patient visits, later - GP; after radical treatment controls are at 3, 6 and 12 months; later each half year up to the 3 year; later once per year. Available from: [https://www.helsedirektoratet.no/pakkeforlop/prostatakreft/oppfolging-og-kontroll-av-prostatakreft#kontroll.](https://www.helsedirektoratet.no/pakkeforlop/prostatakreft/oppfolging-og-kontroll-av-prostatakreft#kontroll)*

***Expert opinion.*

Appendix 12. Cost estimates for health states with prices for 2020, NOK.

Cost parameters for health states	*Cost per year*	*Cost per cycle*	*Standard error**	*Distribution*
Acute gastrointestinal toxicity Grade 0+1	1,512	1,512	453	Gamma
Acute gastrointestinal toxicity Grade 2	1,512	1,512	453	Gamma
Acute gastrointestinal toxicity Grade 3	31,149	31,149	9,345	Gamma
Acute gastrointestinal toxicity Grade 2+	2,994	2,994	898	Gamma
Late gastrointestinal toxicity Grade 0+1, year 1	1,832	458	137	Gamma
Late gastrointestinal toxicity Grade 2, year 1	4,855	1,214	364	Gamma
Late gastrointestinal toxicity Grade 3, year 1	68,299	17,075	5,122	Gamma
Late gastrointestinal toxicity Grade 0+1, year 2	640	160	48	Gamma
Late gastrointestinal toxicity Grade 2, year 2	3,663	916	275	Gamma
Late gastrointestinal toxicity Grade 3, year 2	67,107	16,777	5,033	Gamma
Late gastrointestinal toxicity Grade 0+1, year 3	640	160	48	Gamma
Late gastrointestinal toxicity Grade 2, year 3	3,663	916	275	Gamma
Late gastrointestinal toxicity Grade 3, year 3	67,107	16,777	5,033	Gamma
Late gastrointestinal toxicity Grade 0+1, from year 3	320	80	24	Gamma
Late gastrointestinal toxicity Grade 2, from year 3	320	80	24	Gamma
Late gastrointestinal toxicity Grade 3, from year 3	2,358	590	177	Gamma
Late gastrointestinal toxicity Grade 2+, from year 3	422	105	32	Gamma
Acute genitourinary Grade 2	1,832	458	137	Gamma
Acute genitourinary Grade 3	56,939	14,235	4,270	Gamma
Acute genitourinary Grade 2+	4,587	1,147	344	Gamma
Late genitourinary Grade 2, year 1	3,343	836	251	Gamma
Late genitourinary Grade 3, year 1	64,818	16,204	4,861	Gamma
Late genitourinary Grade 2, year 2	3,343	836	251	Gamma
Late genitourinary Grade 3, year 2	64,818	16,204	4,861	Gamma
Late genitourinary Grade 2, year 3	3,343	836	251	Gamma
Late genitourinary Grade 3, year 3	64,818	16,204	4,861	Gamma
Late genitourinary Grade 2, from year 3	320	80	24	Gamma
Late genitourinary Grade 3, from year 3	1,832	458	137	Gamma
Late genitourinary Grade 2+, from year 3	396	99	30	Gamma
Acute gastrointestinal and genitourinary Grade 0+1	1,512	1,512	453	Gamma
Late gastrointestinal and genitourinary Grade 0+1, year 1	1,832	458	137	Gamma
Late gastrointestinal and genitourinary Grade 0+1, year 2	640	160	48	Gamma
Late gastrointestinal and genitourinary Grade 0+1, year 3	640	160	48	Gamma
Late gastrointestinal and genitourinary Grade 0+1, from year 3	320	80	24	Gamma
Late genitourinary Grade 2+, year 1	6,417	1,604	481	Gamma
Late genitourinary Grade 2+, year 2	6,417	1,604	481	Gamma
Late genitourinary Grade 2+, year 3	6,417	1,604	481	Gamma
Late genitourinary Grade 2+, from year 3	396	99	30	Gamma
Late gastrointestinal Grade 2+, year 1	8,027	2,007	602	Gamma
Late gastrointestinal Grade 2+, year 2	6,836	1,709	513	Gamma
Late gastrointestinal Grade 2+, year 3	6,836	1,709	513	Gamma
Late gastrointestinal Grade 2+, from year 3	422	105	32	Gamma

** Standard error is 30%.*

Appendix 13: Parameters assessed in one-way sensitivity analysis.

Parameters	Base-case value	95% CI		INMB, NOK	
		Low value	High value	Low input outcome	High input outcome
Relative risk measured at 3 months GI2+	0.97	0.25	3.78	-12,952	-14,310
Relative risk measured at 3 months GU2+	0.85	0.61	1.18	-12,067	-14,848
Relative risk measured at 15 months GI2+	0.16	0.14	0.21	-13,212	-13,269
Relative risk measured at 15 months GU2+	1.60	1.36	2.08	-12,949	-13,852
Relative risk measured at 36 months GI2+	0.07	0.00	1.34	-13,089	-19,209
Probability of GI toxicity resolution	0.91	0.50*	0.95*	-12103	-13,340
Probability of GU toxicity resolution	0.81	0.50*	0.95*	-13,366	-13,133
Utilities for insertion with complication	0.76	0.41	0.98	-14,205	-12,642
Utilities for grade 0+1 at age73	0.80	0.41	0.99	-17,187	-11,288
Utilities for grade 0+1 at age74	0.76	0.41	0.97	-18,924	-9,764
Utilities for grade 0+1 at age75	0.76	0.41	0.97	-21,316	-8,308
Utilities for GI grade 2+ at age 73	0.77	0.41	0.98	-10,269	-14,938
Utilities for GI grade 2+ at age 74	0.73	0.40	0.96	-7,538	-17,079
Utilities for GI grade 2+ at age 75	0.73	0.40	0.96	-5,157	-18,690
Utilities for GU grade 2+ at age 73	0.75	0.41	0.97	-12,577	-13,648
Utilities for GU grade 2+ at age 74	0.71	0.40	0.94	-13,537	-13,007
Utilities for GU grade 2+ at age 75	0.71	0.40	0.94	-13,623	-12,944
Cots acute toxicity grade 0+1	1,512	623	2,401	-13,212	-13,248
Costs acute GU tox. Grade 2 +	4,587	1,890	7,284	-13,281	-13,179
Cost acute GI tox. Grade 2+	2,994	1,233	4,754	-13,232	-13,227
Costs late GI tox. Grade 2+_year 1	2,007	827	3,187	-13,696	-12,763
Costs late GI tox. Grade 2+_year 2	1,709	704	2,714	-13,636	-12,823
Costs late GI tox. Grade 2+_year 3	1,709	704	2,714	-13,617	-12,842
Costs late GI tox. Grade 2+_from year 3	105	43	168	-13,236	-13,223
Costs late GU tox. Grade 2+_year 1	1,604	661	2,548	-13,201	-13,259
Costs late GU tox. Grade 2+_from year 1	99	41	157	-13,227	-13,233
Costs late tox. Grade 0+1(GI+GU) year 1	458	189	727	-13,196	-13,264
Costs late tox. Grade 0+1(GI+GU) year 2	160	66	254	-13,208	-13,252
Costs late tox. Grade 0+1(GI+GU) year 3	160	66	254	-13,198	-13,261
Costs late tox. Grade 0+1(GI+GU) from year 3	80	33	127	-13,205	-13,254
Cost of the procedure	1,512	623	2,401	-12,412	-14,048
Price of hydrogel rectal spacer	16,000	6,592	25,408	-4,951	-21,509
Costs anaesthesia	1,902	784	3,020	-12,246	-14,214

**was taken beyond CI to check sensitivity*

Kan vi forebygge stråleskader ved behandling av prostatakreft?

Bruk av nedbrytbar beskytter (SpaceOar™) kan muligens forebygge stråleskader ved behandling av prostatakreft. Dokumentasjonsgrunnlaget er imidlertid svakt på det nåværende tidspunkt. Det viser en EUnetHTA-oversikt.

Hva sier forskningen?

I systematiske oversikter samles og vurderes tilgjengelig forskning. I denne systematiske EUnetHTA-oversikten var spørsmålet: «Kan vi forebygge stråleskader ved behandling av prostatakreft?». Forfatterne av denne rapporten har samlet forskning om effekt og sikkerhet av nedbrytbar beskytter ved strålebehandling av prostatakreft.

Resultatene viser at bruk av nedbrytbar beskytter ved strålebehandling:

- muligens kan føre til en liten forskjell i akutt (opptil 3 måneder etter bestråling) og sen toksisitet (opptil 15 måneder). Vi er usikre på effekten av nedbrytbar beskytter på lengre sikt

- muligens reduserer stråledosen mottatt på rektum, men vi vet ikke om beskytter gir mindre toksisitet

- muligens kan forbedre livskvalitet («quality of life» or QoL) knyttet til tarm og har muligens ingen eller liten effekt på livskvalitet knyttet til urinveier. Vi vet ikke om beskytter påvirker livskvalitet knyttet til seksuell helse.

- muligens kan gi sjeldne prosedyrerelaterte uønskede hendelser som, for eksempel, infiltrasjon i rektum

Basert på det tilgjengelige datagrunnlaget er fordelene med nedbrytbar beskytter usikre, ytterligere forskning er nødvendig for å evaluere effekten av nedbrytbar beskytter.

Resultattabell 1: Toksisitetsutfall. Nedbrytbar beskytter sammenlignet med vanlig praksis ved strålebehandling for prostatakreft**.

Hva skjer?	Antall pasienter		Absolutt effekt (95% konfidensintervall)	Tillit til resultatet[1]
	Nedbrytbar beskytter + Strålebehandling n = 148	Strålebehandling n = 71		
Akutt rektaltoksisitet grad ≥ 2 (0 - 3 måneder etter strålebehandling)	6	3	6 mindre per 1000 (fra 47 mindre til 152 mer) *	⨁⨁◯◯ Liten
Sen rektal toksisitet grad ≥ 2 (3 - 15 måneder etter strålebehandling)	0	1	13 mindre per 1000 (fra 15 mindre til 41 mer) *	⨁⨁◯◯ Liten
Akutt urinveistoksisitet grad ≥ 2 (0 - 3 måneder etter strålebehandling)	56	32	25 mindre per 1000 (fra 156 mindre til 148 mer) *	⨁⨁◯◯ Liten
Sen urinveistoksisitet grade ≥ 2 (3 - 15 måneder etter strålebehandling)	10	3	25 mer per 1000 (fra 23 mindre til 196 mer) *	⨁⨁◯◯ Liten
Akutt og sen rektal -og urinveis-toksisitet grad≥ 2 (median 3 år)	Vi rapporterer ikke tall vi har svært liten tillit til			⨁◯◯◯ Svært liten
Tarm QoL[2] (3-15 måneder etter strålebehandling)	17/148 (11%)	15/71 (21%)	10 færre menn i intervensjons gruppe rapporterte nedgang på 10 poeng	⨁⨁◯◯ Liten
Urinveis QoL[2] (3-15 måneder etter strålebehandling)	14/148 (9%)	9/71 (12%)	3 færre menn i intervensjons gruppe rapporterte nedgang på 12 poeng	⨁⨁◯◯ Liten
Seksuell QoL[2] (36 måneder etter strålebehandling)	Vi rapporterer ikke tall vi har svært liten tillit til			⨁◯◯◯ Svært liten
Prosedyrerelaterte uønskede hendelser	6% av tilfeller infiltrerte beskytter i rektal vegg 6.7% milde uønskede hendelser som ikke krevde behandling 3.3 % milde uønskede hendelser som krevde behandling 2 av 149 menn hadde ingen nedbrytbar beskytter etter innsettings prosedyre grunnet feil plassering av nål			⨁⨁◯◯ Liten
Rektal dose (70 Gy)***	97 % av menn som fikk nedbrytbar beskytter nådde ≧ 25% reduksjon i 70 Gy			⨁⨁◯◯ Liten

Avstand mellom prostata og rektum	Beskytter økte distansen mellom prostata og rektum med 1.1 cm	⊕⊕○○ Liten

[1]Tilliten til resultatet handler om hvor trygge vi kan være på at resultatet gjenspeiler virkeligheten.
[2] Utfall knyttet til tarm-, urinveis- og seksuell-livskvalitet («quality of life» QoL) kan vurderes med spørreskjemaet Expanded Prostate Cancer Index Composite (EPIC-50), hvor høyere verdier betyr bedre livskvalitet.
* Tallene i parentes viser feilmarginen (95 % konfidensintervall) - et mål på hvor usikkert resultatet er på grunn av tilfeldigheter.
**Utfall kun fra RCT, utfall fra ikke-RCT hadde svært liten tillitt og ble ikke rapportert; CTCAE var brukt til å vurdere alvorlighetsgrad av toksisitet og EPIC-50 til å vurdere tarm-, urinveis- og seksuell-livskvalitet.
*** Stråledose måles i Gray (Gy).

Bakgrunn

Prostatakreft er den hyppigste kreftformen blant menn i Norge. Strålebehandling er en av de viktigste behandlingsalternativene for pasienter med prostatakreft. Stråling ødelegger kreftceller med høyenergi røntgenstråler eller andre partikler. Når strålebehandling blir gitt innvendig (også kalt brakyterapi), blir radioaktivt materiale plassert i kreftsvulst eller omgivende vev permanent eller midlertidig. Utvendig strålebehandling gir stråling fra maskinen (lineærakselerator) utenfor kroppen og er den vanligste typen strålebehandling. Høyere stråledoser er assosiert med bedre sykdomskontroll, men kan også forårsake stråleskader på de tilstøtende organene. Vanlige bivirkninger av strålebehandling ved prostatakreft er rektal- og urinveistoksisitet, som kan gi følgende symptomer: rektal blødning, blod i urinen, diaré, lekkasje av urin og avføring, fistler, tarmobstruksjon etc. Hvis symptomer oppstår mellom 0 og 3 måneder etter strålebehandling, omtales det som akutt toksisitet, etter 3 måneder omtales det som sen toksisitet. Alvorlighet av toksisiteter kan graderes ved hjelp av klassifiseringssystemet Common Terminology Criteria for Adverse Events (CTCAE), hvor 0 er ingen symptomer, 1 er milde symptomer, som vanligvis ikke behandles, 2 er moderate, 3 er alvorlige, 4 er livstruende og 5 er død. Utfall knyttet til tarm-, urinveis- og seksuell-livskvalitet («quality of life» QoL) kan vurderes med spørreskjemaet Expanded Prostate Cancer Index Composite (EPIC-50), hvor høyere verdier betyr bedre livskvalitet.

For å gi tryggere behandling og fremme livskvalitet har flere nedbrytbare beskyttere blitt utviklet. Nedbrytbar beskytter settes inn i perirektal rommet (rommet mellom prostata og endetarmen) og øker avstanden mellom rektum og prostata. På denne måten reduseres bestråling av rektum og dermed også risikoen for bivirkninger. EUnetHTA-oversikten inkluderte tre teknologier som har godkjente indikasjoner: SpaceOAR™ (hydrogel), ProSpace System (rektal ballong) og Barrigel™ (ikke-dyrestabilisert hyaluronsyre).

Hva er denne informasjonen basert på?

Forfatterne av EUnetHTA-oversikten gjorde et litteratursøk i aktuelle forskningsdatabaser frem til november 2019. De fant en randomisert kontrollert studie (RCT) som inkluderte 222 personer og en ikke-randomisert kontrollert studie som inkluderte 78 personer. RCTen sammenlignet effekt og sikkerhet av SpaceOAR™ i tillegg til strålebehandling med strålebehandling alene, mens ikke-RCTen inkluderte SpaceOAR™ + strålebehandling, ProSpace System + strålebehandling og strålebehandling alene. Vi har svært liten tillit til utfallene fra

ikke-RCTen og viser derfor ikke resultater fra denne studien her, resultatene er imidlertid presentert i EUnetHTA-oversikten.

Forfatterne av EUnetHTA-oversikten identifiserte videre 8 pågående studier, 3 av dem er RCTer.

Selv om bruk av nedbrytbar beskytter ved strålebehandling ser lovende ut, gir små studier liten og svært liten tillit til dokumentasjonsgrunnlaget. Det var heller ikke mulig å slå sammen resultatene fra flere studier. Forfatterne av EUnetHTA-oversikten nedgraderte tillit på bakgrunn av begrensninger i studiene. Når det er få tilfeller av toksisitet etter strålebehandling, vil fremtidige studier måtte inkludere flere menn som skal få strålebehandling for prostatakreft slik at effektestimatene kan bli sikrere. Dersom ny forskning utføres i fremtiden, kan konklusjonene bli endret.

PICO	Hva lette de etter?	Hva fant de?
Populasjon	Hvem er disse personene?	Menn (> 18 år) med prostatakreft som mottar kurativ strålebehandling. Videre pasientkjennetegn er ikke godt beskrevet, RCTen oppgir alder og stadium på svulst.
Tiltak og sammenligning	Effekt av nedbrytbar beskytter for å forhindre eller redusere rektal toksisitet sammenlignet med ingen beskytter.	De fant tre CE-merkede teknologier med godkjent indikasjon: – SpaceOAR™, produsert av Boston Scientific – ProSpace System, produsert av BioProtect – Barrigel™, produsert av Palette Life Sciences Oversikten omfattet to av de tre teknologiene (hydrogel og ballong) og inkluderte studier som ble gjennomført prospektivt (RCT og ikke-RCT). Studiene brukte utvendig strålebehandling (EBRT).
Utfall	Primært utfall var toksisitet. Sekundære utfall inkluderte livskvalitet knyttet til tarm, urinveier og seksuell helse, reduksjon i stråledose på endetarm,avstand mellom prostata og rektum, samt	RCTen rapporterte på: rektal og urinveistoksisitet, livskvalitet knyttet til urinveier, tarm og seksuell helse, rektal stråledose, avstand mellom rektum og prostata, uønskede hendelser og PSA-verdier. Oppfølgingstiden var 3, 6,12, 15 og 36 måneder. Det ble brukt CTCAE*-klassifiseringssystemet, versjon 4.0 for å måle arvorlighet av toksisiteter og EPIC-50**

	uønskede hendelser, PSA-verdier.	spørreskjema for å måle tarm-, urinveis-, og seksuell livskvalitet.
Setting	Hvilke land, hvilken helsesetting?	RCTen er en multisenter studie utført i USA.
Tillit til resulta-tet	De brukte GRADE for å vurdere tilliten til dokumentasjonsgrunnlaget for hvert utfall.	Tilliten til dokumentasjonsgrunlaget for utfallene var liten eller svært liten. De vanligste begrensningene var: 1) alvorlig risiko for bias, 2) manglende presisjon. RCTen ble vurdert til å ha selektiv rapportering, manglende blinding og stort frafall av menn fra langvarig oppfølging (37%).
*Common Terminology Criteria for Adverse Events (CTCAE) er et sett med kriterier for standardisert klassifisering av bivirkninger av legemidler som brukes i kreftterapi. **Expanded Prostate Cancer Index Composite (EPIC) er spørreskjema utviklet for å overvåke helserelaterte livskvalitetsutfall blant menn behandlet for prostatakreft		

Systematisk oversikt

I systematiske oversikter søker man etter og oppsummerer studier som svarer på et konkret forskningsspørsmål. Studiene blir funnet, vurdert og oppsummert ved å bruke en systematisk og forhåndbeskrevet fremgangsmåte

Tillit til resultatet (GRADE)

Når vi oppsummerer studier og presenterer et resultat, så er det viktig å si noe om hvor mye tillit vi kan ha til dette. Det handler om hvor trygge vi kan være på at resultatet gjenspeiler virkeligheten. GRADE er et system vi bruker for å kunne bedømme tilliten til resultatet. I GRADE vurderer vi blant annet:

- hvor godt studiene er gjennomført
- om studiene er store nok
- om studiene er like nok
- hvor relevante studiene er
- om alle relevante studier er fanget opp

Kilde

Norwegian Institute of Public Health (NIPHNO), National School of Public Health, Management and Professional Development (NSPHMPDB); et al. Biodegradable rectum spacers to reduce toxicity for prostate cancer. Collaborative Assessment. Oslo, Norway: EUnetHTA; 2020. Report No.: OTCA23. [Internet]. [cited 2020 Sep 12].

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Abbreviations

Abbreviation	Meaning
AE	Adverse event
AS	Absolute shortfall
BIA	Budget impact analysis
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CUA	Cost-utility analysis
EBRT	External beam radiation therapy
EQ-5D	European Quality of Life 5 dimensions
GI	Gastrointestinal toxicity
GU	Genitourinary toxicity
GP	General practitioner
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
NMB	Net monetary benefit
NoMA	Norwegian Medicine Agency
PSA	Probabilistic sensitivity analysis
RCT	Randomized controlled trial
RT	Radiation therapy
QALY	Quality-adjusted life-year
QoL	Quality of life
WTP	Willingness-to-pay

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