A Cost-Utility analysis of Hydrogel Rectal Spacer in prostate cancer radiotherapy in Norway

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Abstract

Background: Dose-escalated external beam radiation therapy (EBRT) provides better tumor control for prostate cancer patients, however even with modern radiation delivery techniques, there is a risk for patients to develop gastrointestinal and genitourinary toxicities and erectile dysfunction (ED). Hydrogel rectal spacer SpaceOAR® is a medical device that might prevent developing adverse effects that occurred as a result of radiation therapy of prostate.

Research objective: The main objective of this thesis was to determine the cost-effectiveness of treating prostate cancer patients with SpaceOAR® in conjunction with the EBRT compared to the EBRT alone based on the potential of SpaceOAR® to reduce radiation-induced gastrointestinal and genitourinary toxicities.

Methods: A decision tree and a state-transition Markov model were constructed to compare the costs and health effects from the provider's perspective of SpaceOAR® in adjunct to standard care and standard care alone with a lifetime horizon. The subgroup analysis was conducted for three different proportions of patients suffering from ED (with ED prevalence of 62%, 100% and 0%) before the radiotherapy. Transition probabilities and relative risks were collected from the randomized clinical trial on SpaceOAR®. Costs and health utilities were obtained from the literature. A willingness to pay (WTP) threshold was estimated using absolute shortfall approach. To decrease the decision uncertainty value of information analysis assessed the expected value of additional evidence. The budget impact analysis was performed to estimate the financial consequences of implementing the device in healthcare practice.

Results: Given the lifetime horizon the incremental costs for SpaceOAR® were 13 813 NOK and the incremental effectiveness was 0,01 QALYs. This resulted in an incremental cost-effectiveness ratio of 1 382 413 NOK per QALY gained. If all patients had good erectile function prior to the EBRT, the incremental cost-effectiveness ratio was 238 990 NOK per QALY gained.

Conclusions: The results of this analysis suggests that the application of SpaceOAR® is not cost-effective considering its potential to reduce radiation-induced toxicities. Investigation of structural uncertainty performed by subgroup analysis concluded that HRS can be cost-effective if offered to the patients with good erectile function prior to radiation therapy. However, prioritizing a particular patient group with regards to health state may raise ethical considerations.

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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.

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Abbreviations

AE	Adverse event
BIA	Budget impact analysis
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CUA	Cost-utility analysis
EBRT	External beam radiation therapy
ED	Erectile dysfunction
EQ-5D	European Quality of Life 5 dimensions
EVPI	Expected value of perfect information
EVPPI	Expected value of partial perfect information
GP	General practitioner
HRQoL	Health-related quality of life
HRS	Hydrogel rectal spacer
ICER	Incremental cost-effectiveness ratio
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NoMA	Norwegian Medicine Agency
pEVPI	Population expected value of perfect information
PSA	Probabilistic sensitivity analysis
RCT	Randomized controlled trial
QALY	Quality-adjusted life-year
QoL	Quality of life
WTP	Willingness-to-pay

1 Introduction

Prostate cancer is one of the most frequent types of cancer in Norway and it is a leading cause of deaths due to cancer for men in Norway. Annual report on prostate cancer in Norway estimated 5253 patients diagnosed with prostate cancer, 934 prostate cancer-related deaths and 47 270 patients living with the disease in 2016 (Kreftregisteret, 2018). Due to improved treatment options available to the public, prostate cancer mortality rates are slightly declining. Traditionally, treatment options for prostate cancer are chemotherapy, hormonal therapy, radiotherapy, prostatectomy, and active surveillance.

To eliminate cancer cells, radiation therapy uses gamma rays, x-rays and other types of radiation sources. Radiation therapy (RT) can be delivered internally, mainly known as brachytherapy and externally, also referred to as external beam radiation. Under brachytherapy source of radiation is placed directly in or near the tumor. External beam radiation therapy (EBMRT) is mainly used in modern radiation therapy and is delivered from an external beam machine to the area of interest. Technical advances introduced in recent years, such as intensity-modulated radiotherapy techniques and image-guided radiotherapy, increased the precision in delivery of radiation therapy and lowered the exposure of adjacent tissues to radiation (reduced planning target volumes).

Dose-escalation is required for optimal tumor control. However, even when modern techniques are applied, a part of the anterior rectal wall is exposed while delivering elevated doses of radiation to the prostate. The anterior rectal wall is included in planning target volumes due to the spatial proximity of the anterior rectal wall and prostate (Pinkawa, 2015). Thus, delivering a high dose of radiation may result in a rise of gastrointestinal and genitourinary toxicities, both short-term (acute) and long-term (late) (Kuban et al., 2003). Therefore, the rectum is considered as a dose-limiting organ at risk and there is a need for sparing the anterior rectal wall in order to deliver escalated doses of radiotherapy (Wolf et al., 2015).

The application of spacers between rectum and prostate can be used to decrease the part of rectal wall exposed to radiation and improve the therapeutic effect of high-dose radiotherapy (Mok, Benz, Vallee, Miralbell, & Zilli, 2014). A number of studies evaluated the usage of an inflatable biodegradable balloon, human collagen, rectal rod, hyaluronic acid and polyethylene glycol hydrogel in separating prostate and rectum and, as a result, possible reducing morbidity related to the treatment (Lawrie et al., 2018).

In 2015 U.S. Food and Drug Administration approved the usage of commercially developed polyethylene glycol hydrogel rectal spacer (HRS) SpaceOAR® (Augmenix, Waltham, MA) to increase prostate-rectum space prior to the radiotherapy of the prostate. Hydrogel SpaceOAR® was approved in Canada, Japan, and Australia. In Europe, hydrogel met the requirements of the European Economic Area on health, safety and environmental protection and received CE certification mark (Schörghofer et al., 2019).

The results of recent studies with 3 years of follow-up on comparing the hydrogel rectal spacer application prior to radiation therapy to no hydrogel rectal spacer for the patients having localized prostate cancer has demonstrated favourable clinical outcomes in terms of preventing rectal and genitourinary toxicity and preserving erectile function after radiation therapy (Hamstra et al., 2017, 2018; Mariados et al., 2015).

Several studies in North America and Europe were assessing the cost-effectiveness of HRS (Forero, Almeida, & Dendukuri, 2018; Hutchinson, Sundaram, Folkert, & Lotan, 2016; Levy et al., 2019; Vanneste et al., 2015). No cost-effectiveness analysis that would take into consideration stratification patients on the risk groups, lifetime horizon and perform value of information analysis was identified.

The main objective of this thesis was to perform cost-utility analysis (CUA) of hydrogel SpaceOAR® (Augmenix, Waltham, MA) for patients with prostate cancer undergoing radiation therapy in the Norwegian setting. Following the objective, the major research question is whether HRS SpaceOAR® is cost-effective in preventing gastrointestinal and genitourinary toxicities after dose-escalated external beam radiotherapy of the prostate based on the data at hand. The secondary objective was to capture structural uncertainty by performing subgroup analysis considering that a part of patients has good erectile function at the baseline based on the study by Hamstra et al. (Hamstra et al., 2018) with prevalence of erectile dysfunction of 62% and as well consider possibility of prevalence of ED being 0% or 100% .

The following paper is organized into Background, Theoretical framework, Methods, Input parameters and materials, Results, Discussion, and Conclusion sections. Section 2 explains background information on prostate cancer and adverse events which follows dose-escalated external beam radiation therapy of prostate, risk factors, etymology, and available treatment alternatives. Moreover, it also presents a brief overview of the National reimbursement scheme and priority setting in Norway. Section 3 presents a theory of economic evaluation in the healthcare sector and provides terminology definitions applied in this field. Section 4 provides an overview of the methodology utilized for the cost-utility analysis and study design, including model structure, target population, perspective and time horizon.

Section 5 gives a detailed description of the model input parameters. Section 6 presents the results of the analysis in terms of costs, effects, ICER, value of information analysis and budget impact analysis. In section 7, the findings of the study are interpreted and discussed together with study limitations. Section 8 concludes this paper.

2 Background

2.1 Prostate cancer

Prostate cancer is cancer that occurs in the prostate, a small walnut-shaped gland in the male reproductive system located between penis and urinal bladder. Prostate secrets a fluid, which contributes to nourishment and transport of semen. Prostate cancer mainly occurs later in life, after the age of 50, and its prevalence in men's population increases with aging (Kreftregisteret, 2018). Prostate cancer is mostly slow-growing and the exact causes of it are not known. Risk factors include age, ethnicity, genetic background, family history and possibly dietary habits (Perez-Cornago et al., 2017). Several factors are considered to identify treatment options appropriate for a particular patient. Among them are stage and type of cancer, side effects, patient preferences, and health condition. After prostate cancer was diagnosed, patients are stratified accordingly to the risk group.

Division on risk groups in this paper is based on EAU guidelines on prostate cancer (Mottet et al., 2017) and represented in Table 1. At clinical tumor stages *T1a-c* the tumor is not apparent on the imaging tests or digital rectal examination. At stages *T2a-c* tumor is localized only in the prostate and can be palpated under digital rectal examination. At stages *T3a-b* tumor grown outside the prostate into the adjacent tissues on the one side. At stages *T4a-b* cancer developed to the other areas (bones, bladder, rectum, lymph nodes, etc.).

Table 1. Risk stratification based on EAU guidelines on prostate cancer.

Criteria	**Risk groups**			
	Low risk	**Intermediate risk**	**High risk**	
PSA (Prostate specific antigen)	< 10 ng/ml	10-20 ng/ml	> 20 ng/ml	Regardless PSA
	And	**Or**	**Or**	
Gleason score	6	7	> 7	Regardless PSA
	And	**Or**	**Or**	
clinical Tumor stage (cT)	cT1-2a	cT2b	cT2c	cT3-4 or cN1
Localized				Locally advanced

High level of a protein called prostate-specific antigen (PSA) in the blood may indicate both benign and malignant tumors, as well as prostatitis; therefore, the PSA test is applied for early diagnostic of prostate cancer. To predict patient outcomes and aggressiveness of cancer used Gleason grading system, which lower grades represent well-differentiated cells of histological examination, therefore the cancer is more likely to be less aggressive. Higher

grades indicate a low level of differentiation and are thought to give worth prognosis (Sehn et al., 2018).

As well tumor progression can be classified by TNM (where T – tumor, N – nodes, M – metastasis) staging system. T (T1-4) indicates the development of the primary tumor. N (NX, N0-3) represents the presence of cancer in lymph nodes. M (M0-1) indicates the presence or absence of distant metastasis (O'Sullivan et al., 2017).

2.1.1 Treatment options for prostate cancer

Curative treatment of prostate cancer includes surgical removing of the prostate (prostatectomy) and dose-escalated external beam radiation therapy that can be often combined with hormone therapy. Choosing the treatment option depends mainly on the age of the patients and cancer stage. Older patients with high-risk cancer are frequently treated with radiation therapy (median age is 69 years, mean PSA-value is 10.1 ng/ml), whereas younger patients are treated with low-risk with prostatectomy (median age is 63 years, mean PSA-value is 14.8 ng/ml) (Kreftregisteret, 2018). To decrease potential overtreatment and side-effects associated with the curative treatment of prostate cancer active surveillance is commonly offered to men with low-risk cancer.

Palliative treatment is not aimed to cure cancer and is mostly seeks to improve and prolong life by treating the symptoms associated with discomfort, pain, and stress.

Being the standard treatment option as a curative treatment for men with intermediate, high localized and high locally advanced prostate cancer in Norway, dose-escalated EBMRT is associated with improvement in overall survival (Mok et al., 2014), local and biochemical control (Mottet et al., 2017).

2.1.2 Adverse effects of radiation therapy

Prostate cancer patients may suffer from gastrointestinal toxicity, genitourinary toxicity, and erectile dysfunction, as organs at risk are rectum, urinary bladder, and vessels participating in penile erection. Side effects caused by inadvertent irradiation of adjacent organs can be divided into acute (from receiving radiation therapy up to 3 months) and long-term or late (more than 3 months after radiation therapy) side effects. Adverse effects to bladder and rectum can be graded using Common Terminology Criteria for Adverse Events (CTCAE), or the modified

Radiation Therapy Oncology Group (RTOG) criteria (Table 2) (Cox et al., 1995). Some authors point out the issues of CTC grading system with regard to rectal injuries, as it is unable to concord with a level of rectal injuries at all the time points (Capp et al., 2009).

Table 2. RTOG acute and RTOG/EORTC late radiation morbidity scoring for the lower GI tract and urinal bladder.

	Toxicity grade					
Type	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			Gastrointestinal toxicity			
Acute	No changes	Increased frequency, change in bowel habits, or rectal discomfort not requiring medications or analgesics	Diarrhea requiring parasympatholytic drugs, mucous discharge not necessitating sanitary pads, abdominal or rectal pain requiring analgesics	Diarrhea requiring parenteral support, severe bloody or mucous discharge necessitating sanitary pads, abdominal distention	Acute or subacute obstruction, fistula or perforation, GI bleeding requiring transfusion, abdominal pain or tenesmus requiring tube decompression or diversion	Death directly related to radiation effects
Late	No changes	Mild diarrhea, mild cramping, bowel movement 5 times daily, slight rectal discharge or bleeding	Moderate diarrhea 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
			Genitourinary toxicity			
Acute	No changes	Frequency of urination or nocturia twice pretreatment habit / dysuria, urgency not requiring medication	Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g. Pyridium)	Frequency with urgency and nocturia hourly or more fequenty / dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic / gross hematuria with/without clot passage	Hematuria requiring transfusion / acute bladder obstruction not secondary to clot passage, ulceration, or necrosis	Death directly related to radiation effects
Late	No changes	Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)	Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria	Severe frequency & dysuria; severe telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (<150 cc)	Necrosis/ contracted bladder (capacity < 100 cc); severe hemorrhagic cystitis	Death directly related to radiation effects

In short, for both CTCAE and RTOG Grade 0 denotes no adverse effect; Grade 1 indicates light or mild symptoms, which require no intervention. Grade 2 describes moderate symptoms with an indication for minor non-invasive or local intervention. Severe adverse effects of Grade 3 and 4 limit self-care abilities and indicate the urgent need for intervention. Grade 3 is associated with severe, may require hospitalization, but not immediately life-threatening symptoms, whereas Grade 4 denotes a life-threatening condition, which implies urgent interventions.

The definition of gastrointestinal toxicities comprises a broad variety of symptoms such as constipation, loose stool, blood in the stool, fecal inconsistency, rectal bleeding (Frazzoni, 2015).

Urinal toxicity can outburst with such symptoms as hematuria, dysuria, urinary stricture, obstruction, and frequency. Some symptoms have a tendency to gradually arise after radiation therapy, reaching plateau 3-8 years after treatment. The most commonly reported Grade 3

symptoms are radiation cystitis, obstruction, and incontinence (Rancati, Palorini, Cozzarini, Fiorino, & Valdagni, 2017).

Due to the anatomic proximity of erectile tissues to the field of radiation, ED is a common sequelae of radiation therapy of the prostate. Penile erection can be defined as a vascular phenomenon of elevated blood supply to the erectile tissues. This complex process is highly dependent on the interaction between vascular, psychological, neural and hormonal factors. When the penile erection is not obtainable, or erection is not sufficient for sustaining satisfactory sexual intercourse it is defined as erectile dysfunction (Levine, 2000).

2.1.3 Risk factors and etiology of adverse effects of radiation therapy

The main determinant of the severity of acute and late toxicity is the radiation dose (Shadad et al., 2013). The pathogenesis of radiation-induced side effects to urinary bladder and rectum is not yet clearly elucidated. In both cases occurs the inflammation process, which may result in tissues ischemia, cellular demolition, and edema (Shadad et al., 2013). This gives both genitourinary and gastrointestinal symptoms. “Target cell” theory explains acute adverse effects by epithelial damages to the tissue, whereas late toxicities are associated with injuries to fibroblast and endothelial cells. However, it was suggested that interaction between other factors such as microbiota and enteric nervous system can as well influence GI toxicity (Frazzoni et al., 2015).

A common gastrointestinal complication is radiation proctitis, additionally referred to as radiation proctopathy or pelvic radiation disease. There are some disagreements in the literature on the terminology of a common name for the constellation of GI symptoms that occurred after radiation therapy (Frazzoni et al., 2015). Thus, often damage to the rectum due to radiation therapy is named both as radiation proctopathy and radiation proctitis. Acute symptoms may debut during radiation therapy or within six weeks after radiation therapy. Acute symptoms are characterized by abdominal pain, rectal bleeding, occasional constipation, urgency, diarrhea, mucous discharge (Phan et al., 2009). Chronic radiation proctitis is associated with pain, rectal urgency, rectal bleeding, strictures, rectal fistula or perforation, constipation, fecal incontinence. Patient-connected risk factors are diabetes, smoking, body mass index, history of prior operations in the pelvic area, age, hemorrhoids, connective tissue disease and inflammatory bowel disease (Crohn’s disease and ulcerative colitis) and rectum size. Treatment-related risk factors are the volume of irradiated tissues, dose of radiation and fractioning parameters of radiation therapy (Frazzoni et al., 2015). Acute GI and GU toxicity

may as well predetermine late toxicity (Vranova et al., 2011). History of Diabetes mellitus is also considered as a predictor for GI (Zelefsky et al., 1998).

Regardless of recent developments made in radiation therapy, approximately three-quarters of patients who underwent radiation therapy continue to experience acute radiation proctitis and around 20% suffered from late adverse events (Grodsky & Sidani, 2015). In the randomised control trial (RCT) investigating dose-escalated external beam radiation therapy for intermediate-risk prostate cancer patients conducted by Michalski et al. in 2018, authors reported 8.4 years outcomes of 2% of Grade 1, 11% of Grade 2, 3% of Grade 3 and less than 1% for Grade 4 for GU toxicity and 4% of Grade 1. For GI toxicity it was 4% for Grade 1, 16% of Grade 2, 5% of Grade 3 and less than 1% for Grade 4 and less than 1 for grade 5 (Michalski et al., 2018).

In the 2019 study by Weg et al. (Weg, Pei, Kollmeier, McBride, & Zelefsky, 2019) with 15 years follow-up after dose-escalated IMRT (dose of more than 80 Gy) was concluded that GI toxicities resolved in majority (83 %) of patients who experienced them. On the contrary, GU toxicities may have more chronic form with just half of the patients experienced GU toxicities had a resolution of the symptoms.

The major risk factor of urinary toxicity is urinary function before the radiation (Rancati, Palorini, Cozzarini, Fiorino, & Valdagni, 2017). For this reason, estimating urinary function at the baseline should be obligatory before treatment planning, as it can be considered a dose-limiting factor for some patients. The dose and specific areas of radiation have an association with different symptoms that may occur to the damaged tissue (Rancati et al., 2017). As well, it is suggested that some areas of the bladder are more sensitive to the radiation and thus irradiating them may lead to particular risk escalation of having particular acute and late symptoms. Other risk factors of having acute and late GU toxicity are the history of vascular disease, age, diabetes, use of cardiovascular drugs, antihypertensive medication, prior transurethral resection of the prostate (Rancati et al., 2017).

ED is a complex problem, which can have organic, psychological or mixed causes. Even though the probability of having ED is not predetermined solely by age, ED has a positive association with the age of the patients. When it is not radiation therapy-induced, ED can be as well caused by a number of systemic diseases, which prevent sufficient blood flow to the penis (Levine, 2000). The other risk factors include depression, diabetes, hypertension, smoking, drug abuse, etc. Norwegian pharmaceutical manager states that absolute about 5% of 50-years old men, 10% of 60-years old man and 25-30% of 70-years old men suffer from a complete absence of erection (Legemiddelhåndboka, 2019). Radiation causes neuronal, muscular and vascular

damage (reduction of smooth muscle contend) resulting in an increased risk of ED. EBRT can cause ED in 36-59 % of patients (van der Wielen, Mulhall, & Incrocci, 2007). Prevalence of radiation therapy-induced ED highly correlates with age, comorbidities and baseline function (state and health of erectile tissues before radiation therapy), radiation therapy technique.

2.1.4 Management of radiation therapy adverse effects

The severity and symptoms of the patient's condition determine toxicity management. Despite causing a significant effect on the patient's quality of life, frequently occurred toxicities of grade 1 require no or little treatment. Grade 2 GU toxicity includes incontinence, which requires pads; urethral obstruction, which requires urinary catheterization; symptomatic haematuria, which requires urinary catheterization or bladder irrigation; fistula requires non-invasive intervention. Grade 3 GU toxicity includes haematuria requiring hospitalization, hyperbaric oxygen therapy, eventually radiological or operative intervention; urinary incontinence requiring collagen injections, surgery or clamps; urinary tract obstruction requiring surgical intervention; urinary retention requiring elective radiological or operative intervention; fistula with indication for endoscopic, radiological or surgical intervention, eventually urinary diversion (Rancati et al., 2017).

The main treatment options of radiation proctopathy are medical, endoscopic or surgical therapies (Grodsky & Sidani, 2015). Medical therapy includes anti-inflammatory agents (active component of the drugs is 5-Aminosalicylic acid) (Do, Nagle, & Poylin, 2011), antioxidants (vitamin E, A and C), sucralfate and steroid enemas, formalin therapy, sodium butyrate enemas, hyperbaric oxygen therapy, misoprostol, probiotics, short-chain fatty acids (SCFA) enemas and others. Hyperbaric oxygen (HBO) therapy may improve compromised blood flow to the rectal wall by neovascularisation. Antioxidants are claimed to have a limiting effect on tissue damage in radiation therapy. HBO is mainly not widely available treatment option used mostly by specialized centers. SCFA enemas are associated with stimulating proliferation of colonic mucosa and arteriole wall vasodilation and thus improving blood flow (Do et al., 2011). Among endoscopic treatments are argon plasma coagulation, laser therapy, cryoablation, radiofrequency ablation. Argon plasma coagulation is thought to have an ability to control superficial bleedings. Surgical procedures are used as a last resort in severe cases of rectal bleedings, perforation, obstruction and fistulous disease (Bansal, Soni, Kaur, Chauhan, & Kaushal, 2016). To improve symptoms control appropriate lifestyle adjustments are required

such as active life-style and high-fiber diet. Even though there is a vast variation in treatment approaches of radiation proctitis, general management strategy acquires using non-invasive options first and then gradually progress following the symptoms. Grade 1and 2 of chronic proctitis mostly require medical therapy using anti-inflammatory agents, antioxidants as a first choice and with SCFA and HBO therapy if symptoms proceeds. Treatment of grade 3 may include the same options as grade 1 and 2 plus formalin and argon plasma coagulation. Grade 4 will usually require surgical intervention (Do et al., 2011). However, some controversy in disease management is present due to low quality of evidence on treatment options of radiation proctitis (few RTC, small sample size, short follow-up and high clinical heterogeneity in studies) (Denton, Andreyev, Forbes, & Maher, 2002; van de Wetering et al., 2016). It should be noticed, that episodic nature of symptoms, absence of the diagnostics criteria for the radiation proctopathy complicates the common perception of the treatment options.

The first-line treatment of ED is oral PDE-inhibitors: sildenafil (product name is "Viagra®"), tadalafil (marketed under the trade name "Cialis®") and vardenafil (marketed under the trade name "Levitra®"). The other treatment choice includes penile injections, surgical interventions (penile prostheses are applied when PDE5-Is are ineffective) and vacuum devices (Mahmood et al., 2016). However, neither the first nor second line of ED treatment is not subject to reimbursement in Norway as a treatment for ED.

Application of HRS SpaceOAR® between rectum and prostate allows to avoid acute and late side effects of irradiation of prostate and to maximize tumor radiation dose.

2.1.5 Product applications technique, indications and adverse events

Injection of HRS SpaceOAR® can be performed in the ambulatory setting under local, general, or spinal anesthesia. Hydrogel injection is usually combined with other procedures, such as brachytherapy or placing fiducial markers to improve prostate targeting. The choice of anesthesia is mainly determined by the procedure hydrogel injection is combined with.

After the patient is placed in a lithotomy position 18-gauge needle is injected transperineally. Procedure is performed under transrectal ultrasound (TRUS) guidance (Mok et al., 2014). To separate the anterior rectal wall and Denonvilliers` fascia hydrodissection technique (injection of saline water or lidocaine mixed with saline) is used in a volume of 10-20 ml. Successful hydrodissection is a binding prerequisite in order to proceed with hydrogel spacer injection. When the 10 ml of a liquid hydrogel is injected into hydrodissected space, it polymerises within 10 seconds and forms a soft, flexible gel-like structure. The solution of a

hydrogel is obtained by simultaneous mixing of accelerator solutions and polyethylene glycol powder when it passes Y-connector before proceeding into the needle (Müller et al., 2016). The procedure technique is described in detail by Montoya et al. (Montoya, Gross, & Karsh, 2018). Separation achieved by injecting the spacer varies from 7 to 15 mm (Mok et al., 2014; Weber et al., 2012). The hydrogel remains solid for 3 months and later degrades by hydrolysis leaving the body via renal filtration (Mok et al., 2014). Under the procedure, there is a risk of penetration of adjacent tissues with the needle.

Hydrogel spacer can be used for patients with intermediate and low-risk prostate cancer undergoing high-dose radiation therapy. It is also possible to use a spacer in the T3 stage of cancer patients if the tumor is advanced in the opposite direction from the rectal wall (Müller et al., 2016).

Patients with locally advanced prostate cancer (when dissemination of tumor cells is possible), patients who have active bleeding disorders should not be offered the spacer. Patients who had prior prostate surgery, or any other previous treatment of prostate (for example RT, cryotherapy), patients with active inflammation or infection process near the area of injection (perineum, urinary or gastrointestinal tract), chronic renal failure, ongoing anal or perirectal disease should be offered the procedure after thorough evaluation of clinician (Mariados et al., 2015; Müller et al., 2016).

In the RCT conducted by Mariados et al. (2015) there were no device- or procedure-related adverse events, infections or serious bleedings. The study population included 222 patients, with 149 in the spacer arm. This study included patients with T1 and T2 stage of prostate cancer, Gleason score lower or equals 7, Zubrod performance status between 0 and 1 and prostate-specific antigen (PSA) concentration of lower or equal 20 ng/ml.

Studies by Whalley et al., Picardi et al., and Schörghofer et al. on HRS application prior to the radiation therapy included patients with stage T3 and even few cases of T4, Gleason score higher than 8 and PSA higher than 20 ng/mL (Picardi et al., 2016; Schörghofer et al., 2019; Whalley, Hruby, Alfieri, Kneebone, & Eade, 2016).

To investigate adverse events associated with HRS insertion several studies were detected. Three articles (Song et al., 2013; Uhl et al., 2014, 2013) were produced on the same perspective, multi-center, single-arm study. Out of 52 patients included in study 4 were excluded from further analysis. For two patients there was no hydrogel injection, for one it was inadvertent rectal wall injection and in one case it was improper polymer reconstruction. The thickness of the spacer at the midgland was bigger than 5 mm for 44 out of 48 patients. Three patients experienced procedure-related events such as rectal wall penetration, urinary retention

and bladder penetration, which resolved without further sequelae. One patient experienced a device-related event (proctitis). Procedural modifications were made after these events occurred resulting in no further device or procedural adverse events.

The study by Whalley el at. reports that in 29 out of 30 patients intervention was performed successfully. In one case hydrogel was injected in the rectal wall (Whalley, Hruby, Alfieri, Kneebone, & Eade, 2016).

In study designed to assess the late grade 2 toxicity rate after injection of by Chapet et al. one out of 36 patients included in the study developed hematoma behind the bladder, which was removed by laparotomy. However, authors are uncertain if it was due to the injection or placing the fiducial markers (Chapet et al., 2015).

In a retrospective analysis by Schörghofer et al. (Schörghofer et al., 2019) were evaluated patients after implantation of a balloon or gel spacer, where 139 received gel and 264 a balloon. Spacer option was not random and depended on the availability of the device. The insertion of the spacer was originally planned for 494 patients, but in 4.45% of patients hydrodissection was not successful.

Prospective phase 2 clinical trial by Chao et al. had 31 participants reported no adverse event connected either with the procedure or with the device (Chao, Lim Joon, et al., 2019) after injection of hydrogel spacer prior to radiation therapy.

Another study by Chao et al. with 76 participants included patients with clinical stage T1-T3 prostate cancer and reported that all of the patients successfully underwent hydrogel injection with no adverse events related to the device or procedure (Chao et al., 2018).

2.1.6 Review of effectiveness of HRS in literature

The literature review resulted in the identification of several relevant observational studies on the topic of the clinical effectiveness of HRS. This includes tree systematic reviews and one RCT, three guidelines (one by Cancer Care Ontario (CCO), another by National Comprehensive Cancer Network (NCCN) and the third one by National Institute for Health and Care Excellence (NICE)) and one summary with critical appraisal.

Three systematic reviews on usage of spacers in radiation therapy were performed in Canada by Forero et al. (Forero et al., 2018), the UK by Lawrie et al. (Lawrie et al., 2018), and Switzerland by Mok et al. (Mok et al., 2014). Mok et al. (2014) focused on polyethylene-glycol, hyaluronic acid, biodegradable balloons, and collagen implants. The study concluded that increasing prostate-rectum distance is associated with reducing the volume of rectum exposed

to radiation and maximum dose delivered to rectum under radiation therapy. Forero et al. (2018) reported that injecting SpaceOAR® hydrogel spacer lowers exposure to radiation of the rectal wall. However, the review concluded based on the collected evidence it is unclear if the lowering of rectal-dose volume contributes to a better quality of life and decreased levels of toxicities. In a systematic review by Lawrie et al. (2018), it was reported that there is low-certainty evidence on the association between both balloon and hydrogel spacer application and reduction or other differences in gastrointestinal toxicity outcomes.

Mariados et al. (2015) first published 15-months findings from single-blinded, multi-institutional RCT in 2015. The study included 222 patients randomized in spacer and control arm with 149 patients in spacer arm. Mariados et al. report no difference in acute (less than 3 months after radiation therapy) adverse events between the two groups. Outcomes of late rectal toxicity (3-15 months) favour spacer arm (2% vs 7%, P = 0.044) (Mariados et al., 2015). 3 years results of RCT published by Hamstra et al. and Karsh et al. involved 63% of patients from the original patient population. Studies found lower incidence rate of grade ≥1 and grade ≥2 rectal toxicity in spacer arm (2% vs 9.2%, P=0.028; 0% vs 5.7%, P=0.012, respectively). There was no difference between study groups in incidents rates of urinal late toxicity of grade ≥1 and grade ≥2. Results on quality of life in three publications from the same RCT were measured by EPIC questioner (Hamstra et al., 2017; Karsh et al., 2018).

In the retrospective study by te Velde et al. with 125 patients in total and 65 of them in the hydrogel spacer arm was found that reduction of rectal dose resulted in the reduction of diarrhea. However, there was no evidence found that SpaceOAR® improves the outcomes for the patients in terms of proctitis, hemorrhoids and fecal incontinence (te Velde, Westhuyzen, Awad, Wood, & Shakespeare, 2017).

The study conducted by Pinkawa et al. with 167 participants, 101 of them was in HRS arm showed that hydrogel spacer injection has no effect on acute rectal toxicity, but improves outcomes of late rectal problems. Patients were selected into HRS arm depending on their preferences and responsible radiation oncologist. Outcomes were measured with a validated questionnaire (Expanded Prostate Cancer Index Composite, EPIC) (Pinkawa et al., 2017).

In a non-randomized study by Walley et al. with 30 patient in the spacer group and 110 in the control group was reported no difference in incidents of grade 1 and grade 2 gastrointestinal toxicity (43% vs 51% and 0%vs 45% in spacer and control group, respectively). There were fewer incidents of grade 1 late toxicities in HRS group (16.6% vs 41.8%, P=0.04) (Whalley et al., 2016).

Guidelines by CCO in Canada concluded that preselected patients with prostate cancer usage of HRS may result in the lower toxicities incidence rate and preserve the quality of life (Chung, Brown, D'Souza, Koll, & Morgan, 2019). NICE guidelines in the UK resumed sufficiency of current evidence for insertion of spacer to decrease toxicity for prostate cancer patients (NICE, 2017). NCCN guidelines in the USA suggested the usage of HRS to improve the immobilization of prostate in cases when it is not possible to lower side effects or increase oncologic cure rate with other techniques (NCCN Guidelines, 2018).

In 2019 the report by Canadian Agency for Drugs and Technologies in Health (CADTH) stated that the current evidence is not adequate to assess the benefits of HRS usage and to reduce present uncertainty further high-quality studies needed. As well, the report points out the other possible options to reduce adverse events after radiation therapy for prostate cancer patients (high-fiber diet, optimization of radiation dose, radiation therapy technique) (Chao, MacDougall, & de Nanassy, 2019)

Several other studies have been published on the use of SpaceOAR® with different radiation therapy options and with comparison to other spacers (M. Chao et al., 2018; M. Chao, Lim Joon, et al., 2019; M. Chao, Ow, et al., 2019; Fischer-Valuck, Chundury, Gay, Bosch, & Michalski, 2017; Hedrick et al., 2017; Juneja et al., 2015; Pinkawa et al., 2011; Rucinski et al., 2015; Ruggieri et al., 2015; Schörghofer et al., 2019; Trager, Greenberger, Harrison, Keller, & Den, 2018; van Gysen, Kneebone, Alfieri, Guo, & Eade, 2014; Weber et al., 2012; Wilton et al., 2017; Wolf et al., 2015). However, their quality can be argued due to various sorts of bias, small sample size, and short follow-up. It was detected a vulnerability of not randomized studies to the confounding and selection bias. Thus, there is a possibility of prior selection of patients with better health for participating in HRS arm. From the published RCT it was unclear whether the patients were blinded during all the period of trial or just at the randomization. As well, it was unclear whether the clinicians were unaware of the randomization between treatment groups.

There is no available at hand clinical data on the effectiveness of SpaceOAR® with other prostate cancer therapies (i.e. hormone therapy, surgery). However, clinical opinion suggests that there should be no impact on those mentioned above.

2.2 National Health Care system and the National Reimbursement Scheme

Based on the principals of equality, fairness, quality of services and free choice of the provider Norwegian National Health Care system is predominantly publicly owned and mainly financed by taxes. National Insurance Scheme, membership in which is universal and mandatory, covers all residents of the state. The possibility to purchase private insurance is limited. The municipalities, the four regional authorities, and the State form three levels of the National health care system. Both Parliament, as a legislative body, and, as an executive body, Government along with the Ministry of Health and Care Services are responsible for the provision of national health policy, budgeting, and licensing institutions at the national level. While four regional authorities are in charge of provision, planning, and financing of specialist care, municipalities are responsible for social services and primary health care provision in correspondence to local demand. Thus, the provision of health care services is decentralized. Health care expenditures per capita in 2017 in Norway were 10.4 % whereas average amongst European Union countries is 9.6 % (OECD & European Union, 2018).

To ensure equal access to medication regardless of income and economic status preapproved medicines are subjects for general reimbursement. Preapproved reimbursement through the National Insurance Scheme bases on the disease severity and treatment duration. Patients partly bear the cost burden of treatment with out-of-pocket payments, which are set up to a certain limit by a parliament each year and in 2019 the limit is 2369 NOK (HELFO, 2019). Once the out-of-pocket limit is reached, the exemption card will provide the patient with a free health care service. To be a part of the national reimbursement scheme pharmaceuticals require approvement by the Norwegian Medical Agency (NoMA). The reimbursement for medicines that are not covered by general reimbursement for individual patients is decided by the Norwegian Health Economics Administration (Helseøkonomiforvaltningen, HELFO).

2.3 Priority setting

In the light of increasingly constrained budgets in the healthcare sector worldwide including Norway, together with increasing demand for health care due to technological innovations and growing population, the need of priority setting to ensure equal access to treatment across patient groups has become evident. Priority setting within health care is especially hard due to its complexity and quantity of stakeholders. On an individual level,

healthcare professionals make decisions regarding the patients' health and have a primer contact with a patient and his relatives, whereas strategical decisions regarding resource allocation within the healthcare sector are made by politicians. The Framework for the priority setting within health care sector was established by governmental commissions such as the Lønning I (1987), the Lønning II (1997), the Norheim Commission (2014), and the Magnussen Working Group (2015) (Norwegian Ministry of Health and Care Services, 2017). The overarching aim of priority-setting in the Norwegian healthcare sector is achieving "biggest number of healthy life years for all people, fairly divided between them"(Ottersen et al., 2016). The first commission represented five levels of priority setting, grading mostly on the severity of the condition (NOU 1987: 23). In later report Lønning II it was recommended three bases for priority: expected benefit, criteria of severity and cost-effectiveness (NOU 1997: 18). Norheim Commission came up with three revised after Lønnings II priority setting criteria, which were recommended to apply ubiquitously to the health care sector and considered collectively. The recommended criteria were: the health-benefit-, the resource- and the health-loss criteria (NOU 2014:12). While the health-benefit criterion suggests that an increase in expected health benefit results in higher priority, resource criterion states that intervention with fewer resources used should be prioritised. Expected health benefit can be measured by prolonged patients life (increased survival) and improved patients quality of life (pain reduction, improvement in psychological and physical state, a decrease of psychological and physical discomfort). Thus, quantification of the benefit criterion can be done using the term "healthy life years", which accommodated the abovementioned points. The resource criterion is suggested to be widely used especially at the clinical level, where health care professionals continuously are making decisions about resource allocation and prioritization. The health-loss criterion recommends that increase in expected health-loss over the lifetime of the patient will lead to a higher priority of intervention. Thus, the intention was that this criterion reflects previous, current and future health state of the patient or group of patients. Cost-effectiveness analysis takes a major place in this framework (NOU 2014:12).

However, the health-loss criterion was vastly criticized, as it potentially may result in unequal access to health care for the patients with nearly equal future health loss and needs. Therefore, a new working group, known as "Magnussen group" was appointed by the government in 2015. Its task was to work out a framework on assessing the severity of the disease in priority setting within the healthcare sector. The report was issued later in 2015 suggesting recommendations for assessing severity and willingness-to-pay thresholds contingent on the levels of severity (Magnussen, 2015).

2.3.1 Quantification of severity and absolute shortfall

While in the clinical setting qualitative measurement mostly defines severity, in priority setting for the health care sector severity becomes quantitative assessment with the practical application in health economics calculations. Operationalizing quantitatively the severity criterion enabled the possibility of evaluating whether the intervention is within the budget of interest, as well referred to as willingness-to-pay (WTP) threshold – the maximum amount of money that can be spent to gain additional healthy life year. WTP threshold enhances following the increase of severity grade.

The Magnussen group recommended that priority of intervention should raise following the increase of conditions severity. The severity assessment is based on:

- risk of death or loss of function;
- the degree of physical and mental function loss;
- level of pain, physical or mental discomfort.

To operationalize severity four approaches were considered by the Magnussen group. The concluding recommendation was to incorporate "absolute shortfall" of healthy life years as a key characteristic of conditions severity. "Healthy life years" defines both health losses and health gains in terms of both improved quality of life (QoL) and increased survival (Magnussen, 2015). Thus, the absolute shortfall can be explained as how many healthy life years are lost as a result of early death or decreased QoL under the disease duration, or the future loss of healthy life years. A staircase model was suggested by the Magnussen group includes six severity levels with six thresholds for each group accordingly. The overview of the absolute shortfall is represented in Table 3. Thus, for the severity group 6 with an absolute shortfall of 20 + healthy life years, the maximum WTP threshold equals 825 000 NOK (per life-year). And accordingly, for the severity group 1, with absolute shortfall ranging from 0 – 3.9, maximum WPT threshold equals 275 000 NOK per healthy life year.

Table 3. Relationship between absolute shortfall of healthy life years, and willingness-to-pay (WTP) threshold per additional healthy life years.

	Severity group					
	1	**2**	**3**	**4**	**5**	**6**
Absolute shortfall of healthy life years	0 - 3.9	4 - 7.9	8 - 11.9	12 - 15.9	16 - 19.9	20 +
WTP threshold per additional healthy life years, NOK	275 000	385 000	495 000	605 000	715 000	825 000

**Source: På ramme alvor, alvorlighet og prioritering (2015)*

3 Theoretical framework

3.1 Economic evaluation

Decision-makers in the healthcare sector on all levels, for instance, policymakers, hospitals, and other stakeholders, daily face the situation when they need to make a decision choosing one alternative course of action above the other, keeping in mind budget constrain and opportunity cost. Since resources are scarce, a decision made on financing a particular intervention results in not financing the other intervention, which potentially may be a better deal for the money. Thus, there is a need to have a framework to inform the choice. Economic evaluation enables to inform and advise the decision-making process by a comparative analysis of alternative interventions in terms of consequences and costs of both of them (Drummond, Sculpher, Torrance, O'Brien & Stoddart, 2005). It allows identifying whether the use of money on the intervention being efficient and on policymakers level whether the intervention is eligible for reimbursement. The opportunity cost of prioritizing one intervention can be assessed in the health benefits (for instance quality-adjusted life years (QALYs) gained, life-years saved) which might have been gained had the next best intervention was prioritized.

Economic evaluation has a common format approaching cost, but the approach to the consequences or benefits differs. Hence, it can take the form of the cost-effectiveness analysis (CEA), where effects are quantified in natural units – life-years gained, cost-benefit analysis (CBA), where effects are expressed in monetary units or cost-utility analysis (CUA), where effects are estimated in quality-adjusted life years (QALYs). In this way, when two or more interventions are compared, economic evaluation explicitly defines the opportunity cost of the alternatives.

Economic evaluation can be either trial-based or model-based. Trial-based studies generate data on costs or resources used alongside with data on health effects, which provides a possibility to assess the cost-effectiveness of the intervention. It is extensively debated that, even though being a “golden standard” in regards to bias and confounding, randomized controlled trials may contain some weaknesses in terms of limited time horizon, external validity, they are costly, limited choice of compotators, they may not provide all evidence to estimate cost-effectiveness and they are not always possible to conduct. Following vast consideration on the appropriate trial framework, pragmatic or “real world” studies were suggested to replace or support RCTs (Coyle, Davies, & Drummond, 1998; Briggs, Claxton & Sculpher, 2011). Model-based economic evaluation represents simplified reality and uses a

wide variety of data sources as RCTs, various kinds of registers and administrative databases, clinical experts, observational, clinical and other studies and therefore can perform an extrapolation from intermediate to final endpoints, incorporate evidence for head-to-head comparison of alternatives, extend the result of a clinical trial. However, due to the complexity of the "real world" and limited capacity to simulate multiple complexities it is argued that models are not able to correctly reflect reality.

There are several decision-analytical models, which are frequently used in economic evaluation, including discrete event simulation, decision tree, and Markov model. Being the simplest form of modeling technique, the decision tree has some issues including not explicit time definition and while modeling chronic conditions with multiple numbers of possible consequences decision trees may become very complex (Drummond et al., 2005).

Based on a series of states in which patient can be at a certain time, Markov model allows handling the issues of the increased complexity (Briggs et al., 2011). The probability of staying in a particular state may change over some time period, termed cycle. "No memory" is the main disadvantage on Markov model, which is usually solved by adding additional states.

Depending on the viewpoint from which costs and effects are evaluated, economic evaluation can be performed from the provider, societal, industry and international perspective and the choice of the perspective is a matter of aim and context of the study. NoMA recommends to apply provider perspective, thus including if relevant the costs for transportation to the treatment, out-pocket payments of the patients and their relatives, patients and relatives time consumption connected to the treatment. Effect on the mortality, patients and relative's quality of life should also be included if relevant (Statens legemiddelverk, 2018).

3.2 Health outcomes

There are several instruments to measure the quality of life, which can be divided into two categories: disease-specific and generic. Enabling to measure the effect, disease-specific instruments limit the possibility of comparing intervention within a particular disease. Generic instruments, such as EQ-5D, SF-6, HUI, measure a variety of dimensions both social, mental and physical well-being and mostly express measurements in quality-adjusted life years (QALYs). When effects are measured with a common tool, it allows comparing interventions across the diseases and thus, defining the opportunity cost. QALY accounts for both quality of life, measured from 0 to 1 and referred to as weights, and length of life, estimated in years.

While measuring utility, 0 represents “death” and 1 “perfect health”. However, some conditions may result in values below zero, if one thinks that experiencing this health state is worth than death. QALY is obtained by multiplying the quality of life by the time the patient was in a particular health state. Utilities can be collected from the general public, patients or health care professionals. Pursuing the same goal of measuring the quality of life, instruments differ in the way they are constructed by the number of severity levels and dimensions. Weights can be obtained by the direct method, using, for instance, visual analog scale (VAS), standard gamble, time trade-off (TTO), or indirectly using multi-attribute health state classification (QWB, EQ-5D, HUI, SF-6D) (Drummond et al., 2005). Additionally, QALY as a measure of effect has been approved by NoMA. Different instruments and patient populations from which utilities were elicited may be a source of uncertainty and variability in the model.

NoMA recommends, as a rule, to use EQ-5D to report quality of life outcomes. If outcomes are reported with other instruments they should be converted into EQ-5D. Outcome data should as well be age-adjusted, as the quality of life deteriorates with increasing age (Statens legemiddelverk, 2018).

3.3 Cost-utility analysis

The method of economic evaluation when QALY is applied to measure the effect is called cost-utility analysis and can be classified as a type of cost-effectiveness analysis (CEA). The CUA is commonly used to guide resource allocation policy of decision-makers with respect to both budget constrain and benefit maximization. The CUA, as a preferred method for cost-effectiveness analysis, was recommended by the National Institute of Health and Care Excellence (NICE, 2012) in the UK and NoMA in Norway (Statens legemiddelverk, 2018).

The primary results of CUA are estimating incremental cost-effectiveness ratio (ICER), which is a ratio of incremental costs to incremental effects. For instance, the ICER in a current model, where applying hydrogel rectal spacer (HRS) would be an intervention compared to “do nothing” or Standard Care alternative, would be as follows:

$$ICER_{HRS} = \frac{Cost_{HRS} - Cost_{do\ nothing}}{QALY_{HRS} - QALY_{do\ nothing}} = \frac{Incremental\ cost}{Incremental\ effect} \quad (1)$$

.

If the ICER estimates in a negative value, then HRS may be either dominated (more expansive, but less effective) or dominant (cheaper than alternative and more effective). The result of the CUA as any other cots-effectiveness analysis depends on the willingness to pay (WTP) per QALY obtained.

3.4 Sensitivity analysis

Each economic evaluation deals with some degree of uncertainty and thus may result in misleading of decision-maker. Sensitivity analysis is used to handle and analyze the effect of uncertainty in the analysis and in this way contribute to the decision-making process.

Deterministic sensitivity analysis represents the change in the outcomes of the analysis, as a result of the change in a certain input parameter or set of parameters. One-way sensitivity analysis provides a possibility to track if the outcome is sensitive to a change in one parameter of interest (Drummond et al., 2005). When the changes in the output are the consequences of varying of the two parameters together within a certain range it is called a two-way sensitivity analysis. However, this type of analysis does not provide us with the probability of occurring each of the possible scenarios.

Probabilistic sensitivity analysis (PSA) handles the parameter uncertainty of all parameters simultaneously and enables one to estimate the probability of intervention to be cost-effective at different thresholds and in this way makes quantification of decision uncertainty (Drummond et al., 2005). Both NoMA and NICE recommend using PSA in health economic evaluation. To express parameter uncertainty a defined probability distribution for each parameter will provide a range of values this parameter may potentially take. Later, probabilistic estimates of each parameter are simultaneously collected to provide a single output value. This procedure is called Monte Carlo simulation and is repeated as usual 10 000 times. It enables both to express decision uncertainty and to consequently continue analysis with the value of information assessment.

After the simulation, the results are presented in the form of the joint density of incremental costs and incremental effects on the cost-effectiveness plane and later on cost-effectiveness acceptability curves (CEAC) and cost-effectiveness acceptability frontier (CEAF) graphs. Both CEAC and CEAF are defined by the position and form of the joint density of incremental costs and incremental effects on the cost-effectiveness plane. A cost-effectiveness plane is divided into four quadrants: southwest (SW), and northwest (NW), northeast (NE),

southeast (SE) (Briggs et al., 2011). If intervention dominates the compotator, it is located in the southeast quadrant. In northwest quadrants located interventions, which are more costly and less effective. When intervention is more effective and more costly, it falls into the northeast quadrant, while southwest quadrant contains less costly and less effective interventions.

3.5 Cost-effectiveness acceptability curve

To represent the probability of the treatment option of being cost-effective at a given level of WTP threshold cost-effectiveness acceptability curves (CEACs) were plotted. The results of PSA are used to estimate total effects (E) and costs (C) for a given number of simulations, in this paper it is 10 000 and later calculates net monetary benefit (NMB) for an every cost-effectiveness threshold (λ), employing the formula:

$$NMB = \lambda * \mathrm{E} - \mathrm{C} \qquad (2)$$

The alternative with higher NMB is then cost-effective at a particular WTP threshold and this alternative was identified for each of 10 000 simulations. The proportion of iterations with higher NMB illustrates the probability of alternative being cost-effective given the particular threshold or range of thresholds (Barton, Briggs, & Fenwick, 2008). However, the optimal alternative cannot be identified from the CEAC. Therefore, the cost-effectiveness acceptability frontier (CEAF) was applied to illustrate the probability that the optimal alternative is cost-effective at given values of WTP (Barton et al., 2008).

3.6 Value of information

As data for the model is collected from different sources, uncertainty connected to both parameters and model assumptions is an unavoidable issue of the model-based approach. Opportunity loss may occur if an ineffective alternative is preferred. No or postponed decision, would as well causes health forgone, in the case where the alternative should have been implemented. Value of information analysis (VOI) can be employed to assess the expected value of resolving the uncertainty associated with estimates of the model, evaluating if the information at hand is sufficient to adopt the intervention or the further research is required (Ophuis et al., 2018). If it is so, to investigate what king of future research or evidence is needed.

EVPI

Expected value of perfect information (EVPI) estimates in monetary terms simultaneously elimination of all uncertainty surrounding the parameters for an individual patient or case. Even though any additional evidence would not be able to resolve all the uncertainties, EVPI provides a measure for maximum value for additional research. EVPI is obtained from the results of PSA by deducting expected net-benefit with current information from expected net-benefit with perfect information.

Firstly, expected net-benefit with current information is defined by finding an alternative *j*, which will maximize NB with the information at hand and unknown parameters θ:

$$Max_j \, E_\theta NB(j, \theta) \qquad (3)$$

Perfect information would inform the decision-maker which alternative maximizes NB by revealing the true values for all the parameters θ. However, in reality, they are unknown. Therefore, expected net-benefit with perfect information is calculated by averaging the highest net-benefits between all the alternatives for each iteration:

$$E_\theta Max_j NB\ (j, \theta) \qquad (4)$$

Afterward, EVPI is calculated by the following formula:

$$\text{EVPI} = E_\theta Max_j NB\ (j, \theta) - Max_j \, E_\theta NB(j, \theta) \qquad (5)$$

Population EVPI

While assessing EVPI, it is important to take in consideration all patients, which may benefit from this decision during the expected lifetime horizon of intervention. In case, if EVPI for the population is higher than the costs of extra research, it might be cost-effective to perform it. The population expected value of perfect information is calculated by scaling up the individual EVPI with an estimated incidence of cases (I), which require the use of this intervention, each year over the effective lifetime of the new (t):

$$pEVPI = EVPI. \sum_{t=1,2\ldots,T} I_t \,/(1+r)^t \qquad (6)$$

Expected value of perfect information for parameters

The analysis of perfect parameter information identifies the key parameters, whose uncertainty results in decision uncertainty and gives the direction for future research, taking in consideration WTP threshold. Expected value of perfect information for parameters (EVPPI) for the particular parameter or group of parameters is calculated by deducting expected value with current information from the expected value with perfect information about the parameter(s) (Briggs et al., 2011). Hence, defining the perfect information about a set of parameters or one parameter as θ1, gives the possibility to detect intervention, which maximizes the expected NB over the other uncertain parameters θ2:

$$EVPPI_{\theta 1} = E_{\theta 1} Max_j E_{\theta 1|\theta 2} NB\ (j, \theta 1, \theta 2) - Max_j\ E_{\theta} NB(j, \theta) \quad (7)$$

As all parameters are uncertain (θ = θ1+ θ2), θ in the EVPPI formulae is the same as used in EVPI calculations. After calculating EVPPI; the outer loop is created by running the simulations for all the remaining uncertain parameter(s) θ2 with the fixed values of the parameter(s) of interest in inner loop θ1. To provide sufficient results the procedure is repeated multiple times. As it is recommended by Briggs et al. (2011) at least 1000 iterations in the inner and outer loop produce enough samples for future analysis.

VOI analysis in this paper was performed applying a non-parametric approach described by Briggs et al. (2011).

3.7 Budget impact analysis

A budget impact analysis (BIA) is aimed to assess financial consequences and affordability of the decision at hand for the health care provider and with this secure effective resource allocation. It is performed by comparing the expenditures associated with introducing and maintaining intervention over the definite number of years with expenditures associated with Standard Care over the same number of years. Expenditures should be compared yearly and NoMA in its guidelines suggests 5 as an appropriate number of years over which, the BIA should be calculated. This should provide decision-maker with information on how costly the implementation of new intervention would be, when in time the costs will occur and when eventually the costs of intervention would be lower than Standard Care.

In this paper, the BIA is conducted for the primary analysis considering 5 years time horizon. No discounting was performed on either cost or patient population. The BIA, as well as this paper itself, is calculated from the Norwegian healthcare provider's perspective. The methods described in International Society for Pharmacoeconomics and Outcomes (ISPOR) task force report by Sullivan et al. (Sullivan et al., 2014) and NoMA guidelines (Statens legemiddelverk, 2012) were used in BIA assessment. The patient population was increased following the prognosis of the future prostate cancer incidence by Tom Børge Johannesen (Johannesen, 2019) from the Norwegian Cancer register.

3.8 Review of cost-effectiveness studies

It was identified several studies on assessing the cost-effectiveness of HRS for prostate cancer patients undergoing radiation therapy.

Cost-utility analysis conducted in 2015 by Vanneste et al. compared the cost and utilities of EBRT with and without spacer with 5-year time horizon using a Markov Model. Authors estimated the total cost for spacer group to be €3144 (€1700 was spacer treatment cost) and €1604 for the comparator. EBRT with spacer gained 0,028 quality-adjusted Life Years (QALY) compared to the comparator (3.570 vs 3.542), which resulted in incremental cost-effectiveness ratio (ICER) of €55 880 per QALY gained. Considering the ceiling ratio (threshold) of €80 000, the intervention had 77% probability of being cost-effective (Vanneste et al., 2015).

In 2016, Hutchinson et al. constructed a decision tree model to evaluate the cost-effectiveness of HRS. Authors compared the costs of rectal toxicities over a 10-year time horizon and across three radiation therapy techniques. Both direct and indirect costs were included in the analysis. Data on toxicity rates were taken from the literature, indirect costs were acquired from the literature, whilst direct costs data for GI complications and standard follow-up were derived from the author's institution. The results of the analysis were dependent on different radiation therapy modalities. The study assessed total cost of conformal radiation therapy to be higher with HRS ($3.428 vs. $3.946) than without, with an incremental cost of $518. The spacer was instantly cost-effective for dose-escalated SBRT (Hutchinson et al., 2016).

In a European study carried out by van Wijk et al. in 2017, it was aimed to identify the patients who will benefit from HRS insertion by creating a prediction model with a virtual internal rectum spacer. The model was tested on 8 patients with virtual spacer balloon implants

and 8 patients with virtual HRS. The real spacers were implanted to 23 patients (8 with HRS and 15 with balloon). Cost-effectiveness analysis, based on the model developed by Vanneste et al., estimated that HRS was cost-effective to 2 out of 8 patients at WTP threshold of 80 000 EURO. The conclusion was that the HRS is not cost-effective for all patients and decision on insertion of the HRS should be based on the assessment of the individual patient data (van Wijk et al., 2017).

Forero et al. in 2018 the examined the cost-effectiveness of HRS and performed a budget impact analysis to estimate the monetary consequences of the intervention. The study was conducted in Canada. Authors assessed ICER of CAD $191 230 for avoiding one additional case of rectal toxicity with a grade equal or higher than 2. In addition, it was concluded that data was too unreliable for QALY calculation. Budget impact analysis evaluated costs of treating 70 patients to be higher with HRS added on (CAD $388 015.60 and CAD $189 901.26 respectively). Costs included costs of complication, procedure, and device itself (Forero et al., 2018).

In 2018 Levy et al. conducted a cost-effectiveness analysis of HRS in the US comparing EBRT alone EBRT + HRS with the 5-year time horizon. Authors constructed a multistate Markov model assessing three possible settings for the procedure: ambulatory surgery center, physician office, and hospital outpatient. Subgroup analysis was performed for patients having a good erectile function at the baseline. Data on adverse effects of radiation therapy and erectile dysfunction were derived from recent published RCT (Hamstra et al., 2017; Mariados et al., 2015). Data on costs and utilities were acquired from the literature and discounted at 3% rate annually. The analysis demonstrated incremental effectiveness of 0.0371 QALYs, ICER was $96 440 per QALY gained for patients undergoing HRS injection in hospital and $39 286 per QALY gained for patients having the procedure done in an ambulatory facility. With the willingness to pay (WTP) of $100 000 HRS had 44.21 % probability of being cost-effective in the hospital setting (Levy et al., 2019).

4 Methods

4.1 Patient population

The patient population consists of males, aged 69, with intermediate, high-localized and high locally-advanced prostate cancer, who was referred to the dose-escalated external beam radiation therapy of prostate. The analysis was based on the Norwegian setting, where low-risk patients or/and young patients are not treated with radiation therapy as usual. 69 years is a median age for men in Norway for both prostate cancer diagnosis and to get curative radiation therapy (Kreftregisteret, 2018). The application of HRS is possible and considered to be safe for stage T1 and T2 of prostate cancer. For patients with T3 hydrogel, injection is possible in case if the tumor is advanced in the opposite direction from the insertion location. Exclusion criteria include active bleeding disorders, active inflammation or infectious disease in the area of interest, previous treatment of prostate with radiotherapy, cryotherapy and high-intensity focused ultrasound. The decision for these patients as well as for patients with stage T3 prostate cancer is made individually by the clinician. It was estimated that HRS may be applied to 50% of patients with stage T3 prostate cancer.

The patient population for the secondary analysis involves the same cohort of men now taking into account their erectile function prior to radiotherapy. Three possible prevalence subgroups were considered: all men have good erectile function at the baseline; all men experience erectile dysfunction (ED) at the baseline; prevalence of ED is 62% at in study by Hamstra et al (Hamstra et al., 2018), which was conducted along with RCT for HRS SpaceOAR®.

4.2 Comparator

The comparator is Standard Care of prostate cancer patients referred to receive curative treatment in the form of dose-escalated external beam radiation therapy. Standard Care is described in the treatment pathway (package) for prostate cancer (Helsedeiktoratet, 2019) and National action program with guidelines for diagnostic, treatment and follow-up of prostate cancer by Norwegian Directorate of Health (Solberg et al., 2015). As usual, after being referred to radiation therapy, patients undergo 3 ordinary planning meetings with a clinician for radiation therapy and one complex planning meeting, where golden markers are inserted. In Norway,

patients are offered dose-escalated external beam radiation therapy delivered during 38 sessions with a total dose of 78 Gy.

After radiation therapy patients are recommended to visit a medical professional at 3, 6 and 12 months for follow-up, later each half-year to the third year after radiation therapy and after that yearly. First two meetings patients have in an out-patient setting with a clinician. General practitioners perform all later controls.

4.3 Intervention

Intervention includes inserting Hydrogel Spacer SpaceOAR® (Augmenix, Inc.) between prostate and rectum prior to the radiation therapy, at the same time with golden markers insertion. The procedure is done once. After injected as a liquid between the anterior rectal wall and Denonvilliers` fascia hydrogel polymerases to form a barrier of soft, biodegradable gel approximately 10 - 15 mm in thickness. It was estimated that the mean overall time of the procedure is 16 min with SD of 7, 8 min (Hatiboglu, Pinkawa, Vallée, Hadaschik, & Hohenfellner, 2012). During the course of radiation therapy spacer remains stable. Absorption of spacer occurs around six months after the injection (Pinkawa et al., 2011). The procedure requires one clinician and one nurse to perform.

Based on effectiveness studies described in Section 2, the insertion of SpaceOAR® minimizes the adverse effects after radiation therapy such as genitourinary and gastrointestinal toxicity and may help to preserve erectile function.

4.4 Perspective

For this cost-utility analysis of HRS SpaceOAR®, a provider perspective was adopted. The broader provider perspective considers solely health outcomes for the patient, direct medical costs associated with the treating prostate cancer patients with radiation therapy, patient’s out-pocket payments with respect to the treatment. The direct costs include costs associated with consultations prior to radiation therapy, delivering radiation therapy and costs of follow-up.

Following NoMA recommendations an approximate cost associated with GP consultation was estimated as a sum of patient out-pocket payment and reimbursement multiplied by two (Statens legemiddelverk, 2018).

4.5 Health outcomes

Quality-adjusted life-years (QALYs) are the primary outcomes of the current analysis. HRS does not influence the mortality, thus life years gained will be equal in the Standard Care and intervention group. For the main analysis, QALYs were estimated with age-dependent EQ-5D and HUI3 valuation instruments separately to assess the magnitude of difference between instruments. Secondary analysis was performed employing just the EQ-5D instrument.

4.6 Choice of model

To assess the long-term health effects and costs of the treatment a decision tree and a state-transition Markov model were developed. Fig. 1 represents a decision tree for the primary analysis, whilst Fig. 2 represents a decision tree for the secondary analysis.

The decision tree reflects possible prognoses for an individual as a result of the intervention. The decision addressed in the tree on the Fig. 1 is which of the alternatives is more cost-effective in preventing incidents of adverse events connected to the irradiation of prostate, in particular, genitourinary and gastrointestinal toxicity, Standard Care of delivering radiation therapy or Standard Care with additional HRS insertion. The decision is represented by a decision node, a square box, at the start of the decision tree on the left. Following the alternative pathways, which goes from the decision node and represent effects of intervention and comparator, individual through the chance nodes (circles) moves to the right part of the tree. Branches of the tree represent events. Each branch that goes from a chance node of the tree is assigned with the probability of a particular event happening. The sum of probabilities coming from the same chance node equals 1. By multiplication of branch and subsequent pathway probabilities are calculated. In the decision tree in Fig. 1 there are 3 pathways for the Standard Care group and 9 for the intervention. Being mutually exclusive, the sum of the probabilities for each alternative equals 1.

Depending on the cancer stage, the patient population is divided into three risk groups: intermediate-risk group, high-localized risk group, and high-locally advancer risk group. Patients diagnosed with prostate cancer are referred to as radiation therapy. Prior to it, they will or will not be inserted with HRS. HRS insertion procedure may be successful, or procedure or device-related adverse event might occur (improper polymer reconstruction, rectal wall penetration, the low thickness of the spacer). As well, patients who could receive HRS may fall under the exclusion criteria or will not be inserted due to the impossibility of hydrodissection.

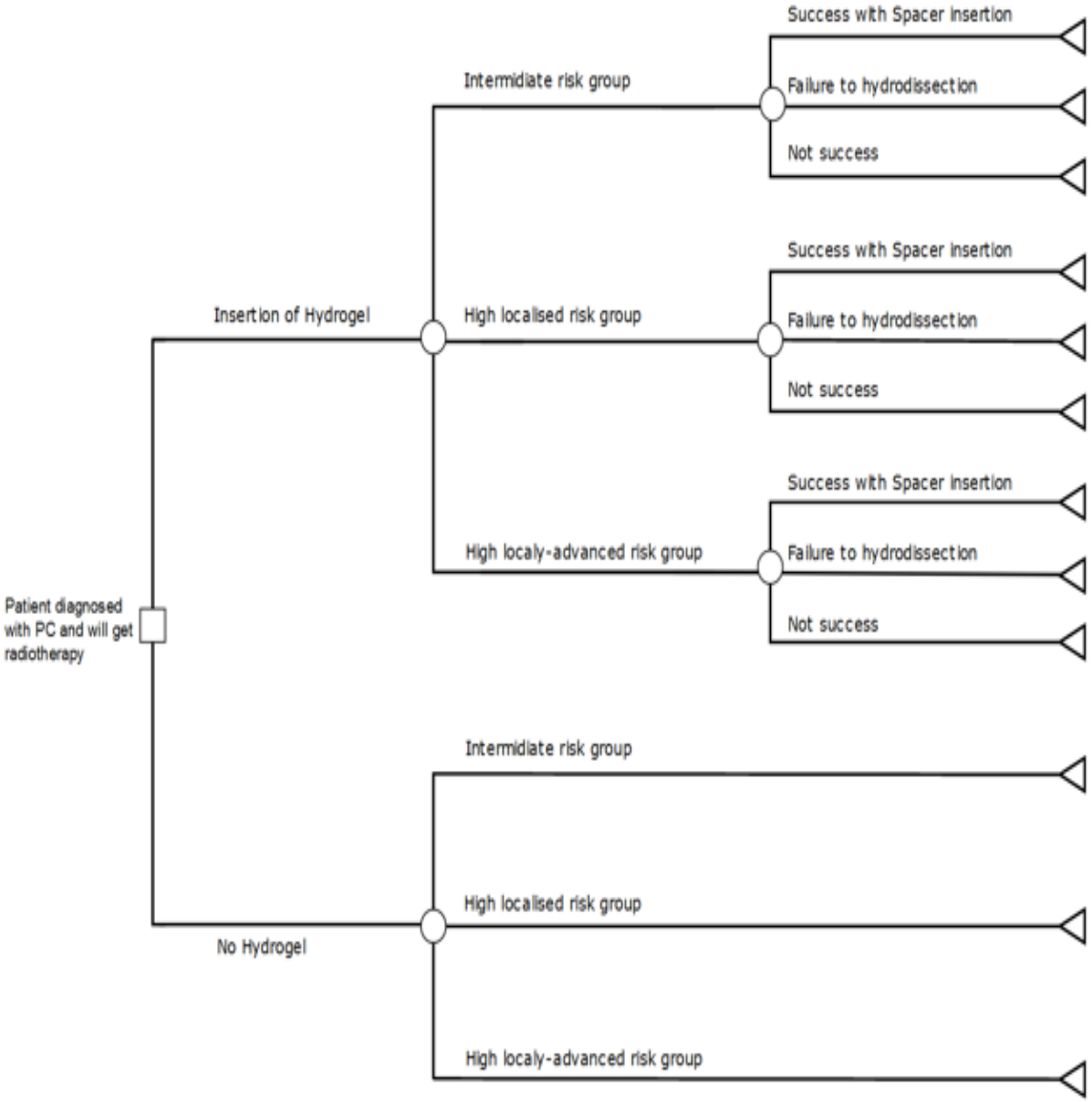

Figure 1. Decision tree for the main analysis comparing Standard Care to Standard Care with HRS.

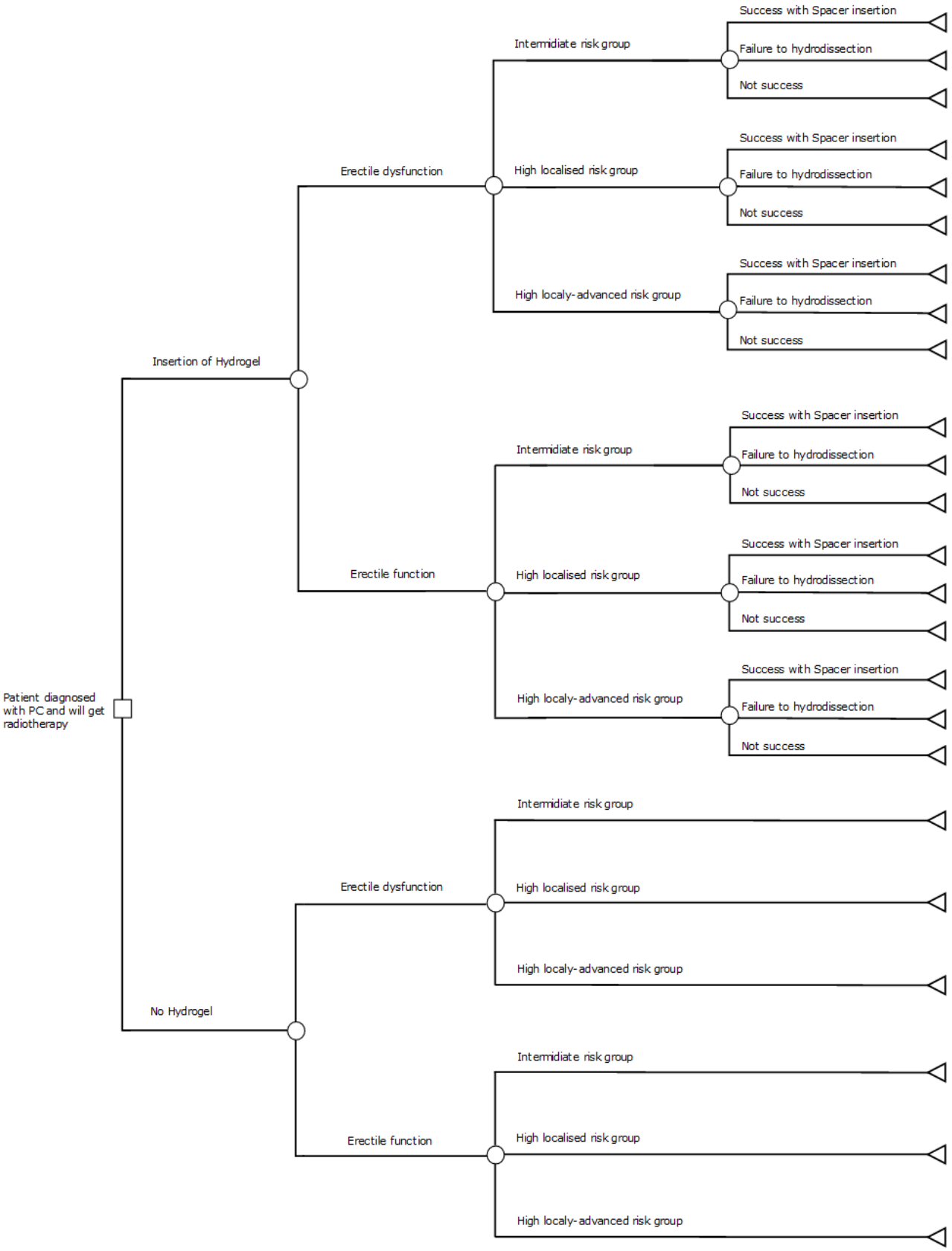

Figure 2. Decision tree for the secondary analysis comparing Standard Care to Standard care with HRS, considering that a part of the patients has a good erectile function at the baseline.

The decision addressed in the tree on Fig. 2 is similar to the decision tree in Fig.1, but in this case to the GI and GU toxicities ED added on, given that a part of the patient population has good erectile function /erectile dysfunction/prevalence of ED 62% prior to the radiotherapy. Here patients will start the decision tree as well at the decision node (square box) on the left side of the tree and proceed to move to the right following the alternative pathways.

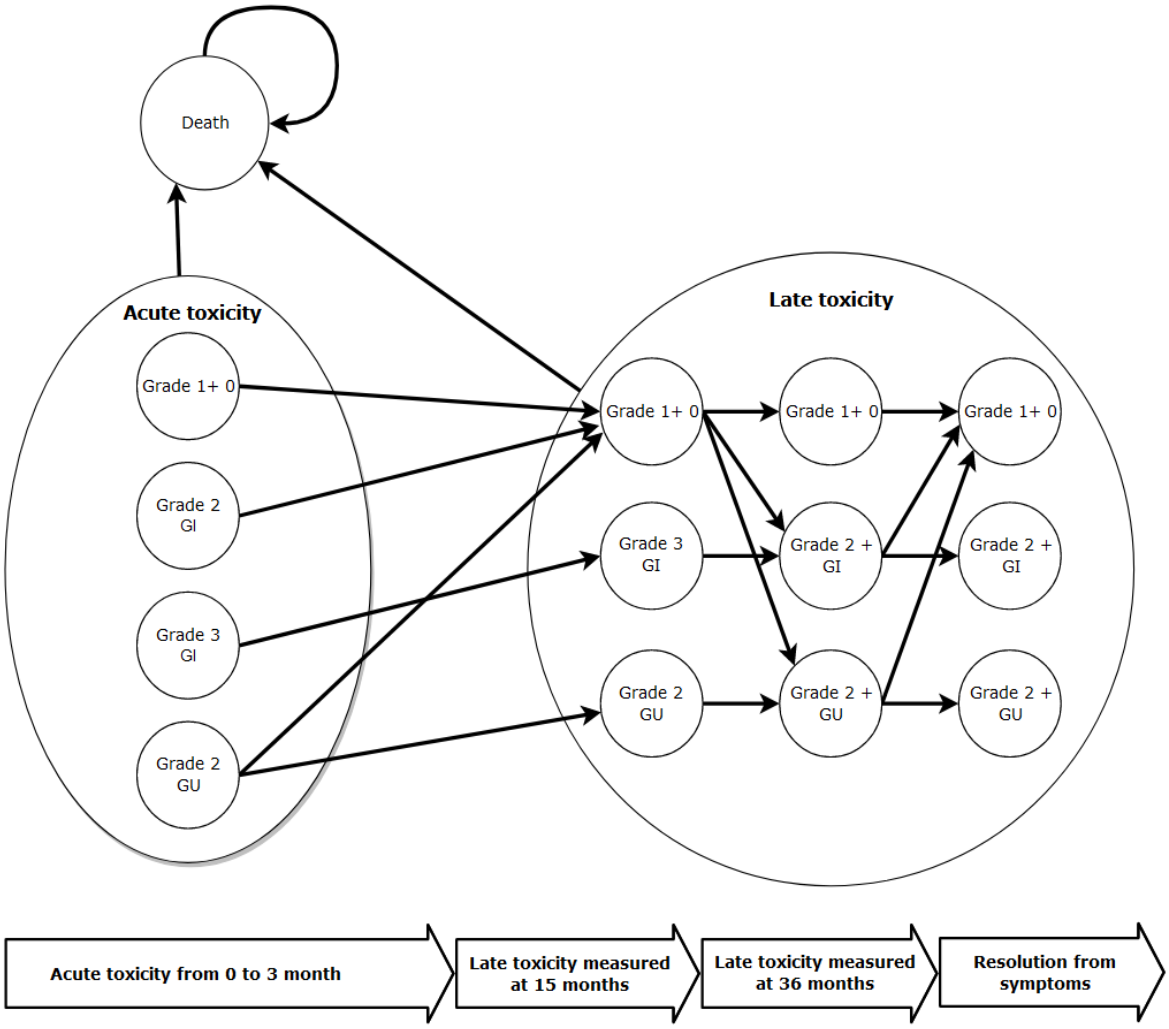

Figure 3. Markov state transition model of gastrointestinal and genitourinary toxicity comparing Standard Care to Hydrogel Spacer SpaceOAR® application along with the Standard Care treatment. Circles in the Markov model represent states. Lines in a Markov model represent transitions between states.

The model consists of two overarching states: acute and late toxicity, and death (All-cause mortality). In acute toxicity, there are following states: no adverse events (Grade 1+0), grade 2 gastrointestinal toxicity (Grade 2 GI), grade 3 gastrointestinal toxicity (Grade 3 GI), grade 2 genitourinary toxicity (Grade 2 GU). Late toxicity is divided on measurements done at 15 months and 36 months. After 12 months and 36 months, some of the patients experience resolution from GU and GI symptoms respectively. Late toxicity contains following states: no adverse events (Grade 1+0), grade 2 gastrointestinal toxicity (Grade 2 GI), grade 3 gastrointestinal toxicity (Grade 3 GI), grade 2 genitourinary toxicity (Grade 2 GU), grade 2 and higher gastrointestinal toxicity (Grade 2+ GI) and grade 2 and higher genitourinary toxicity (Grade 2+ GU).

The model reflects toxicity measurements from the RCT (Hamstra et al., 2017; Mariados et al., 2015) and as well includes some assumptions based on clinical opinion and available literature, mentioned in Section 2. Time in the model goes from left to right. Circles in the Markov model are states. Lines in a Markov model represent transitions between states.

Patients enter the Markov model depending on the outcome of the decision tree and moves between its mutually exclusive states, at time periods named "cycles". From months 0 to months 3 individuals are located in one of the health states (no adverse events (Grade 1+0), grade 2 gastrointestinal toxicity (Grade 2 GI), grade 3 gastrointestinal toxicity (Grade 3 GI), grade 2 genitourinary toxicity (Grade 2 GU)) within overarching state, which is called "Acute toxicity". "Grade 1+0" for both late and acute toxicity contains individuals with grade 0 and grade 1 GI and GU toxicities. This conservative assumption was made, as there is no or very little cost and discomfort for the patient associated with having grade 1 GI or GU. After the third month, individuals are moving to the overarching state "Late toxicity". In RCT there were two measurements of late toxicity at 15 and at 36 months. Consequently from the "Acute toxicity" patients will proceed to the states at 15 months and then at states at 36 months. As there were too few or no observations for the late toxicity states at 36 months, it was made an assumption to merge grade 2 and 3 together for both GI and GU toxicities.

The impact of acute toxicity state on costs and utilities is considered to be 3 months. Some patients will experience the resolution of their symptoms. Time to resolution of late GI toxicity is 36 months (S. R. Hummel, Stevenson, Simpson, & Staffurth, 2012; S. Hummel, Simpson, Hemingway, Stevenson, & Rees, 2010) and late GU is 12 months (Zelefsky et al., 1998). Therefore, patients who experience resolution from the symptoms move from "Grade 2+ GI" and "Grade 2+ GU" back to "Grade 1+0".

For example, if man after radiation therapy experience acute GU toxicity grade 2, he will enter the Markov model in health state "Grade 2 GU". If later he will still have the symptoms of late GU toxicity grade 2 at 15 months and at 36 months, he will be transferred to "Grade 2+GU" at 15 and 36 months. The patient can have a resolution of the symptoms, then he will be transferred to "Grade 1+0" or never have resolution and stay in "Grade 2+GU".

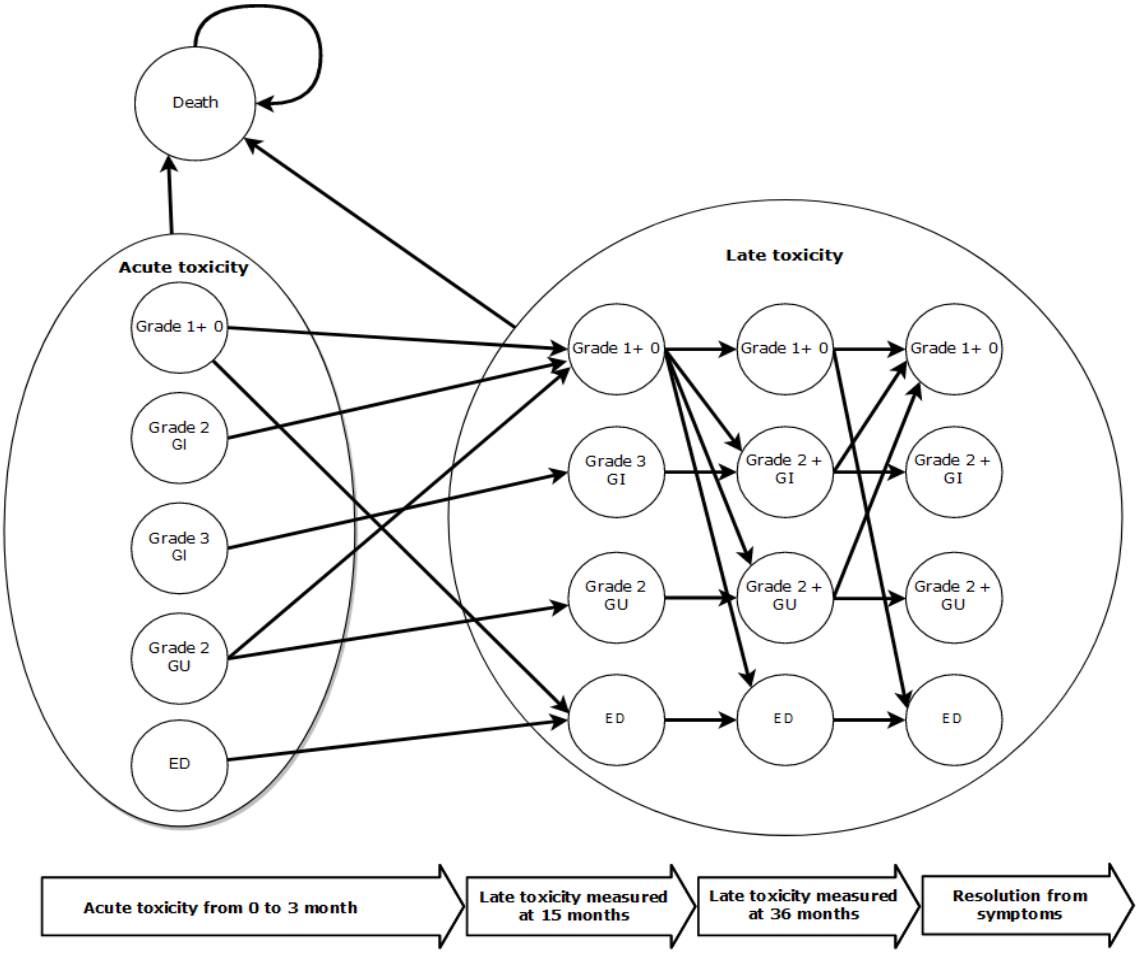

Figure 4. Markov state transition model of gastrointestinal and genitourinary toxicity comparing standard care to Hydrogel Spacer SpaceOAR® application along with the standard care treatment accounting for ED. Circles in Markov model represent states. Lines in a Markov model represent transitions between states.

Description of this model similar to the previous with the addition of "ED" (erectile dysfunction) health state both in acute and late overarching toxicity health states.

An additional state of "Erectile dysfunction" was added to make a model for the secondary analysis. It was assumed that patients cannot be cured of ED, if they had it at the baseline or once they get it, they cannot be cured as well.

Regardless of the state, all the patients have the same probability of dying, which depends on the individual's risk group and time in the model (number of the cycle). "Death" is an absorbing state with no further probabilities out of it.

Cycle length is three months and each cycle patient can be only in one health state. Cost and utilities were assigned for each cycle.

4.7 Half-cycle correction

The transition between states in Markov models occurs in the end or at the beginning of the cycle, but in reality, time of transition may not be known, however, expected to occur somewhere within the cycle, most likely in the middle of it (Naimark, Bott, & Krahn, 2008). Thus, to avoid possible over- or underestimating both cost and health outcomes half-cycle correction was applied to them.

4.8 Time Horizon

NoMA recommends to apply time horizon that should be long enough to represent the difference between alternatives in terms of all possible future costs and effects and an increase in it will not greatly influence the outcome (Statens legemiddelverk, 2018). International Society for Pharmacoeconomics and Outcomes Research (ISPOR) suggests using 120 years as an endpoint of the modeling or following up patients until 99.9% is dead (Siebert et al., 2012). The current model was built with a lifetime horizon with a maximum age of 106 years (Statistics Norway, 2019).

4.9 Discount rate

In order to address future uncertainty, the Norwegian guidelines for economic evaluation recommend discounting future costs and health outcomes at the rate of 4% to recalculate them to the present value (Statens legemiddelverk, 2018).

4.10 Absolute shortfall

The absolute shortfall is defined as an expected loss of future healthy life years due to current health condition and it is the way of quantifying severity. QALY-loss illustrates the loss of healthy life years and consequently the higher the QALY-loss is the more severe condition it is. Estimating absolute shortfall enables to the argument of the decision with choosing of WPT threshold according to the 6 levels of severity defined by Magnussen et al. (2015).

The absolute shortfall is calculated by deducting the mean number god life years left for the particular patient group at the age of interest with standard treatment $P_{age\ 72}$ from the expected god life years for the general population of the same age $QALYs_{age\ 72}$. Formulae is as follows:

$$Absolute\ shortfall = QALYs_{age\ 72} - P_{age\ 72} \qquad (8)$$

Where both $QALYs_{age\ 72}$ and $P_{age\ 72}$ undiscounted numbers were used.

Even though the patient population in this paper are men 69 years of age, the absolute shortfall was calculated for 72 years old men, as 72 years is the mean age when men were diagnosed in 2017. This is because for the patient population was used median age for both getting diagnosis and radiotherapy, but is the calculation of absolute shortfall mean age was applied.

4.11 Software

Current cost-utility analysis and subsequent sensitivity analysis was conducted in Excel 2016. To run simulations for the PSA and EVPI Macros was written in Visual Basic.

4.12 Key assumptions

A series of assumptions were made in relation to the model inputs and the structure of the model in order to perform current cost-utility analysis of HRS insertion for the patients with prostate cancer, undergoing radiation therapy, along with standard care. Key assumptions are as follows:

- Lifetime horizon with three-months cycle length was applied.
- The age was not considered to be a predictor for gastrointestinal and genitourinary toxicities after radiation therapy of prostate and the results of the RCT (Hamstra et al., 2017; Mariados et al., 2015) was assumed to be applicable to the patient population in this paper.
- Patients entering the Markov model belong to a particular risk group and they are not able to change it.

- GI, GU toxicity and ED were modeled together assuming that a person would have been in one of these the states.
- Unsuccessful HRS implantation had no effect on QALYs and costs.
- An absolute shortfall approach is employed for quantification of severity.
- The probability of dying was equal for individuals in the same cycle and risk group, regardless of health states.
- There was no interaction between other forms of treatment for prostate cancer and insertion of HRS and HRS does not influence the possibility of having other curative/palliative treatment for prostate cancer.
- Reoccurrence of the prostate cancer was not considered, as HRS can be applied only once and to my knowledge, there is no evidence that the application of HRS improves mortality.
- Grade 1 for both GI and GU toxicity were merged together with "no toxicity" (grade 0).
- Grade 2 and 3 of both GU and GI toxicities were pulled together for late toxicity measurements at 36 months.
- The assumption on adverse events and exclusion of the patients due to the impossibility of hydrodissection and other reasons were taken from clinical experience and literature on this topic (please, see Section 2).
- If there was a problem with zeroes while calculating relative risks 0,5 was added to all cells (Deeks & Higgins, 2010).
- Acute toxicity is one of the predictors of late toxicity, therefore patients from health state "Grade 1+0" transferred were into the higher state only when there were no people from the high state of a cycle before to cover it.
- No grade 2 or higher toxicities occur after 36 months (Zelefsky et al.,1998).
- The effect of acute toxicity on costs and effects lasted for 1 cycle or 3 months.
- 91 % of patients with late GI toxicities with grade 2+ received resolution of their symptoms after 36 months from onset of the symptoms (Hummel et al., 2012; Zelefsky et al.,1998).
- 64% of patients with grade 2+ GU experienced the resolution of their symptoms after 12 months after onset. The assumption is based on clinical experience and reviewed literature (Hummel et al., 2012; Zelefsky et al.,1998).

- After 36 and 12 months from onset of GI and GU symptoms respectively patients, which remain in grade 2+ GU and GI toxicities may experience some resolution of toxicity and even though they may still maintain bothersome (e.g. urgency, diarrhoea, constipation), which influence their quality of life, but cost impact of those patients would decrease considerably.
- If a person had ED at the baseline or deteriorated from good erectile function to ED, he cannot recover from it.
- ED state does not have an impact on costs, but just on QALYs. The impact of ED on quality of life is assumed to be up to the age of 80 years (Kubin, Wagner, & Fugl-Meyer, 2003).
- Transition probability to ED health state and relative risks for ED applied for the period from 0 to 3 years.
- The prevalence of ED for patients of this age group varies a lot (Eardley et al, 2013). Therefore, it is assumed that the study by Hamstra et al (Hamstra et al., 2018) on sexual quality of life after radiation therapy with HRS is applicable for the patient population in this paper.

5 Input parameters and materials

5.1. Parameter list

The model input parameters were collected from several meta-analysis, systematic reviews, clinical experience, Norwegian population-based registers, and various systematic searches.

A systematic search was performed in PubMed, Elsevier, Google scholar, Oria and Cochrane Library databases for the English language. Search strategy included the following keywords: “space oar hydrogel”, “toxicity”, “spacer prostate cancer”, “radiation proctitis”, “prostate cancer” and in combination with “effectiveness”, “cost-effectiveness”, “long-term”, “costs”, “burden”, “radiation therapy”. Relevant studies on effectiveness, treatment strategies, costs, quality of life, were evaluated in terms of the general quality of evidence (e.g. sample size, randomization procedure), publication date and applicability in a Norwegian setting. The baseline population was based on the median age of Norwegian men to get prostate cancer diagnosis (69 years), the median age of getting radiotherapy (69 years) and the proportion of patients getting radiation therapy in each risk group. The incidence of curative radiation therapy as well is based on the Norwegian population. This data is derived from Prostate cancer rapport for 2017 (Kreftregisteret, 2018).

5.2 Transition and other probabilities

Transition probabilities and relative risks were collected mainly from the one RCT for SpaceOAR® hydrogel, which followed the same group of patients for the period in a total of 36 months (Hamstra et al., 2017; Mariados et al., 2015). Transition probabilities for ED were obtained from the study by Hamstra et al. (Hamstra et al., 2018), who followed the same group of patients. The transition probabilities, included in the model, are adjusted on the probability of dying according to the risk group and age. Firstly, the proportion of people in each state was obtained from the RCT and corrected for the proportion of people who died (Table 4). Later, transition probabilities were calculated from these proportions and converted to 3-months probabilities. These 3-months probabilities can be found in Appendix Table A1.

To convert yearly probabilities into a 3-months probabilities method for calculating probabilities using rates suggested by Drummond et al. (2005) was adopted. The rate can be estimated as follows:

$$r = -[\ln(1 - p)]/t \qquad (9)$$

Where r stands for rate and p for probability at hand and t stands for time. From this equation, probability can be expressed as such:

$$p = 1 - \exp(-rt) \qquad (10)$$

Table 4. The proportion of people in each grade for different risk groups.

	Base case					***Intermediate risk group***				
	States					***States***				
Month	***G1+0***	***GI2***	***GI3***	***GU2***	***Death***	***G1+0***	***GI2***	***GI3***	***GU2***	***Death***
0	1	X	X	X	X	1	X	X	X	X
3	0.514	0.028	0.014	0.444	X	0.514	0.028	0.014	0.444	X
15	0.944	X	0.014	0.042	X	0.931	X	0.014	0.042	0.013
36	0.873	0.057	X	0.070	X	0.837	0.055	X	0.067	0.041
	High localized risk group					***High locally advanced risk group***				
0	1	X	X	X	X	1	X	X	X	X
3	0.513	0.028	0.014	0.444	0.001	0.512	0.028	0.014	0.443	0.003
15	0.925	X	0.014	0.041	0.020	0.920	X	0.014	0.041	0.025
36	0.823	0.054	X	0.066	0.057	0.816	0.053	X	0.066	0.065

Applying the probabilities of dying as they were given resulted in some discrepancies in the percentage of people that should be in the "Death" health state by the end of a particular cycle. The example illustrated in Table 5 for the intermediate risk group. The percentage of patients died of all causes in the intermediate risk group at 15 months was 1.3% and at 36 months it should be 4.1%. However, if we apply 0.028 as the transitional probability to "Death", it will result in 0.04064 at 36 months and with every cycle, the difference will just increase. For this reason, transition probabilities to state "Death" were adjusted in order to give the correct percentage of patients in that health state for each year up to year 13 in the model. True probability was obtained by dividing the difference of the proportion in "Death" state (0.28), on the sum of other proportions of patients from groups that will transition to "Death" (0.93139+0.0139+0.0417). It results in a number 0.028369, which is the applied probability.

Table 5. Example of the calculation of transitional probabilities for intermediate risk group.

Applying original probabilities for "Death" state						***Applying corrected probabilities for "Death" state***				
	Health states					***Health states***				
Month	***G1+0***	***GI2***	***GI3***	***GU2***	***Death***	***G1+0***	***GI2***	***GI3***	***GU2***	***Death***
15	0.93139	X	0.0139	0.04170	0.013	0.93139	X	0.0139	0.0417	0.013
36	0.83721	0.05466	X	0.06713	0.04064	0.83721	0.05466	X	0.06713	0.041

Relative risks were calculated following the instructions described by Briggs et al. (2011) by dividing the likelihood of an event be present in a treatment group on the likelihood

of an event to be present in a control group. In cases where there were no events present and zeroes created computational difficulty, 0.5 was added to all cells (Deeks & Higgins, 2010). To estimate standard error was applied following formula:

$$SE\{ln(RR)\} = \sqrt{\frac{1}{a} + \frac{1}{b} - \frac{1}{a+c} - \frac{1}{b+d}} \qquad (11)$$

In this formula *a* is a number of positive outcomes in group 1, *b* is a number of positive outcomes in group 2, *c* is a number of negative outcomes in group 1, *d* is a number of negative outcomes in group 2.

Relative risks and other parameters are illustrated in Table 6.

Table 6. Relative risks and other probabilities.

Parameters	***Value***	***SE***	***Distribution***	***Source***
RR to 3 months GI grade 2	1.46	0.804	Log normal	(Mariados et al., 2015)
RR to 3 months GI grade3	0.16	1.627	Log normal	(Mariados et al., 2015)
RR to 3 months GU grade 2 and higher	0.85	0.169	Log normal	(Mariados et al., 2015)
RR to 15 months GI grade3	0.16	1.627	Log normal	(Mariados et al., 2015)
RR to 15 months GU grade 2 and higher	1.60	0.642	Log normal	(Mariados et al., 2015)
RR to 36 months GI grade 2 and higher	0.07	1.501	Log normal	(Hamstra et al., 2017)
RR to 36 months ED	0.53	0.313	Log normal	(Hamstra et al., 2018)
Erectile dysfunction at baseline	0.62	0.125	Beta*	(Hamstra et al., 2018)
Erectile function at baseline	0.38	0.075	Beta*	(Hamstra et al., 2018)
Probability of getting ED at year 3	0.62		Dirichlet**	(Hamstra et al., 2018)
Failure of hydrodissection	0.05		Dirichlet	(Schörghofer et al., 2019)
Not success placement of spacer	0.10		Dirichlet	(Uhl et al., 2013 Song et al., 2013)
Success insertion of HRS	0.85		Dirichlet	
Probability of being in intermediate risk group	0.393		Dirichlet	(Kreftregisteret, 2018).
Probability of being in a high localized risk group	0.317		Dirichlet	(Kreftregisteret, 2018).
Probability of being in a high locally advanced group	0.290		Dirichlet	(Kreftregisteret, 2018).
Transitional probability of GI resolution	0.910	0.182	Beta*	(Hummel et al., 2012; Zelefsky et al.,1998)
Transitional probability of GU resolution	0.640	0.128	Beta*	(Hummel et al., 2012; Zelefsky et al.,1998)

**Standard error is 20%*
***Method suggested by Drummond et al. (2005) was applied to calculate cycle probabilities*

Assumptions on adverse events probabilities for HRS insertion were collected from a study by Ulh et al (Uhl et al., 2013), Song et al (Song et al., 2013) and Schörghofer et al. (Schörghofer et al., 2019).

Probability expresses the likelihood of an event happening over some time period and can take numbers from zero to one. For the purpose of assessing uncertainty by applying

probabilistic sensitivity analysis, a specific distribution was assigned for each probability parameter with respect to its specific properties (e.g. Dirichlet, gamma, beta, log-normal distributions) (Briggs et al., 2011). For relative risks is was assigned log-normal distribution, for transition probabilities Dirichlet and Beta. Standard error for Beta distribution was 20%.

5.3 Mortality parameters

Probabilities of dying with respect to the risk groups and age were obtained from the Cancer Registry of Norway (Cancer Registry of Norway, 2019) for the first 13 years of state-transition model. For the further years, probabilities of dying were collected from Statistics Norway (Statistics Norway, 2019). Mortality data for the first 13 years after radiation therapy is presented in Table 7 for prostate cancer patients, stratified by the risk groups. Inclusion criteria were 69 years old at the start of curative radiation therapy. Data from the year 14 and to the rest of life is presented in Table 8. All-cause mortality was applied to all patients. Patients who had brachytherapy are as well included in the mortality data, as there are very few of these patients each year and they as well may have a HRS insertion. However, they were not modeled separately because brachytherapy is not a popular treatment option with very low number of patients. Beta distribution was applied to mortality parameters with Standard error 20%.

Table 7. All-cause mortality of prostate cancer patients with respect to the year after radiation therapy, %.*

Years after radiotherapy	***Intermediate***	***High risk localized***	***High risk localized advanced***
	Dead from all causes	***Dead from all causes***	***Dead from all causes***
1 (69 years)	1.0	1.6	2.2
2 (70 years)	2.5	3.8	4.3
3 (71 year)	4.1	5.7	6.5
4 (72 years)	7.0	9.4	9.4
5 (73 years)	9.1	11.7	13.6
6 (74 years)	12.8	15.3	17.4
7 (75 years)	16.2	19.3	21.6
8 (76 years)	20.0	22.7	25.4
9 (77 years)	23.1	27.6	29.4
10 (78 years)	28.1	32.5	34.6
11 (79 years)	31.1	37.0	39.1
12 (80 years)	34.7	41.8	44.6
13 (81 year)	40.5	44.0	50.3

** data provided by the Cancer Register of Norway with observation year from 2004 to 2017, 2019. Cancer Registry is not responsible for the presentation or interpretation of the numbers*

*Table 8. Age-specific all-cause probabilities of death**.*

Age	*Probability of death/year, %*	*Rate*	*Cycle probability*	*Standard error**	*Probability*
82 years	6	0.017	0.016	0.003	Beta
83 years	7	0.019	0.019	0.004	Beta
84 years	9	0.022	0.022	0.004	Beta
85 years	9	0.023	0.022	0.004	Beta
86 years	11	0.029	0.028	0.006	Beta
87 years	12	0.032	0.032	0.006	Beta
88 years	13	0.035	0.035	0.007	Beta
89 years	16	0.044	0.043	0.009	Beta
90 years	17	0.045	0.044	0.009	Beta
91 year	18	0.049	0.047	0.009	Beta
92 years	21	0.059	0.057	0.011	Beta
93 years	21	0.060	0.058	0.012	Beta
94 years	25	0.071	0.068	0.014	Beta
95 years	29	0.085	0.081	0.016	Beta
96 years	28	0.081	0.077	0.015	Beta
97 years	31	0.094	0.089	0.018	Beta
98 years	35	0.109	0.103	0.021	Beta
99 years	38	0.121	0.114	0.023	Beta
100 years	47	0.158	0.146	0.029	Beta
101 year	44	0.145	0.135	0.027	Beta
102 years	26	0.074	0.071	0.014	Beta
103 years	42	0.135	0.127	0.025	Beta
104 years	37	0.117	0.111	0.022	Beta
105 years	20	0.054	0.053	0.011	Beta
106 years	N/A	N/A	N/A	N/A	N/A

** Standard error is 20%*

*** Statistics Norway, 2019 available from: https://www.ssb.no/befolkning/statistikker/dode*

5.4 Utilities

Utility measurements performed alongside RCT used Expanded Prostate Cancer Index Composite (EPIC) questionaries' to assess health-related quality of life. However, following the guidelines health outcomes should be measured with EQ-5D instrument (Statens legemiddelverk, 2018).

Shimizu et al. assessed how comorbidity, age and disease-specific function affects the quality of life of 323 patients. Utility scores were elicited using EQ-5D and SF-36 questionnaires. This study was excluded as the utility values of intercept from multivariate analysis using a generalized linear model for EQ-5D and SF-36 were at around 0.56 and covariates such as a urinary function or bowel function were around 0.001, so it was unclear

the method of calculating the values for GI and GU toxicity of different grades. As well, the age of the patients was not defined clearly.

Age-specific EQ-5D values were elicited from the study by Burström et al. (Burstrøm, Johannesson, & Diderichsen, 2001). These values were decreasing with the increasing age of the patients. Data from Shimizu et al. was used to identify decrements for GI, GU and ED (Table 9). Approach on calculating age-dependant utilities employing Shimizu et al. study where suggested by Hummel et al. (Hummel et al., 2012; Hummel et al., 2010). When the decrements were identified, they were multiplied with utility value for a certain health state. For example, for the men of 69 years old EQ-5D value equals 0.8. If after radiation therapy this person experiences grade 2 GI symptoms, utility value will be calculated as a ratio between worst and best utility score for the bowel function multiplied by age-specific utility ((0.91/0.94)*0.8=0.77). The results are presented in Table 10.

To estimate utility values for joint health states such as Utility for grade 0+1 GI and GU, toxicity minimal model suggested by Dale et al was applied (Dale, Basu, Elstein, & Meltzer, 2008). For utility values of grade 2 and higher for both GI and GU toxicities mean between utilities of these states was calculated. Beta distribution with standard error of 20% was applied for all of the utility values.

If ED was experienced by the population in the model, utility decrements were applied in cases where the utility of ED had lower values than utilities of compared health states. Decrements were calculated from Table 10 by deducting the utility of ED from the utility of the particular health state.

Table 9. Utility scores from the study by Shimizu et al.

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
ED	
erectile function	0.93
erectile dysfunctions	0.89

*Table 10. Age-dependant utility values applying EQ-5D***.*

Age of the patient	GI toxicity grade					GU toxicity grade					GI+GU	Erectile	
	grade0+1	grade 1+2*	grade 2	grade 2+3*	grade 3	grade0+1	grade 1+2*	grade 2	grade 2+3*	grade 3	0+1**	function	dysfunction
69	0.80	0.79	0.77	0.74	0.71	0.80	0.77	0.75	0.73	0.71	0.80	0.80	0.77
70	0.80	0.79	0.77	0.74	0.71	0.80	0.77	0.75	0.73	0.71	0.80	0.80	0.77
71	0.80	0.79	0.77	0.74	0.71	0.80	0.77	0.75	0.73	0.71	0.80	0.80	0.77
72	0.80	0.79	0.77	0.74	0.71	0.80	0.77	0.75	0.73	0.71	0.80	0.80	0.77
73	0.80	0.79	0.77	0.74	0.71	0.80	0.77	0.75	0.73	0.71	0.80	0.80	0.77
74	0.76	0.75	0.74	0.71	0.68	0.76	0.74	0.71	0.70	0.68	0.76	0.76	0.73
75	0.76	0.75	0.74	0.71	0.68	0.76	0.74	0.71	0.70	0.68	0.76	0.76	0.73
76	0.76	0.75	0.74	0.71	0.68	0.76	0.74	0.71	0.70	0.68	0.76	0.76	0.73
77	0.76	0.75	0.74	0.71	0.68	0.76	0.74	0.71	0.70	0.68	0.76	0.76	0.73
78	0.76	0.75	0.74	0.71	0.68	0.76	0.74	0.71	0.70	0.68	0.76	0.76	0.73
79	0.76	0.75	0.74	0.71	0.68	0.76	0.74	0.71	0.70	0.68	0.76	0.76	0.73
80	0.76	0.75	0.74	0.71	0.68	0.76	0.74	0.71	0.70	0.68	0.76	0.76	0.73
81	0.76	0.75	0.74	0.71	0.68	0.76	0.74	0.71	0.70	0.68	0.76	0.76	0.73
82	0.76	0.75	0.74	0.71	0.68	0.76	0.74	0.71	0.70	0.68	0.76	0.76	0.73
83	0.76	0.75	0.74	0.71	0.68	0.76	0.74	0.71	0.70	0.68	0.76	0.76	0.73
84	0.76	0.75	0.74	0.71	0.68	0.76	0.74	0.71	0.70	0.68	0.76	0.76	0.73
85	0.76	0.75	0.74	0.71	0.68	0.76	0.74	0.71	0.70	0.68	0.76	0.76	0.73
86	0.76	0.75	0.74	0.71	0.68	0.76	0.74	0.71	0.70	0.68	0.76	0.76	0.73
87	0.76	0.75	0.74	0.71	0.68	0.76	0.74	0.71	0.70	0.68	0.76	0.76	0.73
88	0.76	0.75	0.74	0.71	0.68	0.76	0.74	0.71	0.70	0.68	0.76	0.76	0.73
89	0.72	0.71	0.70	0.67	0.65	0.72	0.70	0.68	0.66	0.65	0.72	0.72	0.69
90	0.72	0.71	0.70	0.67	0.65	0.72	0.70	0.68	0.66	0.65	0.72	0.72	0.69
91	0.72	0.71	0.70	0.67	0.65	0.72	0.70	0.68	0.66	0.65	0.72	0.72	0.69
92	0.72	0.71	0.70	0.67	0.65	0.72	0.70	0.68	0.66	0.65	0.72	0.72	0.69
93	0.72	0.71	0.70	0.67	0.65	0.72	0.70	0.68	0.66	0.65	0.72	0.72	0.69
94	0.72	0.71	0.70	0.67	0.65	0.72	0.70	0.68	0.66	0.65	0.72	0.72	0.69
95	0.72	0.71	0.70	0.67	0.65	0.72	0.70	0.68	0.66	0.65	0.72	0.72	0.69
96	0.72	0.71	0.70	0.67	0.65	0.72	0.70	0.68	0.66	0.65	0.72	0.72	0.69
97	0.72	0.71	0.70	0.67	0.65	0.72	0.70	0.68	0.66	0.65	0.72	0.72	0.69
98	0.72	0.71	0.70	0.67	0.65	0.72	0.70	0.68	0.66	0.65	0.72	0.72	0.69
99	0.72	0.71	0.70	0.67	0.65	0.72	0.70	0.68	0.66	0.65	0.72	0.72	0.69
100	0.72	0.71	0.70	0.67	0.65	0.72	0.70	0.68	0.66	0.65	0.72	0.72	0.69
101	0.72	0.71	0.70	0.67	0.65	0.72	0.70	0.68	0.66	0.65	0.72	0.72	0.69
102	0.72	0.71	0.70	0.67	0.65	0.72	0.70	0.68	0.66	0.65	0.72	0.72	0.69
103	0.72	0.71	0.70	0.67	0.65	0.72	0.70	0.68	0.66	0.65	0.72	0.72	0.69
104	0.72	0.71	0.70	0.67	0.65	0.72	0.70	0.68	0.66	0.65	0.72	0.72	0.69
105	0.72	0.71	0.70	0.67	0.65	0.72	0.70	0.68	0.66	0.65	0.72	0.72	0.69
106	0.72	0.71	0.70	0.67	0.65	0.72	0.70	0.68	0.66	0.65	0.72	0.72	0.69

** taking mean*
***using a minimum model to predict utilities for joint health states(Dale et al., 2008)*
****values are based on the studies by Burström et al., Shimizu et al. and Hummel et al.*

In addition to EQ-5D instrument, the main analysis was calculated with QALYs measured by generic utility instrument the Health Utilities Index (HUI3). Data were collected from 585 patients with a mean age of 72.6 years presented in a study performed in Canada in 2013 by Krahn et al. (2013). Age-dependant utility values from the multiple regression were calculated following the method presented in the article. Table 11 presents a part of the multiple regression from the study by Krahn et al. (2013). According to it a mean score for a certain patient group can be calculated by the multiplication of the values of the continuous covariates deducted with their observed means with their estimated coefficients, later adding these products to the coefficients corresponding to the particular values of the categorical covariate (Krahn et al., 2013). For example, estimation of grade 0+1 GI for 69 old patient from Table 11: 0.8633 + (69 -72.64)*(-0.0027) - 0.0037 + (87.495 - 84.6)*0.0013 = 0.87. Results presented in Table 12. To calculate all utilities Prostate Cancer Index score was needed, which ranged from 0 (worst) and 100 (best). Mean values, therefore, were taken for each Prostate Cancer Index group. No decrements were calculated for ED, because ED gave higher utility value than being in the state grade 1+0 GI and GU.

Table 11. Part of the multiple regression and Prostate Index Score variables from the study by Krahn et al.

Parameter	***Coefficient estimate***
Intercept	0.8633
Age	-0.0027
Radiation therapy	-0.0037
PCI bowel function	
- 25-50 (taken mean 37.5) assume grade 3 toxicity	37.5
- 50-75 (taken mean 62.5) assume grade 2 toxicity	62.5
- 75-99.99 (taken mean 87.495) assume grade 0+1 toxicity	87.5
PCI urinary function	
- 25-50 (taken mean 37.5) assume grade 3 toxicity	37.5
- 50-75 (taken mean 62.5) assume grade 2 toxicity	62.5
- 75-99.99 (taken mean 87.495) assume grade 0+1 toxicity	87.5
PCI erectile function	
- 25-50 (taken mean 37.5) assume erectile dysfunction	37.5
- 75-99.99 (taken mean 87.495) assume erectile function	87.5
Observed group means for centred variables:	
- age	72.6
- PCI urinary function	79
- PCI bowel function	84.6
- PCI sexual function	24.5
Symptom related continuous variables:	
- PCI urinary function (centred)	0.0049
- PCI bowel function (centred)	0.0013
- PCI sexual function (centred)	0.0006

Table 12. Age-dependant utility values calculated from multiple regression by Krahn et al. (applying HUI3).

Age of the patient	GI toxicity grade					GU toxicity grade					GI+GU	Erectile	
	grade0+1	grade 1+2*	grade 2	grade 2+3*	grade 3	grade0+1	grade 1+2*	grade 2	grade 2+3*	grade 3	0+1**	function	dysfunction
69	0.87	0.86	0.84	0.82	0.81	0.91	0.85	0.79	0.73	0.67	0.87	0.91	0.88
70	0.87	0.85	0.84	0.82	0.81	0.91	0.85	0.79	0.72	0.66	0.87	0.90	0.87
71	0.87	0.85	0.84	0.82	0.80	0.91	0.84	0.78	0.72	0.66	0.87	0.90	0.87
72	0.87	0.85	0.83	0.82	0.80	0.90	0.84	0.78	0.72	0.66	0.87	0.90	0.87
73	0.86	0.85	0.83	0.81	0.80	0.90	0.84	0.78	0.72	0.66	0.86	0.90	0.87
74	0.86	0.84	0.83	0.81	0.79	0.90	0.84	0.77	0.71	0.65	0.86	0.89	0.86
75	0.86	0.84	0.82	0.81	0.79	0.89	0.83	0.77	0.71	0.65	0.86	0.89	0.86
76	0.85	0.84	0.82	0.81	0.79	0.89	0.83	0.77	0.71	0.65	0.85	0.89	0.86
77	0.85	0.84	0.82	0.80	0.79	0.89	0.83	0.77	0.71	0.64	0.85	0.89	0.86
78	0.85	0.83	0.82	0.80	0.78	0.89	0.83	0.76	0.70	0.64	0.85	0.88	0.85
79	0.85	0.83	0.81	0.80	0.78	0.88	0.82	0.76	0.70	0.64	0.85	0.88	0.85
80	0.84	0.83	0.81	0.79	0.78	0.88	0.82	0.76	0.70	0.64	0.84	0.88	0.85
81	0.84	0.82	0.81	0.79	0.78	0.88	0.82	0.76	0.69	0.63	0.84	0.87	0.84
82	0.84	0.82	0.81	0.79	0.77	0.88	0.81	0.75	0.69	0.63	0.84	0.87	0.84
83	0.84	0.82	0.80	0.79	0.77	0.87	0.81	0.75	0.69	0.63	0.84	0.87	0.84
84	0.83	0.82	0.80	0.78	0.77	0.87	0.81	0.75	0.69	0.63	0.83	0.87	0.84
85	0.83	0.81	0.80	0.78	0.76	0.87	0.81	0.75	0.68	0.62	0.83	0.86	0.83
86	0.83	0.81	0.79	0.78	0.76	0.87	0.80	0.74	0.68	0.62	0.83	0.86	0.83
87	0.82	0.81	0.79	0.78	0.76	0.86	0.80	0.74	0.68	0.62	0.82	0.86	0.83
88	0.82	0.81	0.79	0.77	0.76	0.86	0.80	0.74	0.68	0.61	0.82	0.86	0.83
89	0.82	0.80	0.79	0.77	0.75	0.86	0.80	0.73	0.67	0.61	0.82	0.85	0.82
90	0.82	0.80	0.78	0.77	0.75	0.85	0.79	0.73	0.67	0.61	0.82	0.85	0.82
91	0.81	0.80	0.78	0.77	0.75	0.85	0.79	0.73	0.67	0.61	0.81	0.85	0.82
92	0.81	0.79	0.78	0.76	0.75	0.85	0.79	0.73	0.67	0.60	0.81	0.85	0.82
93	0.81	0.79	0.78	0.76	0.74	0.85	0.78	0.72	0.66	0.60	0.81	0.84	0.81
94	0.81	0.79	0.77	0.76	0.74	0.84	0.78	0.72	0.66	0.60	0.81	0.84	0.81
95	0.80	0.79	0.77	0.75	0.74	0.84	0.78	0.72	0.66	0.60	0.80	0.84	0.81
96	0.80	0.78	0.77	0.75	0.74	0.84	0.78	0.72	0.65	0.59	0.80	0.83	0.80
97	0.80	0.78	0.77	0.75	0.73	0.84	0.77	0.71	0.65	0.59	0.80	0.83	0.80
98	0.79	0.78	0.76	0.75	0.73	0.83	0.77	0.71	0.65	0.59	0.79	0.83	0.80
99	0.79	0.78	0.76	0.74	0.73	0.83	0.77	0.71	0.65	0.58	0.79	0.83	0.80
100	0.79	0.77	0.76	0.74	0.72	0.83	0.77	0.70	0.64	0.58	0.79	0.82	0.79
101	0.79	0.77	0.75	0.74	0.72	0.82	0.76	0.70	0.64	0.58	0.79	0.82	0.79
102	0.78	0.77	0.75	0.74	0.72	0.82	0.76	0.70	0.64	0.58	0.78	0.82	0.79
103	0.78	0.77	0.75	0.73	0.72	0.82	0.76	0.70	0.64	0.57	0.78	0.82	0.79
104	0.78	0.76	0.75	0.73	0.71	0.82	0.76	0.69	0.63	0.57	0.78	0.81	0.78
105	0.78	0.76	0.74	0.73	0.71	0.81	0.75	0.69	0.63	0.57	0.78	0.81	0.78
106	0.77	0.76	0.74	0.72	0.71	0.81	0.75	0.69	0.63	0.57	0.77	0.81	0.78

** taking mean*

*** using a minimum model to predict utilities for joint health states (Dale et al., 2008)*

5.5 Costs

Estimates for cost components and frequencies of resource use are based on a review of the studies on this topic (Forero et al., 2018; Hutchinson et al., 2016), expert opinion and treatment package (Helsederiktoratet, 2019) for prostate cancer in Norway. Several experts were contacted on this topic. Out-patient costs are calculated based on Norwegian DRG codes for somatic diseases in 2019 released by Norwegian Directorate of Health (Helsedirektoratet, Innsatsstyrt finansiering – regelverk, 2019).

To find the full cost of the procedure DRG-weight was multiplied with a fixed price of DRG for somatic diseases in 2019, which equals 44 654 NOK (Helsedirektoratet, 2019). Costs associated with GP visits are calculated by multiplying honorary from tariffs for GPs and health care personnel (in Norwegian: Normaltariff for fastleger og legevakt) for 2019-2020 with 2.

The calculation of cost components for acute toxicities is presented in Table 13. By costs per state meant costs for being in one of the particular states. As the duration of acute toxicity is 3 months, here costs per state equal costs per cycle.

Detailed cost components calculation for late toxicities is presented in Table 15. Costs per health state are consequently transferred to costs per cycle in Table 16. Cost of the procedure for injecting HRS was unknown. Therefore, it was made a conservative assumption that the cost of the procedure equals DRG code 912A. Costs of radiation therapy are presented in Table 14.

As it was assumed before, late GI toxicity resumes after 3 years from its onset and late GU toxicity lasts 1 year. After toxicities are resumed people move to grade 0+1, but for those who stay in grade 2 and higher costs will decrease as well, as they will experience some resolution of their symptoms.

In grade 3 GI it was a choice between colonoscopy and sigmoidoscopy. Most likely major part of clinicians would choose colonoscopy to be able to check for colon cancer at the same time and exclude the possibility of it.

Table 13. Cost components for acute toxicities (0-3 months) for health states for 2019, NOK.

Procedure/ State	***DRG code***	***DRG weight/cost****	***Costs per state***		***Source***	***Comment***
			Times/ state	***Cost/ procedure, NOK***		
Acute rectal toxicity (0-3 months)						
Acute Grade 0+1 rectal toxicity						
Out-patient visit	912A	0.035	1	1563	Directorate of health*	treatment package for PC
Total cost per state				**1563**		
Acute Grade 2 rectal toxicity						
Out-patient visit	912A	0.035	1	1563	Directorate of health*	treatment package for PC
Total cost per state				**1563**		
Acute Grade 3 rectal toxicity						
Out-patient visit	912A	0.035	1	1563	Directorate of health*	treatment package for PC
ER visit	453B	0.627	1	27998	Expert opinion	
Total cost per state				**29561**		
Acute genitourinary Toxicity						
Acute Grade 0+1 urinary toxicity						
X	X	X	X	X	Expert opinion	
Acute Grade 2 urinary toxicity						
GP visit	copay+public reimb.	320	1	320	Expert opinion	
Outpatient visit (Radiotherapist)	912A	0.035	1	1563	Expert opinion	
Total cost per state				**1883**		
Acute Grade 3 urinary toxicity						
GP visit	copay+public reimb.	320	1	320	Expert opinion	
Out-patient visit (Radiotherapist)	912A	0.035	1	1563	Expert opinion	
Total cost per state				**1883**		

Table 14. Costs for radiation therapy with prices for 2019, NOK

Cost of radiation therapy	***Times/year***	***DRG Code***	***DRG weight/cost***	***Cost per 1 time***	***Total cost for procedure***	***Source***	***Comment***
Radiation therapy (RT)	38	851N	0.035	1 563	59 390	expert opinion	total of 78Gy patient visits 3 times but it is calculated as one DRG value
Policlinic contact for planning RT (Poliklinisk kontakt for ordinær planlegging av stråleterapi)	1	850A	0.359	1 6031	16 031	expert opinion	
Policlinic contact for complex planning of RT (Poliklinisk kontakt for kompleks planlegging av stråleterapi)	1	850B	0.39	1 7415	17 415	expert opinion	when the golden markers and spacer are placed
Total cost for radiation therapy					**92 836**		

Table 15. Costs components for late toxicities for health states for 2019, NOK.

Procedure/ State	*DRG code*		*Costs for year 1/state*		*Costs for year 2/state*		*Costs for year 3/state*		*Cost/year after year 3, NOK*		*Source*
		*DRG weight/ cost***	*Times/ state*	*Cost/ procedure, NOK*	*Times/ state*	*Cost/ procedure, NOK*	*Times/ state*	*Cost/ procedure, NOK*	*Times/ state*	*Cost/ procedure, NOK*	
Late rectal toxicity											
Late Grade 0+1 rectal toxicity											
Out-patient visit (just once at 6 months)**	912A	0.035	1	1563	X		X		X		Directorate of health*
GP visit	copay+public reimb.	320	1	320	2	640	2	640	1	320	Expert opinion
Total cost per state				**1883**		**640**		**640**		**320**	
Late Grade 2 rectal toxicity											
Out-patient visit (just once at 6 months)**	912A	0.035	1	1563	X		X		X		
GP visit	copay+public reimb.	320	2	640	2	640	2	640	1	320	Expert opinion
Out-patient visit	912A	0.035	2	3126	2	3126	2	3126	X		Expert opinion
Total cost per state				**5329**		**3766**		**3766**		**320**	
Late Grade 3 rectal toxicity											
Out-patient visit (just once at 6 months)**	912A	0.035	1	1563	X		X		X		Directorate of health*
GP visit**	copay+public reimb.	320	2	640	2	640	2	640	1	320	Expert opinion
Out-patient visit	912A	0.035	2	3126	2	3126	2	3126	X		Expert opinion
Colonoscopy from year 1 to 3 (1-3years/1 a year)	710O	0.067	1	2992	1	2992	1	2992	X		Expert opinion
Colonoscopy after year 3 (1/10 years)	710O	0.067	X	X	X	X	X	X	0.1	299	Expert opinion
Argon plasma coagulation from year 1 to 3(1-3years/1 a year)	806P	0.041	1	1831	1	1831	1	1831	X		Expert opinion
Argon plasma coagulation after 3 year 1/10 years	806P	0.041	X	X	X	X	X		0.1	183	Expert opinion
Hyperbaric oxygen therapy (30 times once per case)	823U	0.051	10	22774	10	22774	10	22774	X		Expert opinion
Gastroenterologist from year 1 to year 3 (1-3 years/1 time/year)	912A	0.035	1	1563	1	1563	1	1563	X		Expert opinion
Total cost per state				**34488**		**32925**		**32925**		**802**	
Late genitourinary Toxicity											
Late Grade 0+1 urinary toxicity											
X	X	X	X	X	X	X	X	X	X	X	Expert opinion
Late Grade 2 urinary toxicity											
GP visit	copay+public reimb.	320	1	320	1	320	1	320	1	320	Expert opinion
Out-patient visit	912A	0.035	2	3126	2	3126	2	3126	X	X	Expert opinion
Total cost per state				**3446**		**3446**		**3446**		**320**	
Late Grade 3 urinary toxicity											
GP visit	copay+public reimb.	320	1	320	1	320	1	320	1	320	Expert opinion
Out-patient visit (Urologist/Radiotherapist)	912A	0.035	4	6252	4	6252	4	6252	1	1563	Expert opinion
Total cost per state				**6572**		**6572**		**6572**		**1883**	

**Helsederiktoratet. Available from:https://www.helsedirektoratet.no/pakkeforlop/prostatakreft/oppfolging-og-kontroll-av-prostatakreft#kontroll*

***cost is a part of treatment package (pakkeforløp) for PC; first 2 times out-patient, later GP; after radical treatment controls are at 3, 6 and 12 months; later each half year up to the year 3; later once per year*

Table 16. Costs estimates for health states per cycle with prices for 2019, NOK.

Cost parameters for health states	***Cost per year***	***Cost per cycle***	***Standard error****	***Distribution***
Acute Grade 0+1 (GI)	1563	1563	313	Gamma
Acute Grade 2 (GI)	1563	1563	313	Gamma
Acute Grade 3 (GI)	29561	29561	5912	Gamma
Late Grade 0+1 (GI), year 1	1883	628	126	Gamma
Late Grade 2 (GI), year 1	5329	1776	355	Gamma
Late Grade 3 (GI), year 1	34488	11496	2299	Gamma
Late Grade 0+1 (GI), year 2	640	160	32	Gamma
Late Grade 2 (GI), year 2	3766	941	188	Gamma
Late Grade 3 (GI), year 2	32925	8231	1646	Gamma
Late Grade 0+1 (GI), year 3	640	160	32	Gamma
Late Grade 2 (GI), year 3	3766	941	188	Gamma
Late Grade 3 (GI), year 3	32925	8231	1646	Gamma
Late Grade 0+1 (GI), from year 3	320	80	16	Gamma
Late Grade 2 (GI), from year 3	320	80	16	Gamma
Late Grade 3(GI), from year 3	802	201	40	Gamma
Acute Grade 2 (GU)	1883	1883	377	Gamma
Acute Grade 3 (GU)	1883	1883	377	Gamma
Late Grade 2 (GU), year 1	3446	1149	230	Gamma
Late Grade 3 (GU), year 1	6572	2191	438	Gamma
Late Grade 2 (GU), year 2	3446	861	172	Gamma
Late Grade 3 (GU), year 2	6572	1643	329	Gamma
Late Grade 2 (GU), year 3	3446	861	172	Gamma
Late Grade 3 (GU), year 3	6572	1643	329	Gamma
Late Grade 2 (GU), from year 3	320	80	16	Gamma
Late Grade 3 (GU), from year 3	1883	471	94	Gamma
Acute Grade 0+1	1563	1563	313	Gamma
Late Grade 0+1(GI+GU), year 1	1883	628	126	Gamma
Late Grade 0+1 (GI+GU), year 2	640	160	32	Gamma
Late Grade 0+1 (GI+GU), year 3	640	160	32	Gamma
Late Grade 0+1 (GI+GU), from year 3	320	80	16	Gamma
*Late Grade 2+ (GU), year 2***	5009	1252	250	Gamma
*Late Grade 2+ (GI), year 2***	18345	4586	917	Gamma
*Late Grade 2+ (GI), year 3***	18345	4586	917	Gamma
*Late Grade 2+ (GU), year 3***	5009	1252	250	Gamma
*Late Grade 2+ (GI), from year 3***	561	140	28	Gamma
*Late Grade 2+ (GU), from year 3***	1101	275	55	Gamma
*Cost of HRS****	16000	X	3200	Gamma
*Cost of RT****	92836	X	18567	Gamma
*Cost of HRS insertion****	1563	X	313	Gamma

** Standard error is 20%*
*** Costs calculated as a mean costs of states 2 and 3*
****Costs per procedure/device*

6 Results

6.1 Costs and effects of treatment

Total undiscounted costs and effects per person for Standard Care and Standard Care with HRS SpaceOAR® were summarized in Table 17 using a provider perspective. Undiscounted and discounted outcomes were included to illustrate their relationship. Additionally, Table 17 illustrates the effects of the subgroup analysis. It was considered the prevalence of ED of 0%, 62% and 100% at the start of the treatment. Subgroup with the lowest prevalence at the baseline resulted in the highest QALYs.

Costs were omitted for subgroups with ED. As it was assumed, ED health state does not accumulate any costs, so they are equal to the costs of the main analysis. Effects measured with HUI3 resulted in higher QALYs gained, both discounted and undiscounted. All later analysis will be presented with effects measured with EQ-5D.

Table 17. Total direct costs and effects of Standard Care compared to Standard Care with HRS SpaceOAR® per person, cost expressed in NOK, effects in QALYs.

	Standard Care		Standard Care and HRS SpaceOAR®	
	Undiscounted costs	**Discounted costs**	**Undiscounted costs**	**Discounted costs**
Costs	105 564	103 551	119 019	117 363
Effects (EQ-5D)	11.26	8.02	11.28	8.03
Effects (HUI3)	12.59	9.01	12.60	9.02
Effects with ED (EQ-5D) prevalence of ED 100%	10.98	7.80	10.99	7.80
Effects with ED (EQ-5D) prevalence of ED 62%	11.03	7.83	11.06	7.86
Effects with ED (EQ-5D) prevalence of ED 0%	11.10	7.89	11.18	7.95

6.2 Cost-effectiveness threshold

The approach suggested by Magnussen group for quantification of severity was used to establish the cost-effectiveness threshold. From the Guidelines for economical evaluation published by NoMA expected god life years for the general population of the age of 72 are 11.3 and mean number of god life year for this patient group is 8.76 for the main research and 8.01 with account for ED. Undiscounted values were used. Therefore for both models, WTP threshold falls in the first severity group, suggested by Magnussen group and equals 275 000 NOK per QALY.

6.3 Cost-effectiveness analysis

A summary from deterministic cost-effectiveness analysis is presented in Table 18. It illustrates discounted half-cycle corrected overall QALYs and costs gained with the new intervention in comparison to the Standard Care alone from the Norwegian healthcare provider perspective. For the main analysis, Standard Care with HRS resulted in 13 813 NOK of incremental costs and 0, 01 incremental QALYs in comparison with Standard Care alone. This results in ICER of 1 382 413 NOK per QALY gained, which is significantly higher than WTP threshold. Taking into account ED, Standard care with HRS resulted in 0.025 incremental QALYs in comparison with Standard Care alone. This results in ICER of 544 675 NOK per QALY gained, which is as well significantly higher than WTP threshold.

Table 18. Cost-effectiveness results for main and secondary analysis. Directed costs are included. Both costs and effects discounted by 4% per year. Lifetime horizon. Costs are measured in NOK, effects are measured in QALYs (EQ-5D).

Treatment	Total costs	Total QALY	Incremental costs (ΔTotal costs)	Incremental QALY (ΔQALY)	ICER (ΔTotal costs/ΔQALY)
Standard care	103 551	8.02	N/A	N/A	N/A
Standard care+HRS	117 363	8.03	13 813	0.0100	1 382 413
Subgroup where prevalence of ED is 62% at the start of the treatment					
Standard care	103 551	7.83	N/A	N/A	N/A
Standard care+HRS accounting for ED	117 363	7.86	13 813	0.0254	544 675
Subgroup if no of the patients have ED at the start of the treatment (prevalence ED 0%)					
Standard care	103 551	7.89	N/A	N/A	N/A
Standard care+HRS accounting for ED	117 363	7.95	13 813	0.0578	238 990
Subgroup if all of the patients have ED at the start of the treatment (prevalence ED 100%)					
Standard care	103 551	7.80	N/A	N/A	N/A
Standard care+HRS accounting for ED	117 363	7.80	13 813	0.0063	2 199 918

6.4 Deterministic sensitivity analysis

One-way sensitivity analysis was performed for the Standard Care with comparison to Standard Care with HRS, and Standard Care with comparison to Standard Care with HRS accounting for ED (prevalence 62%). The results in one-way sensitivity analysis on Figure 5 is for the Standard Care with comparison to Standard Care with HRS. It represents key parameters, which have an impact on the ICER. The most influence on ICER has a potential change in the proportion of patient who had successful HRS insertion, relative risk for acute

GU toxicity and utility of GI toxicity grade2+, while other relative risks have much lower potential influence.

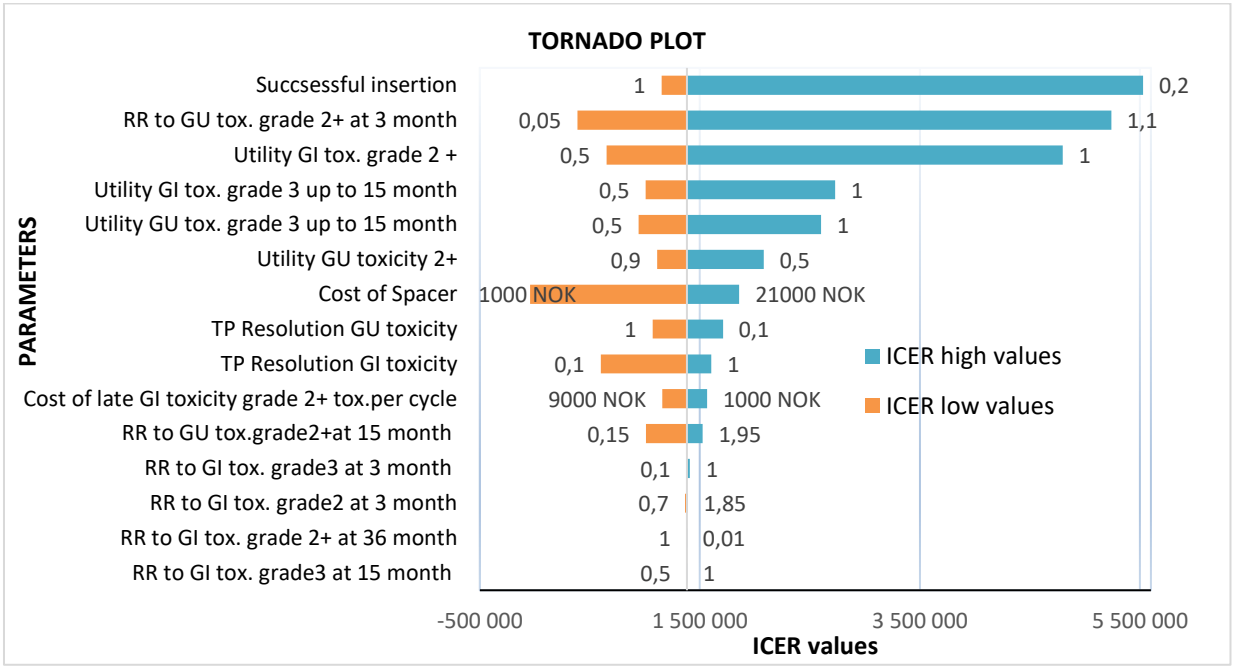

Figure 5. The Tornado plot with results of one-way sensitivity analysis for of Standard Care with comparison to Standard Care with HRS.

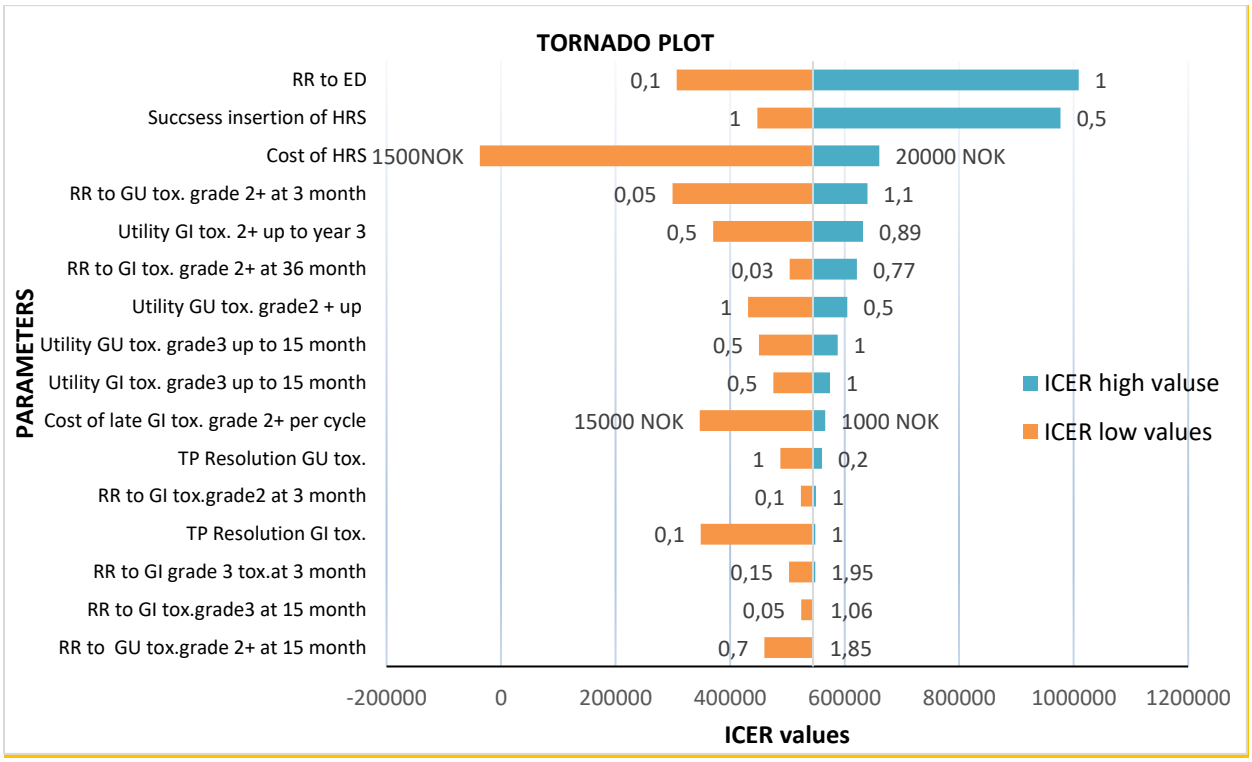

Figure 6. The Tornado plot with results of one-way sensitivity analysis for of Standard Care with comparison to Standard Care with HRS accounting for ED (prevalence 62% at the baseline).

The results of one-way sensitivity analysis for Standard Care with comparison to Standard Care with HRS accounting for ED (prevalence at the baseline 62%), are summarised in Figure 6. Figure 6 illustrates that relative risk for ED, success of insertion of HRS and costs of HRS has the highest potential impact on ICER.

6.5 Probabilistic sensitivity analysis

Figures 7, 8 and 9 represent cost-effectiveness planes with incremental effects on the x-axis and incremental costs on the y-axis. Three alternatives were considered: Standard Care compared to Standard Care with HRS, Standard Care compared to Standard Care with HRS accounting for ED with a prevalence of 62% at the baseline, Standard Care compared to Standard Care with HRS with a prevalence of 0% at the baseline. All planes show distribution from 10 000 Monte Carlo simulations, point, where falls deterministic ICER and WTP threshold of 275 000 NOK.

Simulation on Figure 7 presents the result for the main analysis and places all the ICERs in northeast and northwest quadrant with most of the ICERS above the WTP threshold. If all of the ICERs density is in these quadrants, it indicates that intervention is more costly (lies in north quadrants) than Standard Care and more or less effective (about 63%, or 6325 simulations out of 10 000, of the density, involves with health gains).

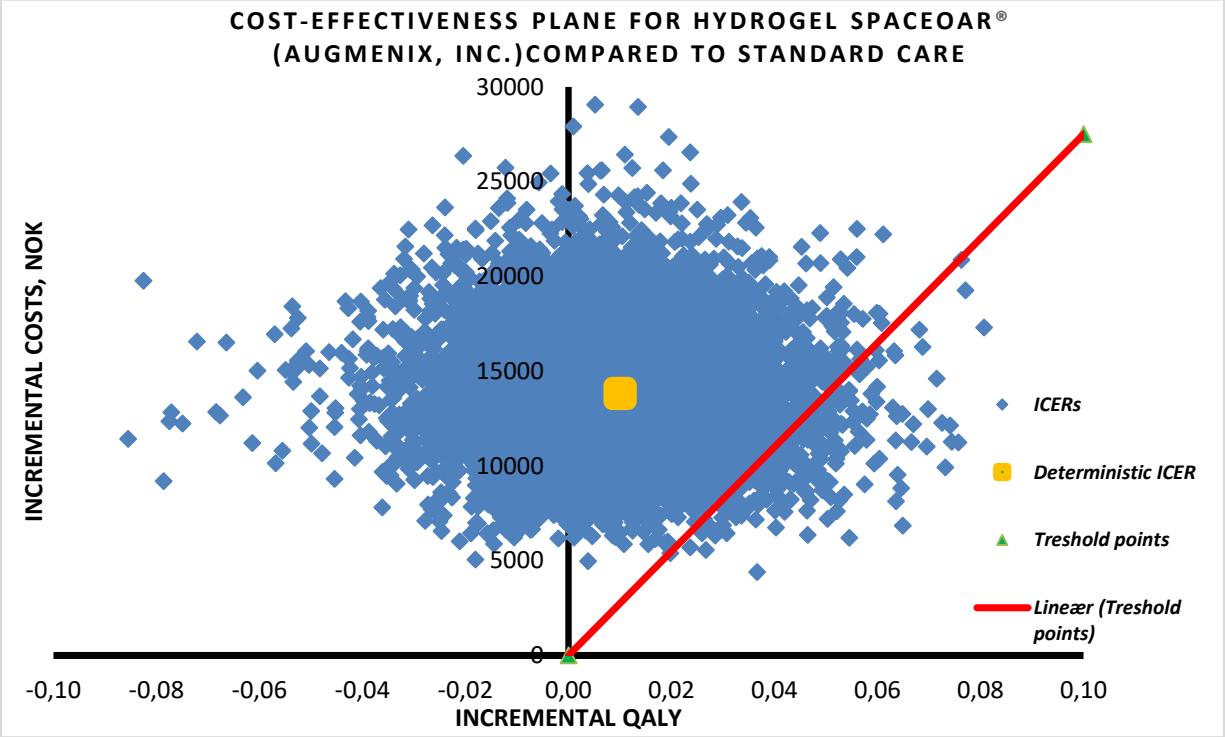

Figure 7. Cost-effectiveness plane for the Standard Care with comparison to Standard Care with HRS.

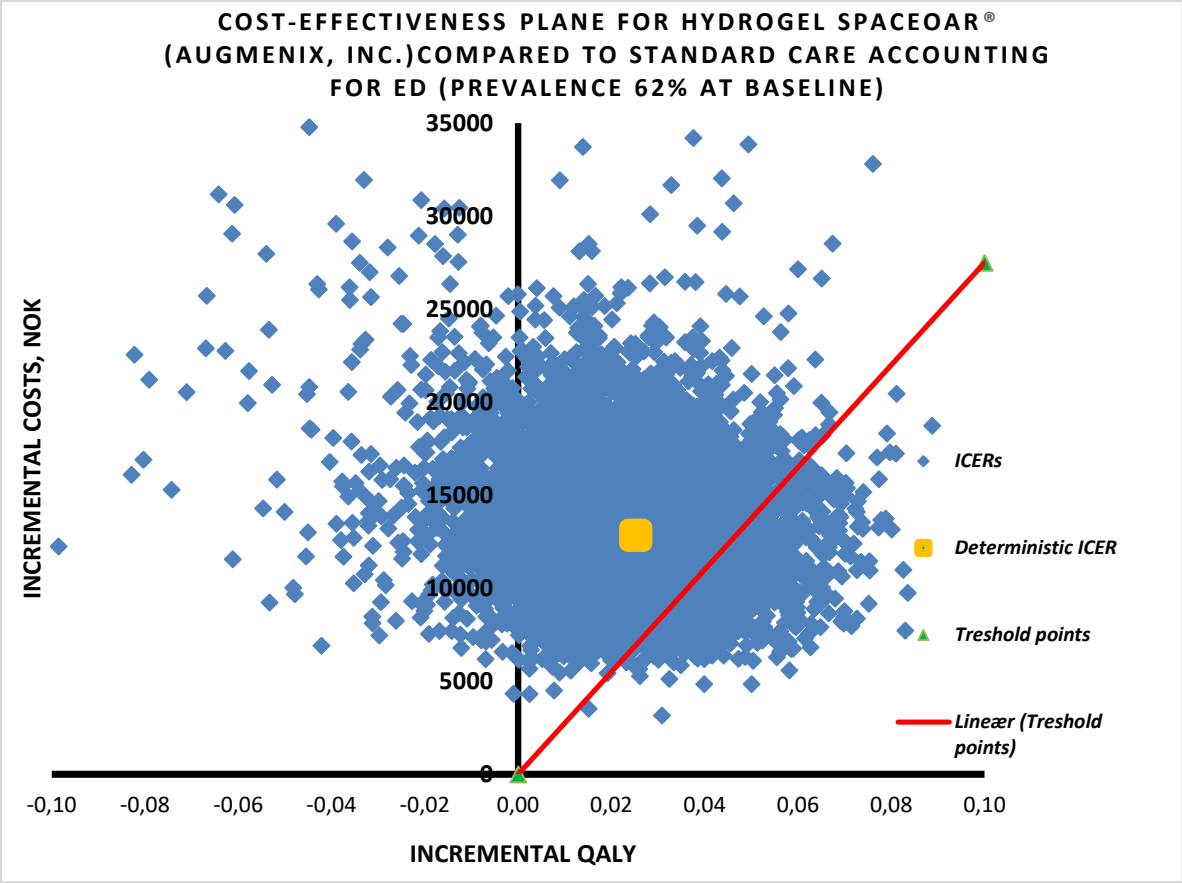

Figure 8. Cost-effectiveness plane for the Standard Care with comparison to Standard Care with HRS accounting for ED (prevalence ED at the baseline 62%).

Simulation in Fig. 8 places all the ICERs as well in the northeast and northwest quadrant with WTP threshold crossing a part of the ICERS density. This time 92%, or 9201 simulations out 10 000 involves health gains, as they are located in the northeast quadrant. Rest 8% of ICERs are located in the northwest quadrant, which indicates that intervention is not effective and more costly in comparison to Standard Care.

The cost-effectiveness plane in Fig. 9 presents results of a simulation for the Standard Care with comparison to Standard Care with HRS accounting for ED (prevalence ED at the baseline 0%). 9838 simulations out of 10 000 are distributed to the northeast quadrant, which indicates, that 98% of density involves health gains, but is more costly than Standard Care. WTP threshold crosses ICERs density almost in the middle.

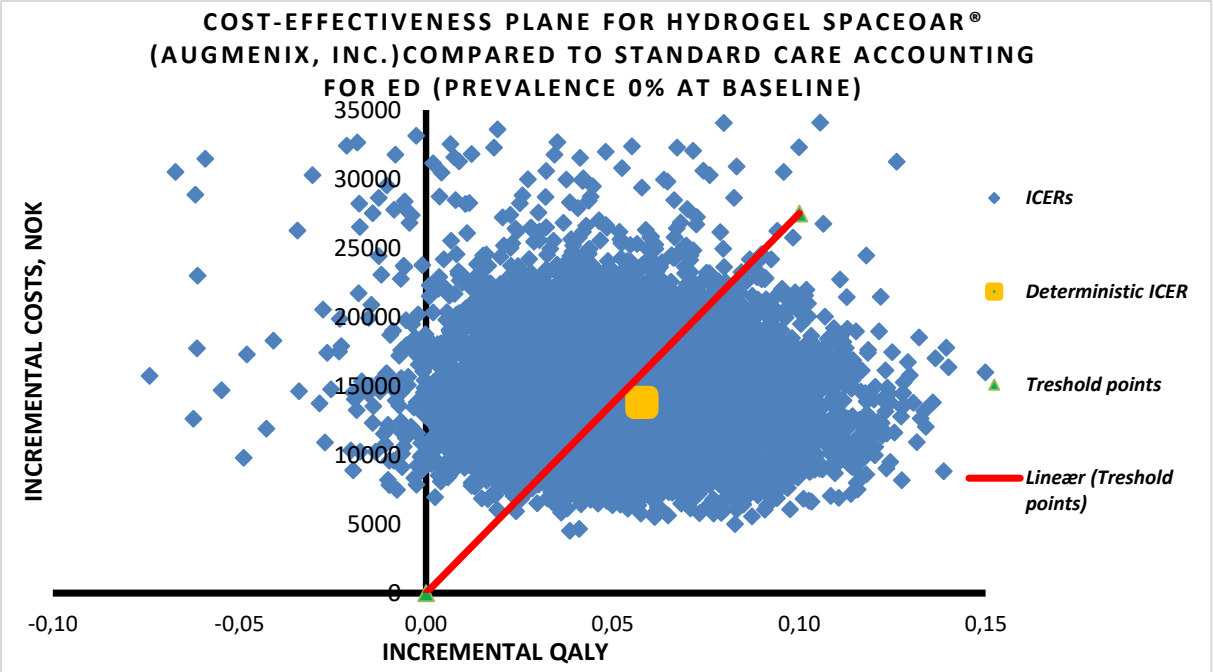

Figure 9. Cost-effectiveness plane for the Standard Care with comparison to Standard Care with HRS accounting for ED (prevalence ED at the baseline 0%).

6.6 Cost-effectiveness acceptability curve and frontier

Utilizing the PSA results in NMB analysis, cost-effectiveness acceptability curves were plotted to illustrate the probability of the intervention being cost-effective compared to Standard Care at a given WTP threshold. Fig. 10 presents CEAC for Standard Care with comparison to Standard Care with HRS, Fig. 12 illustrates CEAC for Standard Care with comparison to Standard Care with HRS accounting for ED (prevalence ED 62% at baseline) and Fig. 14 CEAC shows CEAC for Standard Care with comparison to Standard Care with HRS accounting for ED (prevalence ED 0% at baseline). As CEAC in Fig. 10 results from the joint density of incremental costs and incremental effects illustrated on the cost-effectiveness plane, the CEAC starting point is 0, because none of the density points are cost-saving, and its line asymptotes to values lesser than 1, because around 50% of the density is health gaining. At WTP threshold of 0 NOK per QALY gained the probability of SpaceOAR® to be cost-effective is 0. However, CEAC shows, that the probability of SpaceOAR® being cost-effective raises with an increase of WTH threshold per QALY gained. At WTH threshold of 275 000 NOK/QALY SpaceOAR® has 1% probability of being cost-effective and Standard care has 99% of being cost-effective. At the WTP thresholds values up to 1 800 000 NOK/QALY Standard Care is the preferred

option and at higher WTP threshold values there is no difference between which alternative is to be preferred. Later, at the higher levels of WTP threshold, SpaceOAR® seems to be the preferred option.

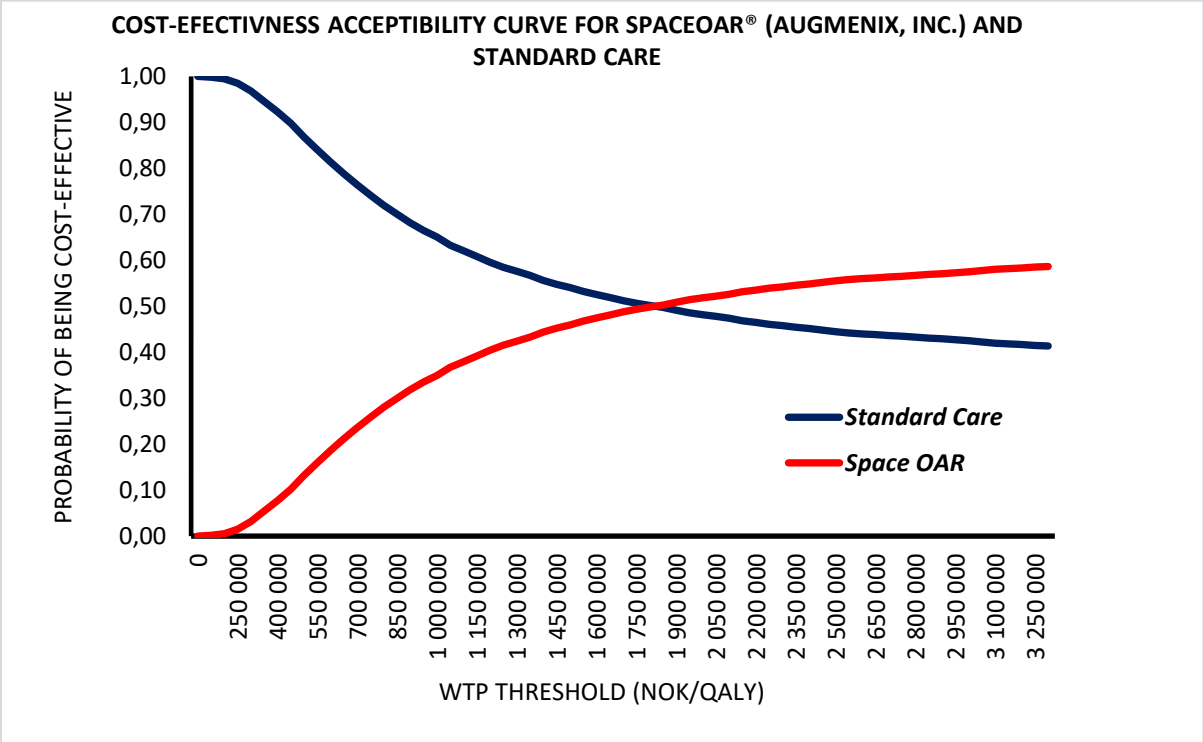

Figure 10. The cost-effectiveness acceptability curve for Standard Care with comparison to Standard Care with HRS.

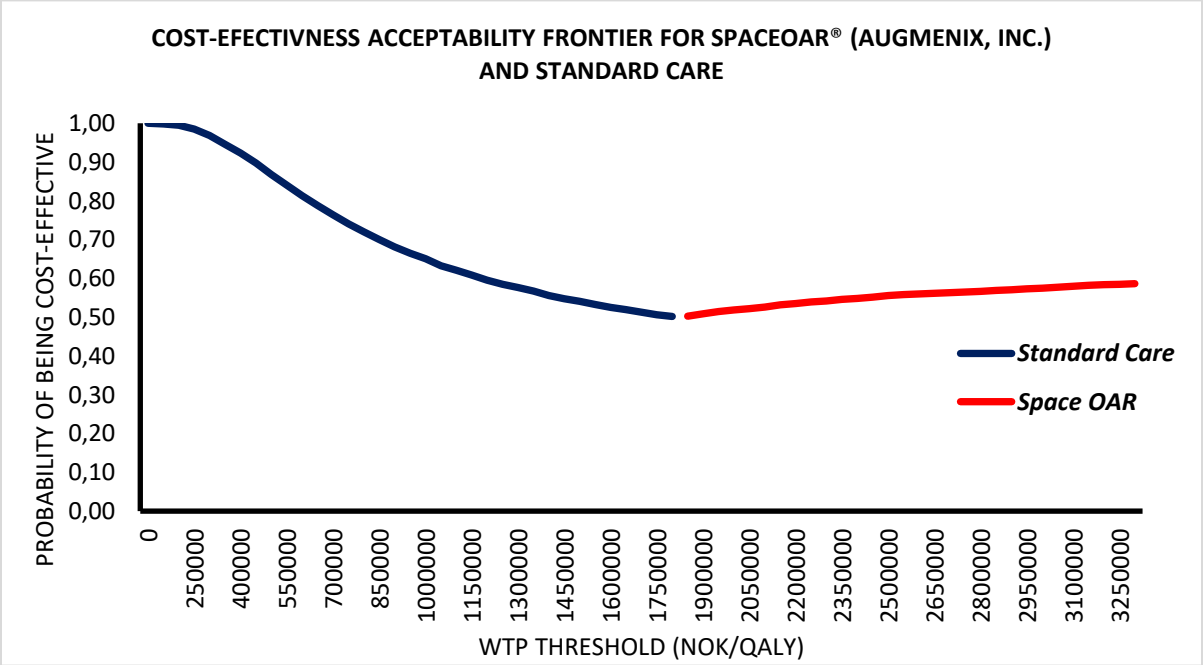

Figure 11. The cost-effectiveness acceptability frontier for Standard Care with comparison to Standard Care with HRS.

CEAF in Fig.11 illustrates the probability of alternative with the highest NB being cost-effective and, as CEAC, shows that at WTP threshold of 275 000 NOK/QALY Standard Care is cost-effective with a probability of 99%. As CEAC, the CEAF illustrates that at WTP threshold of 275 000 NOK/QALY, Standard Care is cost-effective.

On the CEAC, presented in Fig. 12, y-axis shows the probability of Standard Care with comparison to Standard Care with HRS accounting for ED (prevalence ED at baseline 62%) for a range of given WTP thresholds, located on the x-axis. CEAC for intervention (Standard Care + HRS) starts at 0, as none of the density involves cost-saving. At WTP of 0 per QALY gained, the probability of Standard Care with HRS accounting for ED (prevalence at baseline 62%) of being cost-effective is 0. The CEAC, however, shows that with the increase of WTP threshold per QALY gained, the probability of the intervention being cost-effective raises and at the WTP threshold of 275 000 NOK/QALY it reaches 10%. With further hypothetical increase of WTP threshold up to 630 000 NOK/QALY, Standard Care with HRS accounting for ED (prevalence ED at baseline 62%) has 50% probability of being cost-effective and the probability increases with further raise of WTP threshold. However, CEAC for the intervention will not asymptote to 1, as not all the density involves health gains.

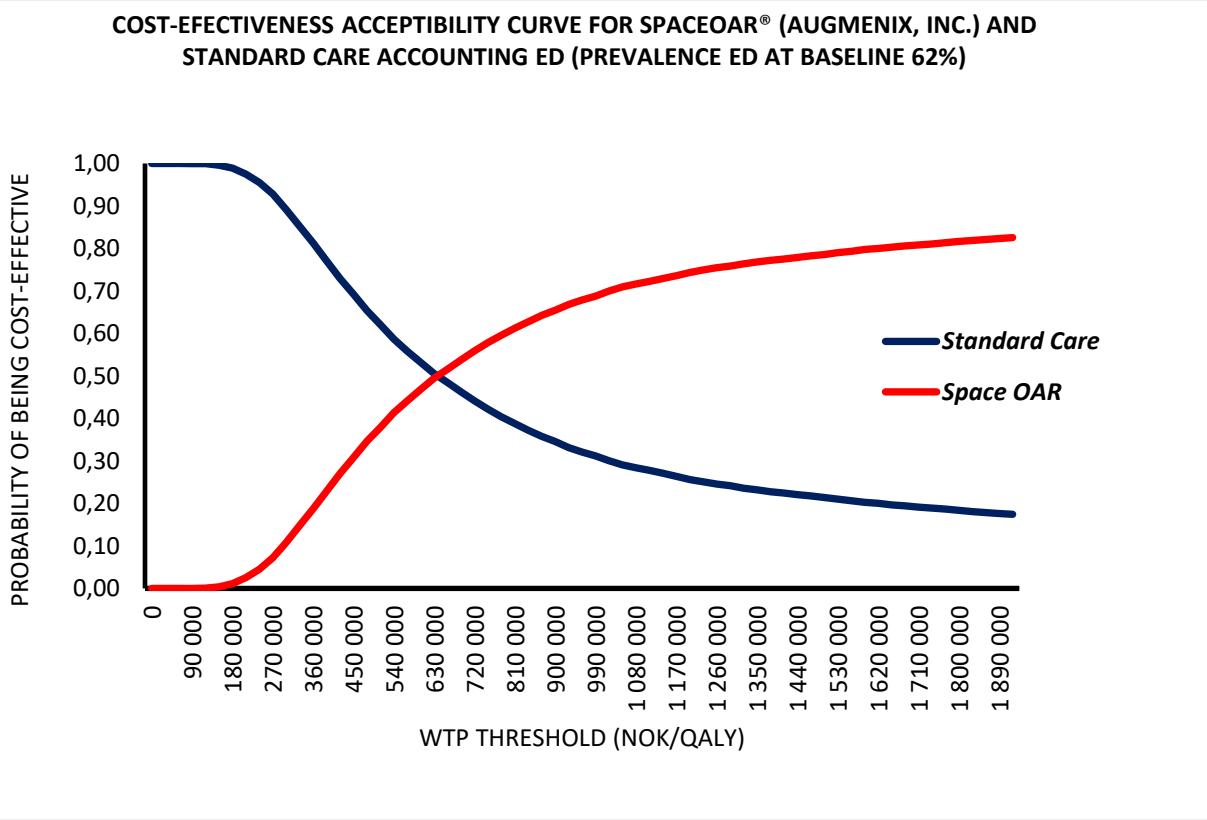

Figure 12. The cost-effectiveness acceptability curve for Standard Care with comparison to Standard Care with HRS accounting for ED (prevalence ED 62% at the baseline).

CEAF in Fig. 13. illustrates the probability of alternative with the highest NB being cost-effective and as CEAC shows that, at WTP threshold of 275 000 NOK/QALY Standard Care is cost-effective with a probability of 99%. From the WTP threshold of 630 000 NOK/QALY and higher intervention (Standard Care + HRS) is considered being a preferred option.

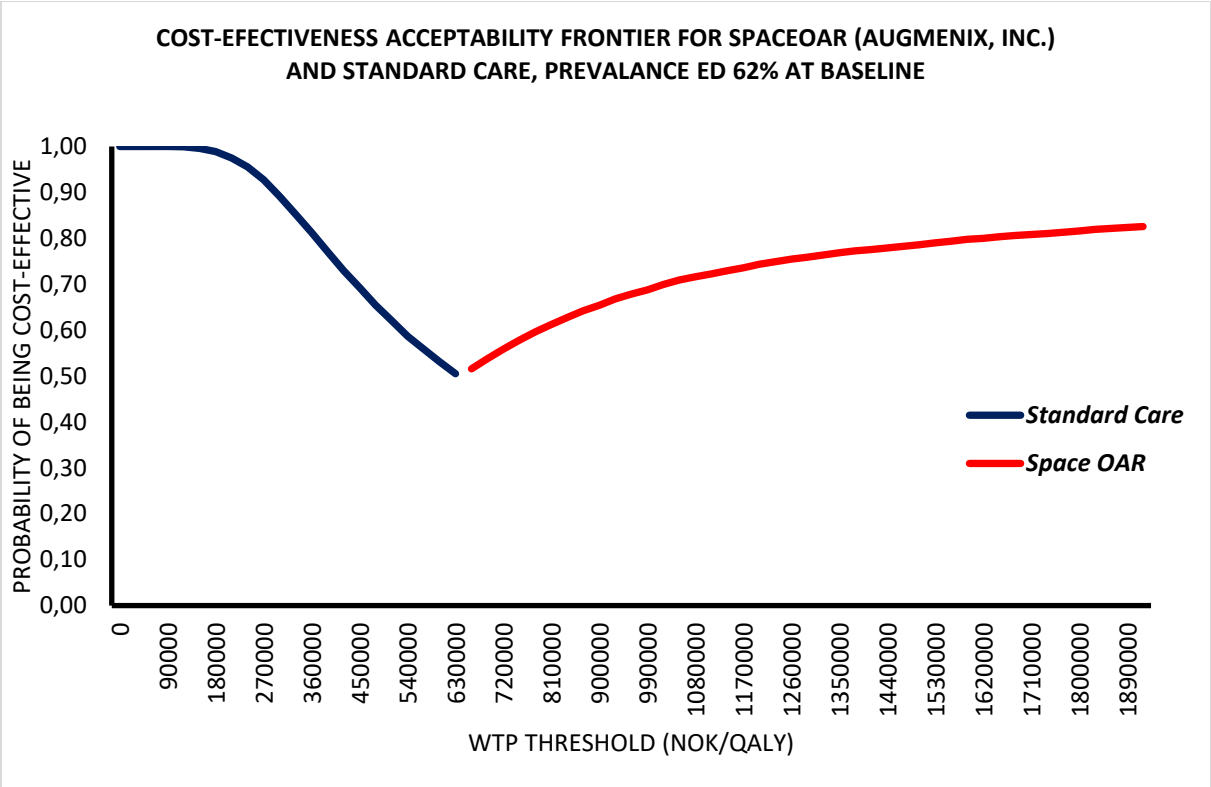

Figure 13. The Cost-effectiveness acceptability for Standard Care with comparison to Standard Care with HRS (prevalence ED 0% at the baseline).

Presented in Fig. 14 CEAC for intervention (Standard Care + HRS), as well, starts at 0 on the y-axis, as none of the density involves cost-saving. The CEAC illustrates that with the increase of WTP per QALY gained, the probability of the intervention being cost-effective raises and at the WTP threshold of 260 000 NOK/QALY it reaches 50%. At WTH threshold of 275 000 NOK/QALY intervention it 53% cost-effective.

CEAF on Fig.15 shows as well that Standard Care being more cost-effective when WTP threshold ranges between 0 NOK/QALY and 260 000 NOK/QALY. With higher values of WTP intervention is considered to be a preferred option.

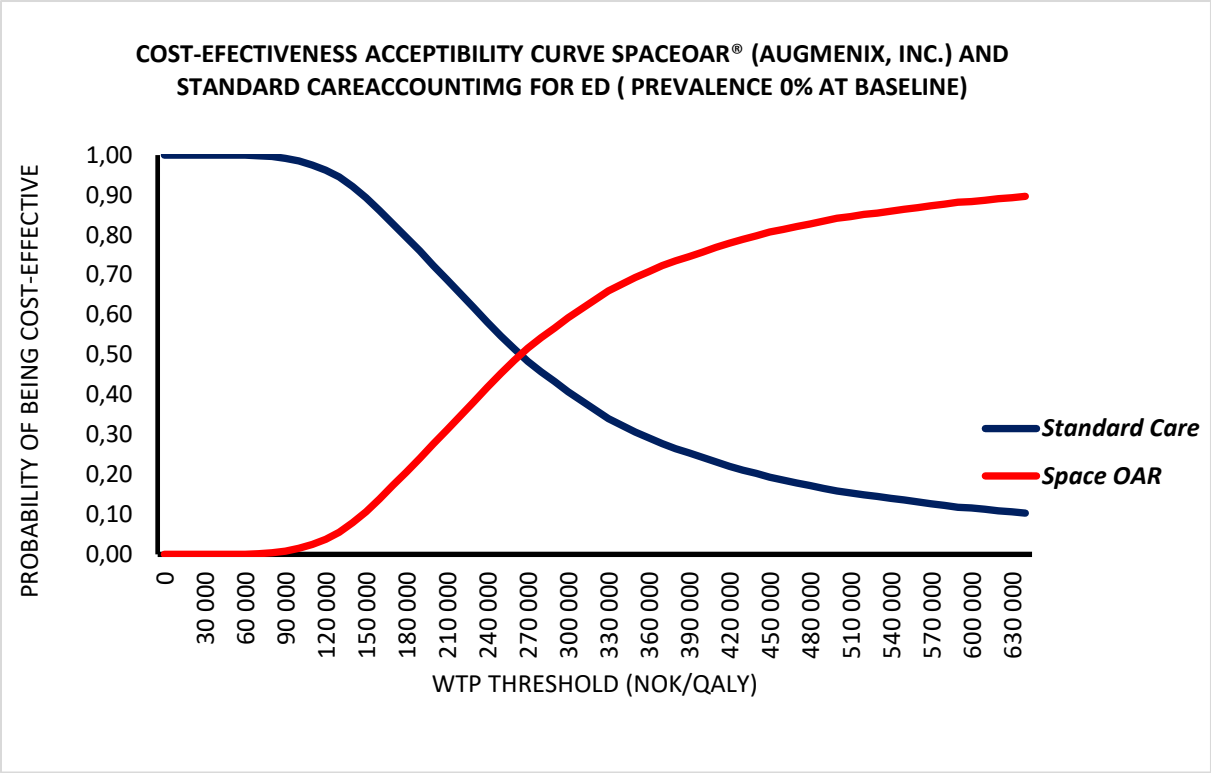

Figure 14. The Cost-effectiveness acceptability curve for Standard Care with comparison to Standard Care with HRS accounting for ED (prevalence ED 0% at the baseline).

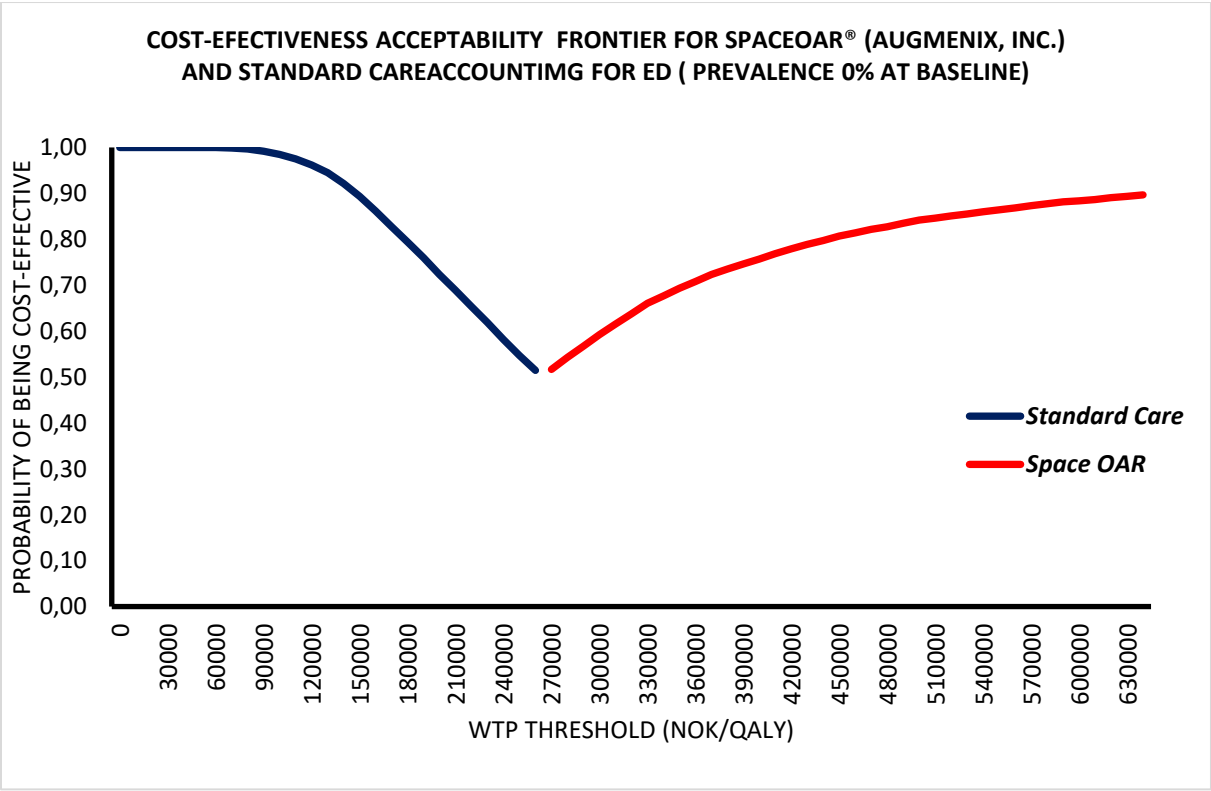

Figure 15. The Cost-effectiveness acceptability frontier for Standard Care with comparison to Standard Care with HRS accounting for ED (prevalence ED 0% at the baseline).

6.7 The expected value of perfect information for individual and population

Fig. 16. demonstrates individual EVPI for a range of WTP thresholds for Standard Care with comparison to Standard Care with HRS. Given a threshold of 275 000 NOK/QALY EVPI has a value of 173 NOK. This suggests that at this particular threshold there is very low uncertainty about the decision. With a hypothetical increase of WTP threshold, the decision will become more uncertain and therefore EVPI staidly raises following the increase of WTP threshold.

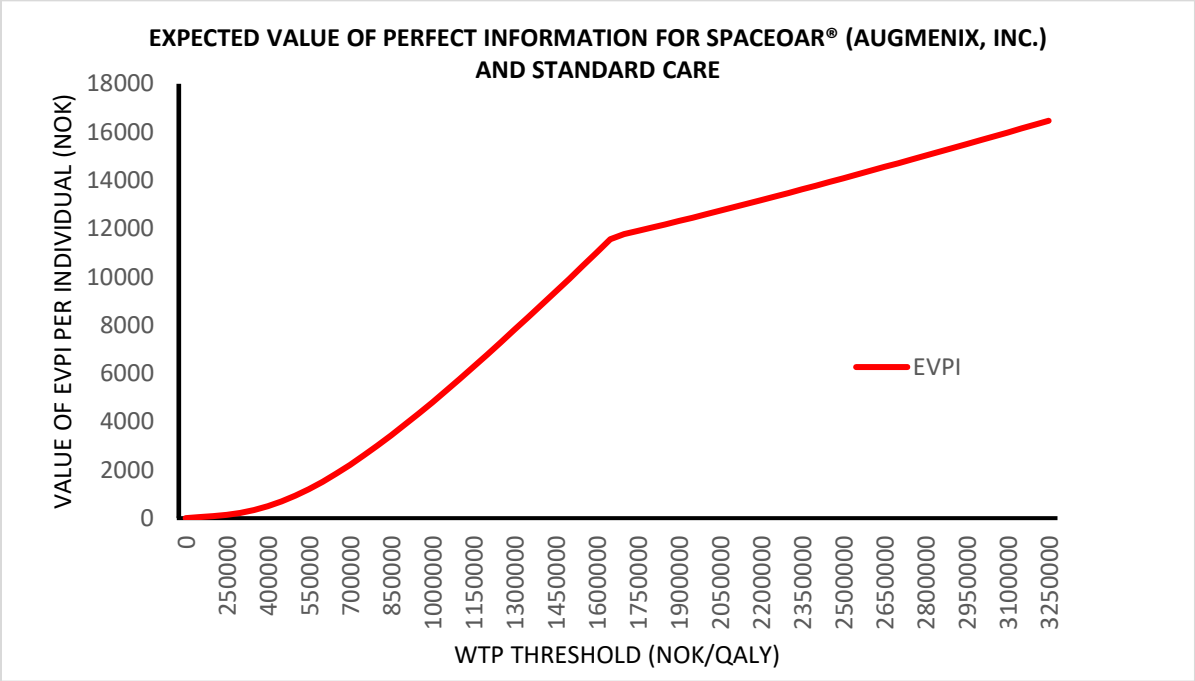

Figure 16. The expected value of perfect information for Standard Care with comparison to Standard Care with HRS.

Generally, pEVPI illustrates the maximum value expressed in monetary terms that can be invested in further research to resolve all uncertainties. While calculating pEVPI all the future patients, as well known as effective population, who can potentially benefit from intervention should be taken into account. Effective population for pEVPPI for primary analysis and secondary analysis with a prevalence of ED of 62% at baseline was estimated to be 2166 patients (Kreftregisteret, 2018) for the first year and effective lifetime of the intervention was assumed to be 10 years. It was accounted for an increase in population during this time with 40% (Johannesen, 2019). The effective population was discounted at 4% rate yearly. Therefore,

an effective population of 20 753 was used. For the subgroup of patients with good erectile function at the baseline effective population was decreased on 62 % and was 7886 patients.

Population EVPI for primary analysis is presented in Fig. 17. Given the WTP threshold of 275 000 NOK/QALY population EVPI is 3 590 269 NOK. This suggests that future research would be potentially cost-effective when the expanses for it would not exceed 3 590 269 NOK. Further research would be considered not worthwhile if it will be more costly than 3 590 269 NOK. With a hypothetical increase of WTP threshold, pEVPI will raise and a decision will contain more uncertainty.

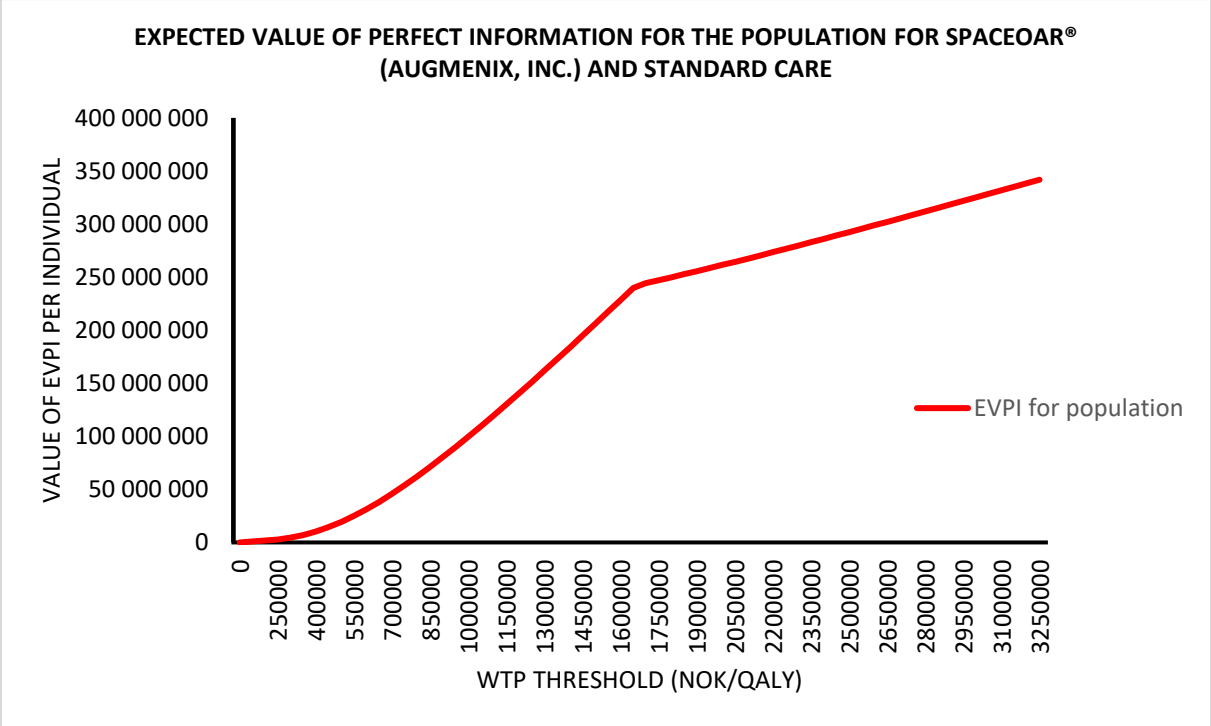

Figure 17. The expected value of perfect information for the population for Standard Care with comparison to Standard Care with HRS.

Fig. 18 and 20 express the individual decision uncertainty in monetary terms (NOK) between the treatment alternatives for the secondary analysis. Relatively low levels of EVPI illustrate the high probability of treatment strategy being cost-effective and with the increase of the uncertainty surrounding the preferred alternative EVPI raises and reaches its maximum when the decision uncertainty is greatest. When WTP threshold is very low, EVPI decreases to almost 0. The overall individual EVPI at WTP of 275 000 NOK was 204 NOK for the analysis with ED prevalence at baseline of 62%, and 3 231 NOK for analysis with ED prevalence at baseline of 0%. For the secondary analysis, results of pEVPI are presented in Fig. 19 and Fig. 21. With WTP threshold of 275 000 NOK/QALY pEVPI for the analysis with ED prevalence at baseline of 62%, was 4 233 612 NOK, and with the prevalence of 0% of 25 481 677 NOK.

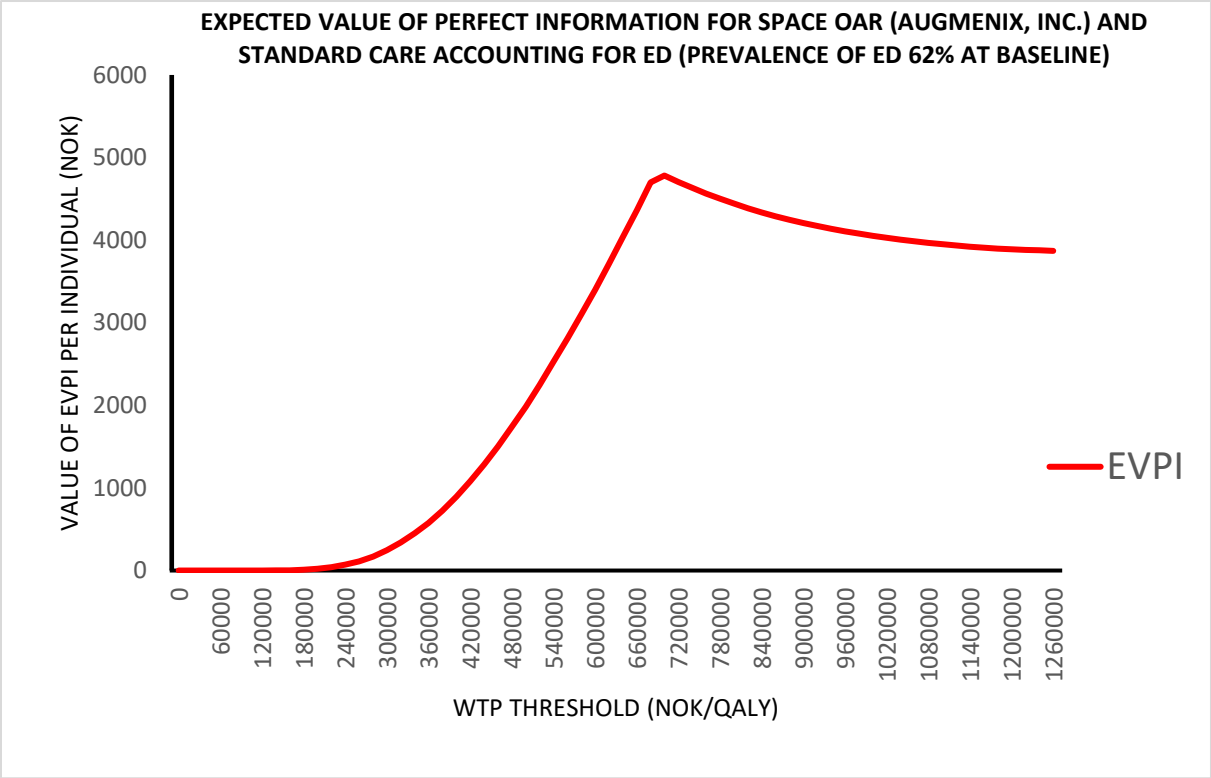

Figure 18. The expected value of perfect information for Standard Care with comparison to Standard Care with HRS accounting for ED (prevalence ED 62% at the baseline).

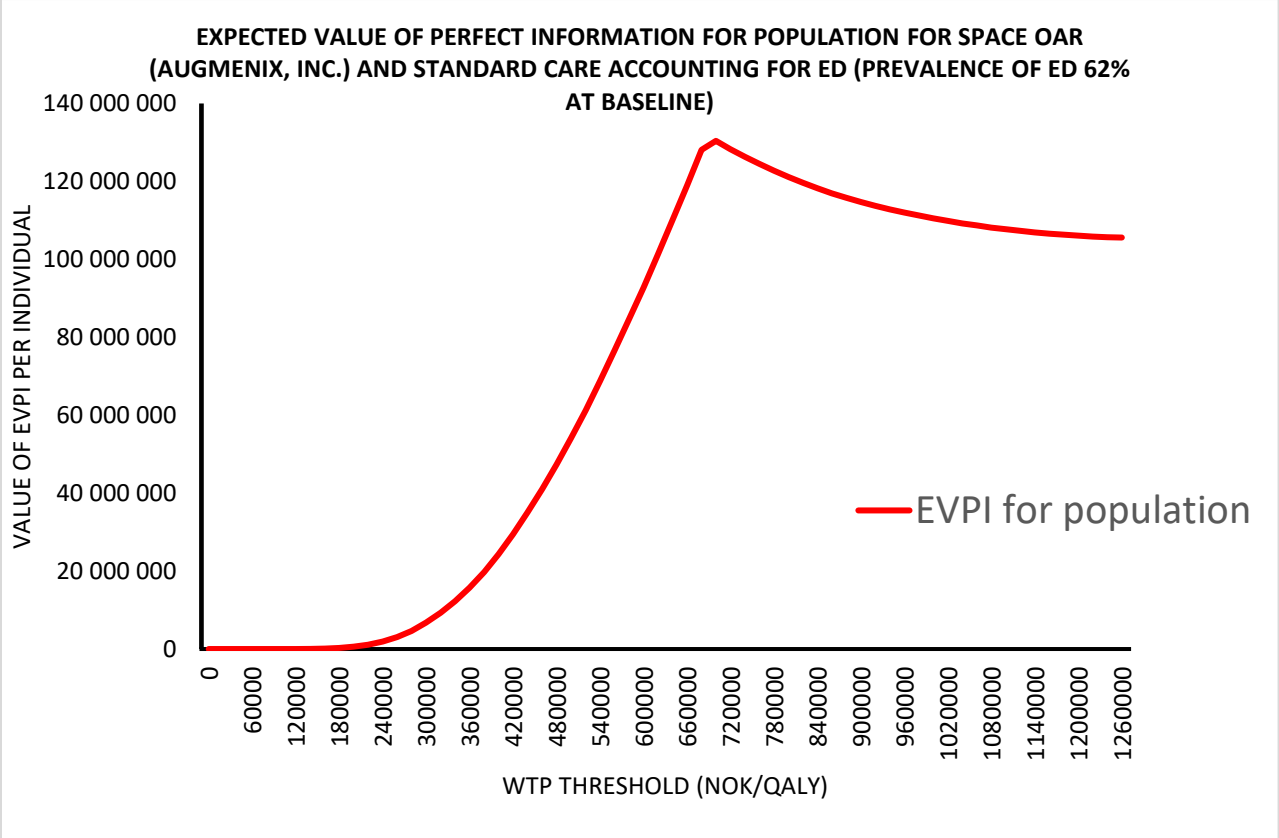

Figure 19. The expected value of perfect information for population Standard Care with comparison to Standard Care with HRS accounting for ED (prevalence ED 62% at the baseline).

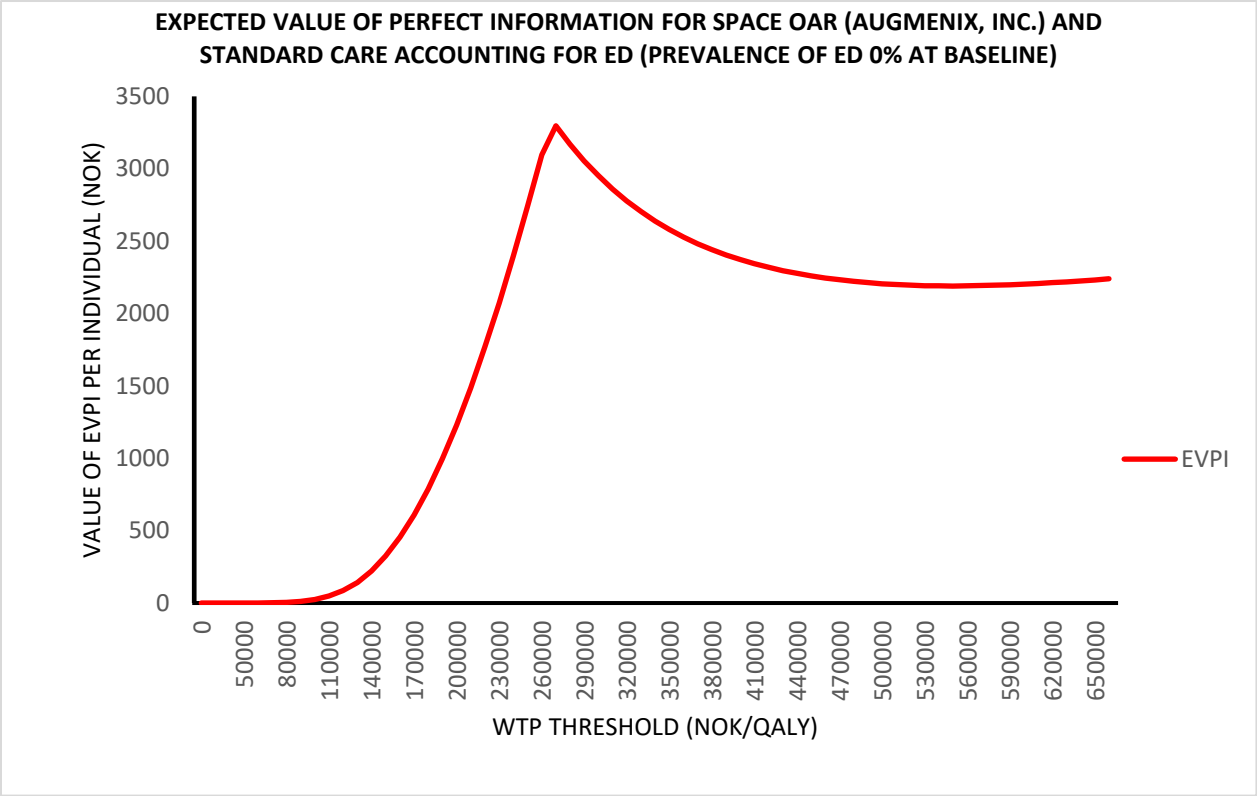

Figure 20. The expected value of perfect information for Standard Care with comparison to Standard Care with HRS accounting for ED (prevalence ED 0% at the baseline).

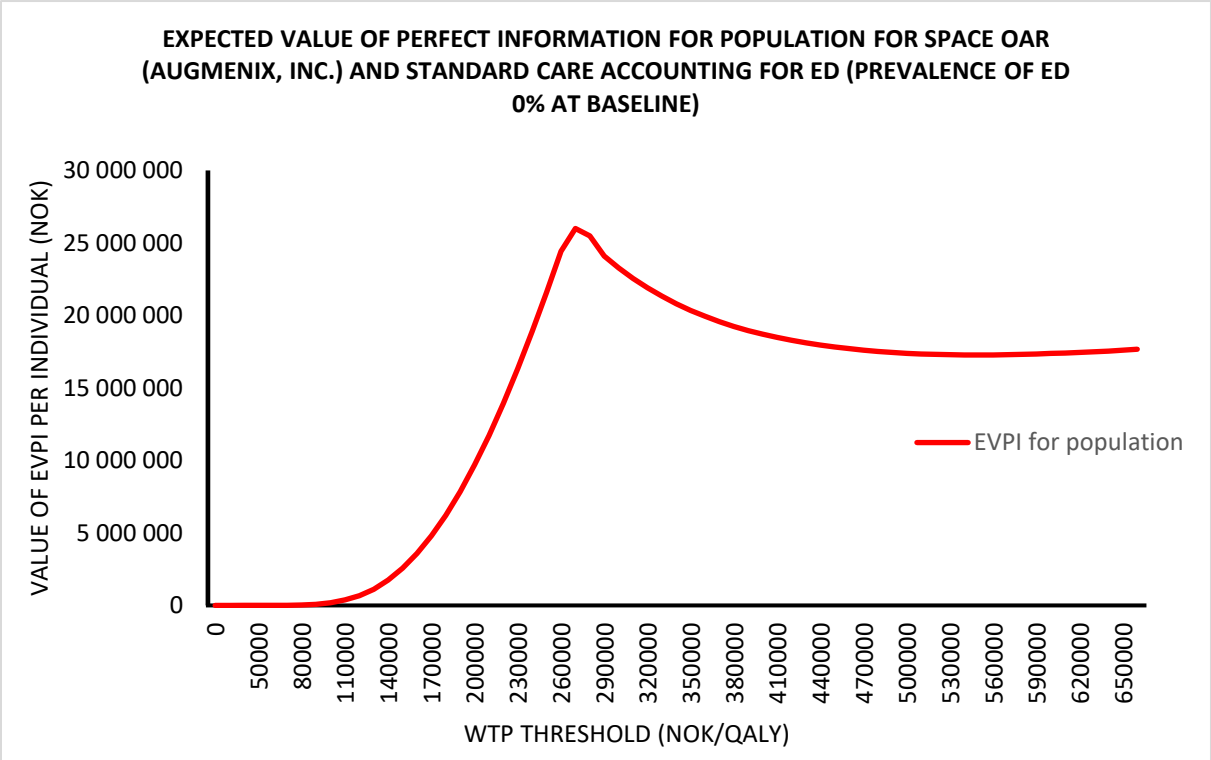

Figure 21. The expected value of perfect information for Standard Care with comparison to Standard Care with HRS accounting for ED (prevalence ED 0% at the baseline).

6.8 Expected value of perfect information for parameters

The EVPPI analysis was conducted for the primary analysis to investigate the impact of parameters on decision uncertainty. For this reason, parameters were grouped in the following categories in accordance with their characteristics: costs, utilities, and probabilities. However, at low levels of the WTP threshold ranging from 275 000 NOK/QALY and up to 500 000 NOK/QALY there were no values for any of the parameters. At a WTP threshold of 500 000 NOK/QALY the most uncertainty was connected to the cost parameters and expressed in 177 mln NOK (Fig. 22). In addition to costs, some uncertainty was associated with probability values.

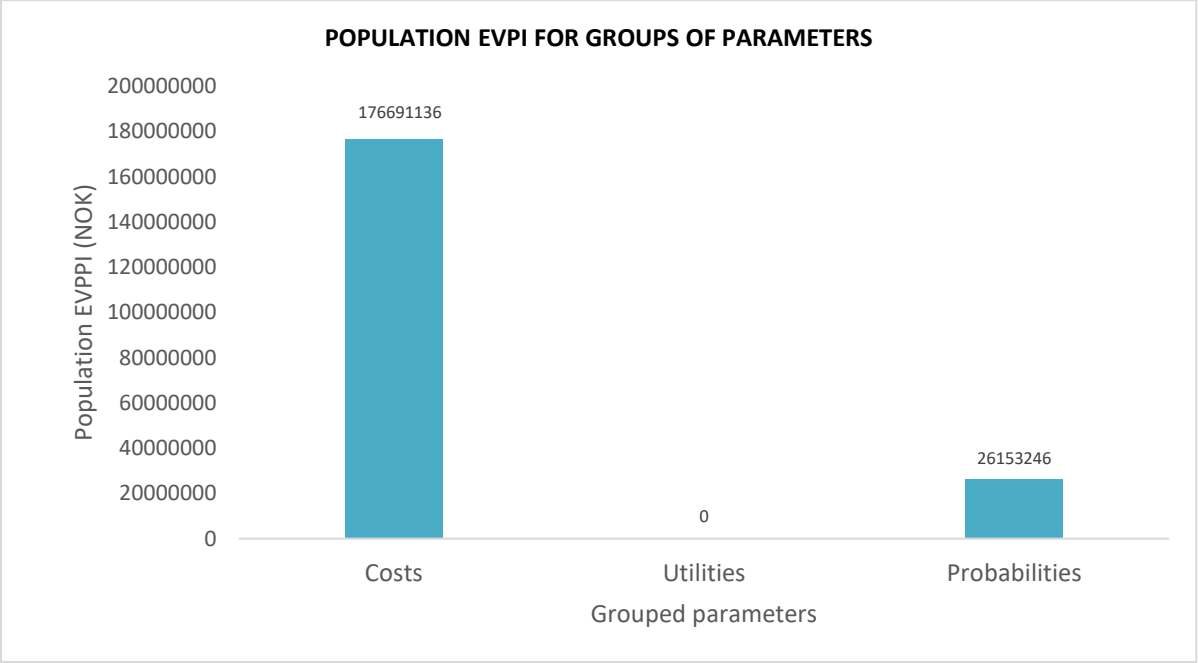

Figure 22. Population expected value of perfect information for groups of parameters. The population EVPPI is expressed in monetary terms (NOK) for WTP threshold of 500 000 NOK.

6.9 Budget impact analysis

To estimate the financial consequences of adopting new intervention BIA was performed. Costs include direct medical costs of radiotherapy of prostate cancer, follow-up, HRS SpaceOAR® and treatment of adverse events such as genitourinary and gastrointestinal toxicities. The costs were used from this model and described in Section 5. DRG weights, fixed

price for treating somatic disease (enhetsprisen) and costs for GP visits are based on the values for 2019.

HRS insertion procedure is done at the same time with golden markers insertion and does not require any additional equipment or personnel, however, the total time will increase approximately on 15-20 minutes for both nurse and clinician. To have a crude estimate on the cost of procedure DRG code 912A (Policlinic consultation for malignant tumor in men reproductive organ (Poliklinisk konsultasjon vedr ondartet svulst i mannlige kjønnsorgan)) was used (Helsedirektoratet, Innsatsstyrt finansiering – regelverk 2019).

The costs of a clinician's education were not included, as the producer provides educational services without charge. The patient population was used accounting for an increase of 40% in 10 years (Johannesen, 2019). BIA was calculated by subtracting the total costs of the intervention (Standard Care + HRS) from the total costs of Standard Care alone. Results, presented in Table 19, illustrate that if being reimbursed intervention will cost from 20 million NOK to 24.5 million NOK extra per year in comparison to Standard Care alone, which means not being reimbursed. Even though HRS helps to save the costs on the treatment of AE after radiotherapy, the costs of the HRS and the procedure play the role in overall exceeding costs of the intervention.

Table 19. Budget impact of having hydrogel spacer SpaceOAR® preapprove for reimbursement to be applied prior to radiation therapy of prostate cancer. For results and costs, estimates for 2019 are used. n=patient population.

			Costs (NOK)		
Treatment strategy	***Year 1***	***Year 2***	***Year 3***	***Year 4***	***Year 5***
	n=2166	***n=2260***	***n=2354***	***n=2448***	***n=2542***
Standard Care with HRS					
Cost of RT and HRS	227 171 750	237 030 342	246 888 933	256 747 524	26 660 6115
Cost of GI and GU treatment	6 727 717	8 939 809	11 339 387	13 440 914	15 302 196
Total	233 899 468	245 970 151	258 228 320	270 188 437	281 908 310
Standard Care alone					
Cost of RT	201 082053	209 808 605	218 535 158	227 261 710	235 988 263
Cost of GI and GU treatment	8 367 760	11 601 593	15 758 107	21 764 559	25 893 416
Total	209 449 813	221 410 198	234 293 265	249 026 270	261 881 679
Budget impact	**24 449 655**	**24 559 952**	**239 35 055**	**21 162 167**	**20 026 631**

7 Discussions

This thesis is the first study devoted to the cost-utility analysis of HRS in the Scandinavian countries and it substantially contributes to the available evidence about the cost-effectiveness of HRS SpaceOAR®. Furthermore, this paper evaluates the cost-effectiveness of applying HRS to specific groups of patients with underlying ED condition and with this captures the structural uncertainty of the model. The objective of this thesis was to provide evidence and aid decision-makers under conditions of uncertainty to make informed decisions regarding reimbursement of HRS SpaceOAR® in Norway.

7.1 Main findings

Considering the possibility of HRS SpaceOAR® to prevent gastrointestinal and genitourinary toxicities after dose-escalated external beam radiotherapy of prostate, HRS SpaceOAR® adjunct to Standard Care was concluded to be less cost-effective in comparison to Standard Care alone from a healthcare provider perspective considering lifetime horizon. The costs and QALYs per person were 103 551 NOK and 8.02 QALYs for the Standard Care group versus 117 363 NOK and 8.03 QALYs for the group with HRS. Costs included direct medical costs for treatment with radiotherapy, treatment of later AE and follow-up costs for the patient. The incremental costs were 13 813 NOK and incremental effects were 0.01 QALY per patient. The deterministic ICER was 1 382 413 NOK per QALY gained and it was significantly above WTP threshold of 275 000 NOK per QALY. Results of this analysis suggest that at the WTP threshold of 275 000 NOK application of SpaceOAR® was not cost-effective and findings from probabilistic sensitivity analysis support the conclusion of Standard Care alone being a preferred option.

Considering baseline prevalence of ED at 62% deterministic ICER for Standard Care + HRS versus Standard Care alone was of 544 675 NOK per QALY gained and is considered not to be cost-effective compared to Standard Care alone. If HRS was applied to the patients with ED prior to the radiotherapy, ICER reached 2 199 918 NOK per QALY gained.

The most cost-effective subgroup was the subgroup where HRS to the patients with underling good erectile function with ICER of 238 990 NOK per QALY gained, which was below the adopted threshold.

The uncertainty associated with decision in this paper was addressed by performing deterministic sensitivity analysis, probabilistic sensitivity analysis and value of information analysis. One-way sensitivity analysis was performed for the primary analysis and secondary analysis with ED prevalence of 62 % at the baseline. The model for the main analysis was most sensitive to fluctuations in the proportion of patients, who got successful insertion of HRS, the relative risk of having acute genitourinary toxicity grade 2 or higher and the utility of gastrointestinal toxicity of grade 2 or higher. With HRS cost of 1000 NOK or less, the ICER falls below zero making intervention a dominant alternative. For the secondary analysis relative risk for ED, success insertion and price of HRS were the most influential parameters.

The results of PSA analysis supported the conclusion of Standard Care being the preferred option for the primary analysis and for the secondary analysis with the prevalence of ED at baseline 62 % and higher, given the WTP threshold of 275 000 NOK per QALY. If the prevalence of ED at the baseline was 0%, HRS was the preferred option from the WTP threshold values of 260 000 NOK per QALY and higher. Investigation of structural uncertainty by performing subgroup analysis concluded that at WTP threshold of 275 000 NOK SpaceOAR® has 53% of being cost-effective if offered to people with good erectile function prior to radiation therapy.

The results of population EVPI suggest what is the maximum amount of money that can be potentially invested in further research to reduce the decision uncertainty. For the primary analysis expected costs of future research should not exceed 3 590 269 NOK. The reason why population EVPI and individual EVPI for primary research illustrates relatively small value is because decision uncertainty at the given WTP threshold of 275 000 NOK is low and CEAF supports this showing that there was 99% of Standard Care alone being cost-effective at this value of WTP threshold. If hypothetically, WTP threshold values would raise, pEVPI will follow it consequently. Population EVPI for secondary analysis with ED prevalence of 62% at the baseline was 4.2 million NOK and with the prevalence of ED of 0% it was 25.6 million NOK. pEVPI for secondary analysis reflects the decision uncertainty represented on the CEAC graphs, with being at a maximum when the decision contained the greatest uncertainty.

The EVPPI was calculated for the primary analysis to identify the direction of the potential future research. However, there was no uncertainty associated with either of the parameters at a WTP threshold values up to 500 000 NOK/QALY. At WTP threshold of

500 000 NOK/QALY, it was identified that further research should be directed mostly on the cost parameters. Some uncertainty was in addition associated with probability parameters.

The results of BIA for the primary analysis estimated the financial consequences for the National Insurance Scheme with additional costs for implementation of HRS varying from 20 million NOK to 24.5 million NOK per year.

7.2 Comparison to previous research

There were identified several studies that were aimed to establish the cost-effectiveness of hydrogel spacers in prostate cancer radiation therapy in Europe and North America, but, to my knowledge, this is the first CUA conducted in a Scandinavian setting.

In a cost-utility analysis by Vanneste et al. in 2015 (2015), ICER was calculated to be 55 880 EURO per QALY gained which will equal for around 596 560 NOK being converted to Norwegian currency and scaled for inflation by November 2019. This number is much lower than in the current study. Standard Care in combination with HRS produces 0.028 QALY more than Standard Care alone. It is higher than in this paper. This might be connected to the different input parameters, mostly for probability and utility parameters. This study was conducted before RCT by Mariados et al. (2015). Utility for GI toxicity grade 2 and higher was 0.727 QALY and it is lower than in this paper. While utility for not having any symptoms was 0.9 QALY and this is higher than in this paper. In addition, it is not stated explicitly age of the patients at the baseline and source for mortality data. GU toxicities and ED were not accounted for. The late GI toxicity was assumed to be irreversible. 5 years' time-horizon was used.

In a study conducted by van Wijk et al. (2017) it was identified that HRS will benefit 2 out of 8 patients. To identify the patients who will benefit the most from HRS insertion authors developed virtual spacer to support their decision model. Their model predicts the geometric results of the insertion of HRS and normal tissue complication probabilities. The study adopted Markov model from the Vaneste et al. (2015). The current study was not assessing the outcomes from this perspective.

The study by Hutchinson et al. (2016), conducted in the US in 2016, estimated cost-effectiveness of SpaceOAR® over the 10 years by building the decision tree and taking into account both direct and indirect costs. It was assumed that a typical patient in the model has a life expectancy of 10 years and prostate cancer stage T1-T2c. The age of the model patient is not given. The incremental costs for 3-dimensional conformal radiation therapy were assessed to be 518 USD, health effects were not measured. This result varied with the change of radiation

dose and estimated complication rates. GI toxicity rates were not taken from the RCT by Mariados et al., just the reduction rates were adopted from there. GU complications were not investigated. These factors could have led to lower incremental costs in the study by Hutchinson et al. than in the current study.

In a Canadian study, conducted in 2018 by Forero et al. (2018) for McGill University Health Centre, estimated ICER for avoiding one additional case of GI toxicity equal grade 2 or higher than grade 2 in CAD $191 230.06 (or approximately 1 352 695 NOK at the current rate by November 2019). GU toxicities were not taken in the evaluation. QALYs were omitted as a measure of health effects due to the author's assumption that data were very unreliable for this purpose. Therefore, the results of their study cannot be compared to the current study as the health outcomes are measured differently. Authors concluded with not approving routine use of HRS in McGill University Health Centre until new evidence will become available. The difference in results with the current study may be due to costs sources. Most of the cost components used by Forero et al. were derived from McGill University Health Centre.

In a cost-effectiveness analysis, conducted by Levy et al. (2018) in the US in 2018, ICER was estimated to be $96 440 per QALY gained (or approximately 905 139 NOK at the current rate by November 2019), which is lower than in the current study. Incremental effectiveness was 0.037 QALY. In this paper, incremental effectiveness was 0.01 QALY. The study by Levy et al. was based on the RCT by Mariados et al. (Mariados et al., 2015) and Hamstra et al. (Hamstra et al., 2017). There are a few reasons why there are different results between this paper and study by Levy et al. First is that different sources for measuring health effects were used. In the analysis in this paper age-dependant estimates for QALYs were applied and they were measured with EQ-5D instrument (for more details, please look at the Section 5.4) and in study by Levy et al. they used QALYs estimated with Self-Administered Quality of Well-Being-SA Scale (QWBSA) (Stewart, Lenert, Bhatnagar, & Kaplan, 2005). There are some differences in the QALY values. In study by Levy et al. Intestinal toxicity QALY equals 0.63 and urinary toxicity equals 0.83, whereas in current paper for 69 year old man grade 2 GI it is 0.84 and grade 2 GU 0.79 and QALYs deteriorates with time. The other reason may be connected for the different sources for mortality data together with difference in assumption about the impact of GU and GI toxicities on costs and on QALYs. In addition, the authors applied 5 years time horizon.

7.3 Strengths

In line with the purpose of this cost-utility study, the current analysis contributes to the wider knowledge of the cost-effectiveness of application of HRS SpaceOAR® in dose-escalated external radiation therapy in Norway.

For the purpose of this analysis, especially for calculating costs (depicting cost components for the treatment practices used in Norway and frequencies of the procedures), establishing rates of adverse events and duration of the both late GI and GU, identifying target population clinicians in Scandinavia and Norway were contacted.

This study explored the effect of ED as a parameter that contributes to the structural uncertainty of the model. Additionally, it was performed a thorough literature search.

In order to decrease underestimating mortality among target population data on mortality for the relevant population was requested from the Norwegian Cancer register and applied in the model. Mortality data were included according to the risk groups.

7.4 Limitations

This paper has several limitations mainly associated with model assumptions, model structure and parameter uncertainty, which could have influenced the incremental effects and/or costs and therefore ICER.

Most of the input parameters for this model were taken from a single RCT. However, there is a wide range of studies on AE after dose-escalated external beam radiation therapy, which suggests that levels of GU and GI toxicities might be higher. However, there is no consensus between studies. Worth mentioning RCTs by Michalski et al. (Michalski et al., 2018) and Dearnaley et al. (Dearnaley et al., 2016) which presented cumulative 5 years incidence rate of GI toxicity grade 2 and higher at 13.7% and 21 % respectively and for GU grade 2 and higher 9.1%, and 12% respectively. These levels are much higher than in the RCT used in this paper. AE in the abovementioned studies was measured with a different classification tool RTOG and this might have influenced the levels of AE. In study by Redmond et al. (Redmond, Dolbec, Fawaz, Flood, & Giri, 2018), which investigated hospital burden of GI and GU toxicities over mean follow-up time of 7.8 years, 23 out of 112 patients were admitted to emergency department with late onset of toxicity, 9 of those had more than one admission, 25 patients were investigated for GU toxicity and 47 for GI toxicity. 21 out of these 47 got argon coagulation

therapy. This may strongly suggest that costs and effects might be underestimated as they were based on expert opinion, literature and the RCT and not on real-world data. If this is so, then the HRS might be more cost-effective than it is concluded in this paper.

Another limitation is associated with transition probabilities being acquired from the US study, which might not be representative of a Norwegian patient population.

The other controversial topic is time from dose-escalated external beam radiation therapy to the point when most of the patients will experience the onset of AE symptoms and its duration. (Catton et al., 2017; Dearnaley et al., 2016; Kuban et al., 2008; Michalski et al., 2018; Weg et al., 2019; Zelefsky et al. 1998, Zelefsky et al., 2008). Time to onset for GI may vary from 3 to 39 months or even more. A few cases of late onset of GI toxicities could still be detected in studies with longer follow-up and in clinical practice. Time to onset of GU symptoms varied even more from 3 to nearly 60 months. So, the results of different studies on this topic varied significantly. The median time to resolution of the symptoms and proportion of patients, who experience resolution as well differs from study to study. The model does not account for the patients, who can experience toxicities later in life. A small group of patients can experience the onset of symptoms of GI and GU many years after radiotherapy (Weg et al., 2019).

It was challenging to estimate and collect data on the costs of patient's transportation together with productivity loss at work, as following population group may be approaching pension age or already be out on pension, thus these cost inputs were not included.

Costs associated with treating patients in case of unsuccess insertion were not included as it was hard to estimate costs components and in the literature on AE of HRS insertion, most of the cases required no treatment (please, see Section 2).

Some assumptions in this analysis such as the age of target population, the proportion of people in different risk groups and effective population were based on the Annual report on prostate cancer in Norway for 2017, issued in 2018 (Kreftregisteret, 2018). Later rapports would change these parameters.

Uncertainty associated with cost parameters derives from the fact that both GI and GU acute and late toxicities can come in a variety of different symptoms, each of which requires specific treatment.

Concerning model structure, it was assumed that one person can be just in the one health state, but in reality, one person can experience all three health states at once. For instance, man can have grade 3 genitourinary toxicity, ED and suffer from grade 2 gastrointestinal toxicity.

The other limitation derives from the assumption on the prevalence of ED at the age of 69 years and how it behaves with an increase of age in the Norwegian population. This may greatly influence the results of secondary analysis. As well, input data for the model derives from the study (Hamstra et al., 2018), which was conducted for the same patient population as the RCT by Mariados et al., (2015) and Hamstra et al. (2017), but the sample group at the end of the follow-up was small and therefore, the conclusions may be biased.

Another limitation connected to ED is the assumption that ED is not possible to cure and that this state does not produce any costs. There are several treatment options, including phosphodiesterase type 5 (PDE5) inhibitors, penile injections vacuum devices and others, that currently are not reimbursed in Norway. There is a wide debate on whether they will be remunerated. In such a case, ICER of HRS would decline following the incremental costs. This possibility was not accounted for in the model.

Androgen deprivation therapy (ADT) not included in the analysis. However, androgen deprivation therapy alone and in combination with radiotherapy has a detrimental effect on erectile function (White et al., 2014). In addition, this negative effect can be influenced by pre-existing comorbidities such as a history of diabetes, cardiovascular diseases, hypertension and intake of other drugs. The current model is not accounting for the possible negative effects of androgen deprivation therapy and other comorbidities on erectile function.

Utility decrements for the HRS insertion procedure were not applied, as the data on the actual effect of the procedure itself on quality of life is limited.

7.5 Recommendations for future research

The measurements of GI and GU complications after radiation therapy of prostate cancer vary in recent randomized controlled trials on comparing different dose-escalated external beam radiation therapy techniques and therefore the real burden of these toxicities for both provider and patients might be underestimated (Dearnaley et al., 2016; D. A. Kuban et al., 2008; Michalski et al., 2018; Weg et al., 2019; Zelefsky et al.).

There is a need to perform cost-effectiveness analysis with additional evidence on the usage of HRS from randomized control studies and real-world data with a larger patient population and longer follow-up period on both incidence of toxicities, costs, quality of life and other patient-oriented outcomes.

8 Conclusions

This thesis was prompted by the need for assessing the cost-effectiveness of HRS SpaceOAR® in dose-escalated EBRT of the prostate in Norway. The decision tree and a Makrov model were created to explore costs and health effects of treatment strategies (EBRT+HRS was compared to EBRT alone) with a lifetime horizon. Aiming to capture structural uncertainty of the model it was performed subgroup analysis considering patients erectile function prior to radiation therapy.

The findings from this cost-utility analysis suggest that implementing of hydrogel spacer SpaceOAR® for preventing GI and GU toxicities is not cost-effective with the data at hand and based on the applied assumption to be correct. The probabilistic sensitivity analysis supports this conclusion.

Acknowledging a patient's heterogeneity spacer might be more cost-effective for preselected groups of patients who are at risk of developing late radiation-induced AE. In a study by Vanneste et al. (Vanneste et al., 2016) is was developed a decision rule to identify patients, who will benefit most from HRS insertion based on clinical risk factors.

HRS can be cost-effective if it is offered to the patients with good erectile function at the baseline. However, there might be some ethical considerations with regard to applying good erectile function, as a criterion for receiving or not receiving HRS.

References

Bansal, N., Soni, A., Kaur, P., Chauhan, K., & Kaushal, V. (2016). Exploring the Management of Radiation Proctitis in Current Clinical Practice. *JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH*. Available from: https://doi.org/10.7860/JCDR/2016/17524.7906

Barton, G. R., Briggs, A. H., & Fenwick, E. A. L. (2008). Optimal Cost-Effectiveness Decisions: The Role of the Cost-Effectiveness Acceptability Curve (CEAC), the Cost-Effectiveness Acceptability Frontier (CEAF), and the Expected Value of Perfection Information (EVPI). *Value in Health*, *11*(5), 886–897. Available from: https://doi.org/10.1111/j.1524-4733.2008.00358.x

Briggs, A., K. Claxton, and M.J. Sculpher. (2006). *Decision modelling for health economic evaluation*. Reprint 2011. ed. Handbooks in health economic evaluation series. Oxford: Oxford University Press.

Burstrøm, K., Johannesson, M., & Diderichsen, F. (2001). Swedish population health-related quality of life results using the EQ-5D. *Quality of Life Research*, (10), 621–635.

Capp, A., Inostroza-Ponta, M., Bill, D., Moscato, P., Lai, C., Christie, D., … Denham, J. W. (2009). Is there more than one proctitis syndrome? A revisitation using data from the TROG 96.01 trial. *Radiotherapy and Oncology*, *90*(3), 400–407. Available from: https://doi.org/10.1016/j.radonc.2008.09.019

Chao, M., Ho, H., Chan, Y., Tan, A., Pham, T., Bolton, D., … Lawrentschuk, N. (2018). Prospective analysis of hydrogel spacer for patients with prostate cancer undergoing radiotherapy. *BJU International*, *122*(3), 427–433. Available from: https://doi.org/10.1111/bju.14192

Chao, M., Lim Joon, D., Khoo, V., Lawrentschuk, N., Ho, H., Spencer, S., … Bolton, D. (2019). The use of hydrogel spacer in men undergoing high-dose prostate cancer radiotherapy: Results of a prospective phase 2 clinical trial. *World Journal of Urology*, *37*(6), 1111–1116. Available from: https://doi.org/10.1007/s00345-018-2502-5

Chao, M., Ow, D., Ho, H., Chan, Y., Joon, D. L., Spencer, S., … Bolton, D. (2019). Improving rectal dosimetry for patients with intermediate and high-risk prostate cancer undergoing combined high-dose-rate brachytherapy and external beam radiotherapy with hydrogel space. *Journal of Contemporary Brachytherapy*, *11*(1), 8–13. Available from: https://doi.org/10.5114/jcb.2019.82836

Chao, Y., MacDougall, D., & de Nanassy, A. (2019). *Hydrogel Spacers for Patients with Prostate Cancer: A Review of Clinical Effectiveness and Cost-Effectiveness* (p. 36). Retrieved from The Canadian Agency for Drugs and Technologies in Health. Available from: https://www.cadth.ca /sites/default/files/pdf/htis/2019/RC1069%20Space%20OAR%20Hydrogel%20Final.pdf

Chapet, O., Decullier, E., Bin, S., Faix, A., Ruffion, A., Jalade, P., … Azria, D. (2015). Prostate Hypofractionated Radiation Therapy With Injection of Hyaluronic Acid: Acute Toxicities in a

Phase 2 Study. *International Journal of Radiation Oncology*Biology*Physics*, *91*(4), 730–736. Available from: https://doi.org/10.1016/j.ijrobp.2014.11.027

Chung, P., Brown, J., D'Souza, D., Koll, W., & Morgan, S. (2019). *Biodegradable Rectal Spacers for Prostate Cancer Radiotherapy*. *(Program in Evidence-based Care recommendation report no.: 21-5)*. Toronto (ON): Cancer Care Ontario. Available from: https://www.cancercareontario.ca/sites/ccocancercare /files/guidelines/full/pebc21-5f.pdf.

Cox, J. D., Stetz, J., & Pajak, T. F. (1995). Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European organization for research and treatment of cancer (EORTC). *International Journal of Radiation Oncology*Biology*Physics*, *31*(5), 1341–1346. Available from: https://doi.org/10.1016/0360-3016(95)00060-C

Coyle, D., Davies, L., & Drummond, M. F. (1998). Trials and Tribulations: *Emerging Issues in Designing Economic Evaluations Alongside Clinical Trials*. *International Journal of Technology Assessment in Health Care*, *14*(1), 135–144. Available from: https://doi.org/10.1017/S0266462300010588

Dale, W., Basu, A., Elstein, A., & Meltzer, D. (2008). Predicting Utility Ratings for Joint Health States from Single Health States in Prostate Cancer: Empirical Testing of 3 Alternative Theories. *Medical Decision Making*, *28*(1), 102–112. Available from: https://doi.org/10.1177/0272989X07309639

Dearnaley, D., Syndikus, I., Mossop, H., Khoo, V., Birtle, A., Bloomfield, D., … Hall, E. (2016). Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *The Lancet Oncology*, *17*(8), 1047–1060. Available from: https://doi.org/10.1016/S1470-2045(16)30102-4

Deeks, J., Higgins J., (2010) Statistical algorithms in Review Manager 5. Retrieved from http://ims.cochrane.org/revman/documentation/Statistical-methods-in-RevMan-5.pdf

Den Norske legeforening. Normaltariff for fastleger og legevakt 2019. Available from: https://normaltariffen.legeforeningen.no/asset/pdf/Fastlegetariffen-2019-2020.pdf

Denton, A. S., Andreyev, J. J., Forbes, A., & Maher, J. (2002). Non surgical interventions for late radiation proctitis in patients who have received radical radiotherapy to the pelvis. In The Cochrane Collaboration (Ed.), *Cochrane Database of Systematic Reviews* (p. CD003455). Available from: https://doi.org/10.1002/14651858.CD003455

Do, N. L., Nagle, D., & Poylin, V. Y. (2011). Radiation Proctitis: Current Strategies in Management. *Gastroenterology Research and Practice*, *2011*, 1–9. Available from: https://doi.org/10.1155/2011/917941

Drummond, M. F. (1987). *Methods for the economic evaluation of health care programmes* (Vol. 41). Available from: http://jech.bmj.com/cgi/doi/10.1136/jech.41.4.355-a

Drummond, M. F., Sculpher, M. J., Torrance, G. W., O'Brien, B. J., & Stoddart, G. L. (2005). M*ethods for the economic evaluation of health care programme*. Third edition. Oxford: Oxford University Press.

Eardley, I. (2013). The Incidence, Prevalence, and Natural History of Erectile Dysfunction. *Sexual Medicine Reviews*, *1*(1), 3–16. Available from: https://doi.org/10.1002/smrj.2

Fischer-Valuck, B. W., Chundury, A., Gay, H., Bosch, W., & Michalski, J. (2017). Hydrogel spacer distribution within the perirectal space in patients undergoing radiotherapy for prostate cancer: Impact of spacer symmetry on rectal dose reduction and the clinical consequences of hydrogel infiltration into the rectal wall. *Practical Radiation Oncology*, *7*(3), 195–202. Available from: https://doi.org/10.1016/j.prro.2016.10.004

Forero, D. F., Almeida, N., & Dendukuri, N. (2018). *Report prepared for the Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC)*. 52. Available from: https://cusm.ca/sites/default/files/micro/m-TAU/muhc_tau_2017_ecmo_a_0.pdf

Frazzoni, L. (2015). Pelvic radiation disease: Updates on treatment options. *World Journal of Clinical Oncology*, *6*(6), 272. Available from: https://doi.org/10.5306/wjco.v6.i6.272

Grodsky, M., & Sidani, S. (2015). Radiation Proctopathy. *Clinics in Colon and Rectal Surgery*, *28*(02), 103–111. Available from: https://doi.org/10.1055/s-0035-1547337

Hamstra, D. A., Mariados, N., Sylvester, J., Shah, D., Gross, E., Hudes, R., … Michalski, J. (2018). Sexual quality of life following prostate intensity modulated radiation therapy (IMRT) with a rectal/prostate spacer: Secondary analysis of a phase 3 trial. *Practical Radiation Oncology*, *8*(1), e7–e15. Available from: https://doi.org/10.1016/j.prro.2017.07.008

Hamstra, D. A., Mariados, N., Sylvester, J., Shah, D., Karsh, L., Hudes, R., … Michalski, J. (2017). Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial. *International Journal of Radiation Oncology*Biology*Physics*, *97*(5), 976–985. Available from: https://doi.org/10.1016/j.ijrobp.2016.12.024

Hatiboglu, G., Pinkawa, M., Vallée, J.-P., Hadaschik, B., & Hohenfellner, M. (2012). Application technique: Placement of a prostate-rectum spacer in men undergoing prostate radiation therapy: *TRANSPERINEAL HYDRODISSECTION TECHNIQUE*. *BJU International*, *110*(11b), E647–E652. Available from: https://doi.org/10.1111/j.1464-410X.2012.11373.x

Hedrick, S. G., Fagundes, M., Robison, B., Blakey, M., Renegar, J., Artz, M., & Schreuder, N. (2017). A comparison between hydrogel spacer and endorectal balloon: An analysis of intrafraction prostate motion during proton therapy. *Journal of Applied Clinical Medical Physics*, *18*(2), 106–112. Available from: https://doi.org/10.1002/acm2.12051

Helseøkonomiforvaltningen (HELFO). (2019). Available from: https://helfo.no/

HELFO.(2019). Egenandelstak for helsetjenester. Available from: https://www.helfo.no/regelverk/egenandeler-for-helsetjenester

Helsederiktoratet. (2019). *Pakkeforøp.Prostatakreft.* Available from*:* https://www.helsedirektoratet b.no/pakkeforlop/prostatakreft

Helsedirektoratet. (2019). *Innsatsstyrt finansiering – regelverk 2019.* IS-2791. Available from:https://unn.no/Documents/Kvalitetsregistre/Norsk-Register-for-Arvelige-og-medfodte-nevromuskulere-sykdommer/ISF-regelverket%202019.pdf

Hummel, S. R., Stevenson, M. D., Simpson, E. L., & Staffurth, J. (2012). A Model of the Cost-effectiveness of Intensity-modulated Radiotherapy in Comparison with Three-dimensional Conformal Radiotherapy for the Treatment of Localised Prostate Cancer. *Clinical Oncology*, *24*(10), e159–e167. Available from: https://doi.org/10.1016/j.clon.2012.09.003

Hummel, S., Simpson, E., Hemingway, P., Stevenson, M., & Rees, A. (2010). Intensity-modulated radiotherapy for the treatment of prostate cancer: A systematic review and economic evaluation. *Health Technology Assessment*, *14*(47). Available from: https://doi.org/10.3310/hta14470

Hutchinson, R. C., Sundaram, V., Folkert, M., & Lotan, Y. (2016). Decision analysis model evaluating the cost of a temporary hydrogel rectal spacer before prostate radiation therapy to reduce the incidence of rectal complications. *Urologic Oncology: Seminars and Original Investigations*, *34*(7), 291.e19-291.e26. Available from: https://doi.org/10.1016/j.urolonc.2016.02.024

Johannesen, T. (2019). *STOR ØKNING I KREFTTILFELLER FRAM MOT 2030*. Kreftregisteret. Available from: https://www.kreftregisteret.no/Generelt/Nyheter/Stor-okning-i-krefttilfeller-fram-mot-2030/

Juneja, P., Kneebone, A., Booth, J. T., Thwaites, D. I., Kaur, R., Colvill, E., … Eade, T. (2015). Prostate motion during radiotherapy of prostate cancer patients with and without application of a hydrogel spacer: A comparative study. *Radiation Oncology*, *10*(1), 215. https://doi.org/10.1186/s13014-015-0526-1

Karsh, L. I., Gross, E. T., Pieczonka, C. M., Aliotta, P. J., Skomra, C. J., Ponsky, L. E., … Shore, N. D. (2018). Absorbable Hydrogel Spacer Use in Prostate Radiotherapy: A Comprehensive Review of Phase 3 Clinical Trial Published Data. *Urology*, *115*, 39–44. Available from: https://doi.org/10.1016/j.urology.2017.11.016

Krahn, M. D., Bremner, K. E., Alibhai, S. M. H., Ni, A., Tomlinson, G., Laporte, A., & Naglie, G. (2013). A reference set of health utilities for long-term survivors of prostate cancer: Population-based data from Ontario, Canada. *Quality of Life Research*, *22*(10), 2951–2962. Available from: https://doi.org/10.1007/s11136-013-0401-1

Kreftregisteret. (Cancer Registry of Norway). (2019). Available from:https://www.kreftregisteret.no/

Kreftregisteret. (Cancer Registry of Norway). (2018). *Årsrapport 2017 med resultater og forbedringstiltak fra Nasjonalt kvalitetsregister for prostatakreft.* Available from*:* https://www.kreftregisteret.no/globalassets /publikasjoner-og-rapporter/ arsrapporter/publisert-2018/arsrapport-2017-prostatakreft.pdf

Kuban, D. A., Tucker, S. L., Dong, L., Starkschall, G., Huang, E. H., Cheung, M. R., … Pollack, A. (2008). Long-Term Results of the M. D. Anderson Randomized Dose-Escalation Trial for Prostate

Cancer. *International Journal of Radiation Oncology*Biology*Physics*, *70*(1), 67–74. Available from: https://doi.org/10.1016/j.ijrobp.2007.06.054

Kuban, D., Pollack, A., Huang, E., Levy, L., Dong, L., Starkschall, G., & Rosen, I. (2003). Hazards of dose escalation in prostate cancer radiotherapy. *International Journal of Radiation Oncology*Biology*Physics*, *57*(5), 1260–1268. Available from: https://doi.org/10.1016/S0360-3016(03)00772-7

Kubin, M., Wagner, G., & Fugl-Meyer, A. R. (2003). Epidemiology of erectile dysfunction. *International Journal of Impotence Research*, *15*(1), 63–71. Available from: https://doi.org/10.1038/sj.ijir.3900949

Lawrie, T. A., Green, J. T., Beresford, M., Wedlake, L., Burden, S., Davidson, S. E., … Andreyev, H. J. N. (2018). Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. *Cochrane Database of Systematic Reviews*. Available from: https://doi.org/10.1002/14651858.CD012529.pub2

Legemiddelhåndboka. (2019). Available from: https://www.legemiddelhandboka.no/T13.3.1/Erektil_dysfunksjon

Levine, L. A. (2000). Diagnosis and treatment of erectile dysfunction. *The American Journal of Medicine*, *109*(9), 3–12. Available from: https://doi.org/10.1016/S0002-9343(00)00655-0

Levy, J. F., Khairnar, R., Louie, A. V., Showalter, T. N., Mullins, C. D., & Mishra, M. V. (2019). Evaluating the Cost-Effectiveness of Hydrogel Rectal Spacer in Prostate Cancer Radiation Therapy. *Practical Radiation Oncology*, *9*(2), e172–e179. Available from: https://doi.org/10.1016/j.prro.2018.10.003

Lønning I.(Edit.). (1997). *Prioritering på ny, Sosial- og helsedepartementet.* STATENS FORVALTNINGSTJENESTE: STATENS TRYKNING.

Magnussen gruppen. (2015). *På ramme alvor - Alvorlighet og prioritering*. Available from: https://www.regjeringen.no/contentassets/d5da48ca5d1a4b128c72fc5daa3b4fd8/paa_ramme_alvor.pdf

Mahmood, J., Shamah, A. A., Creed, T. M., Pavlovic, R., Matsui, H., Kimura, M., … Vujaskovic, Z. (2016). Radiation-induced erectile dysfunction: Recent advances and future directions. *Advances in Radiation Oncology*, *1*(3), 161–169. Available from: https://doi.org/10.1016/j.adro.2016.05.003

Mariados, N., Sylvester, J., Shah, D., Karsh, L., Hudes, R., Beyer, D., … Michalski, J. (2015). Hydrogel Spacer Prospective Multicenter Randomized Controlled Pivotal Trial: Dosimetric and Clinical Effects of Perirectal Spacer Application in Men Undergoing Prostate Image Guided Intensity Modulated Radiation Therapy. *International Journal of Radiation Oncology*Biology*Physics*, *92*(5), 971–977. Available from: https://doi.org/10.1016/j.ijrobp.2015.04.030

Michalski, J. M., Moughan, J., Purdy, J., Bosch, W., Bruner, D. W., Bahary, J.-P., … Sandler, H. (2018). Effect of Standard vs Dose-Escalated Radiation Therapy for Patients With Intermediate-Risk

Prostate Cancer: The NRG Oncology RTOG 0126 Randomized Clinical Trial. *JAMA Oncology*, *4*(6), e180039. Available from: https://doi.org/10.1001/jamaoncol.2018.0039

Mok, G., Benz, E., Vallee, J.-P., Miralbell, R., & Zilli, T. (2014). Optimization of Radiation Therapy Techniques for Prostate Cancer With Prostate-Rectum Spacers: A Systematic Review. *International Journal of Radiation Oncology*Biology*Physics*, *90*(2), 278–288. Available from: https://doi.org/10.1016/j.ijrobp.2014.06.044

Montoya, J., Gross, E., & Karsh, L. (2018). How I Do It: Hydrogel spacer placement in men scheduled to undergo prostate radiotherapy. *The Canadian Journal of Urology*, 6.

Mottet, N., Bellmunt, J., Bolla, M., Briers, E., Cumberbatch, M. G., De Santis, M., … Cornford, P. (2017). EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *European Urology*, *71*(4), 618–629. Available from: https://doi.org/10.1016/j.eururo.2016.08.003

Müller, A.-C., Mischinger, J., Klotz, T., Gagel, B., Habl, G., Hatiboglu, G., & Pinkawa, M. (2016). Interdisciplinary consensus statement on indication and application of a hydrogel spacer for prostate radiotherapy based on experience in more than 250 patients. *Radiology and Oncology*, *50*(3), 329–336. Available from: https://doi.org/10.1515/raon-2016-0036

Naimark, D. M. J., Bott, M., & Krahn, M. (2008). The Half-Cycle Correction Explained: Two Alternative Pedagogical Approaches. *Medical Decision Making*, *28*(5), 706–712. Available from: https://doi.org/10.1177/0272989X08315241

National Comprehensive Cancer Network. (2018). NCCN Guidelines: prostate cancer v. 4.2018. Plymouth Meeting (PA): National Comprehensive Cancer Network. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx

National Institute for Health and Care Excellence. (2017). *Biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer. (NICE interventional procedures guidance IPG590*) Available from: https://www.nice.org.uk/guidance/ipg590#

National Institute for Health Care Excellence, NICE Process and Methods Guides, in Methods for the Development of NICE Public Health Guidance. 2012, National Institute for Health and Care Excellence (NICE) unless otherwise stated. All rights reserved.: London.

Norsk Legemiddelhåndbok. (2019). *T13.3.1 Erektil dysfunksjon*. Available from: https://www.legemiddelhandboka.no/T13.3.1/ Erektil_dysfunksjon

Norheim, F. (Editor.). (2014). *Åpent og rettferdig - prioriteringer i helsetjenesten*. H.-o. omsorgsdepartementet.

Norwegian Ministry, & of Health and Care Services. (2017). *Principles for priority setting in health care – Summary of a white paper on priority setting in the Norwegian health care sector* (p. 72). Available from: https://www.regjeringen.no/contentassets/439a420e01914a18b21f351143ccc6af/en-gb/pdfs/stm201520160034000engpdfs.pdf

OECD, & European Union. (2018). *Health at a Glance: Europe 2018: State of Health in the EU Cycle*. Available from: https://doi.org/10.1787/health_glance_eur-2018-en

Ophuis, R. H., Lokkerbol, J., Haagsma, J. A., Hiligsmann, M., Evers, S. M. A. A., & Polinder, S. (2018). Value of information analysis of an early intervention for subthreshold panic disorder: Healthcare versus societal perspective. *PLOS ONE*, *13*(11), e0205876. Available from: https://doi.org/10.1371/journal.pone.0205876

O'Sullivan, B., Brierley, J., Byrd, D., Bosman, F., Kehoe, S., Kossary, C., … Gospodarowicz, M. (2017). The TNM classification of malignant tumours—Towards common understanding and reasonable expectations. *The Lancet Oncology*, *18*(7), 849–851. Available from: https://doi.org/10.1016/S1470-2045(17)30438-2

Ottersen, T., Førde, R., Kakad, M., Kjellevold, A., Melberg, H. O., Moen, A., … Norheim, O. F. (2016). A new proposal for priority setting in Norway: Open and fair. *Health Policy*, *120*(3), 246–251. Available from: https://doi.org/10.1016/j.healthpol.2016.01.012

Perez-Cornago, A., Key, T. J., Allen, N. E., Fensom, G. K., Bradbury, K. E., Martin, R. M., & Travis, R. C. (2017). Prospective investigation of risk factors for prostate cancer in the UK Biobank cohort study. *British Journal of Cancer*, *117*(10), 1562–1571. Available from: https://doi.org/10.1038/bjc.2017.312

Phan, J., Swanson, D. A., Levy, L. B., Kudchadker, R. J., Bruno, T. L., & Frank, S. J. (2009). Late rectal complications after prostate brachytherapy for localized prostate cancer: Incidence and management. *Cancer*, *115*(9), 1827–1839. Available from: https://doi.org/10.1002/cncr.24223

Picardi, C., Rouzaud, M., Kountouri, M., Lestrade, L., Vallée, J. P., Caparrotti, F., … Zilli, T. (2016). Impact of hydrogel spacer injections on interfraction prostate motion during prostate cancer radiotherapy. *Acta Oncologica*, *55*(7), 834–838. Available from: https://doi.org/10.3109/0284186X.2015.1128118

Pinkawa, M. (2015). Current role of spacers for prostate cancer radiotherapy. *World Journal of Clinical Oncology*, *6*(6), 189. Available from: https://doi.org/10.5306/wjco.v6.i6.189

Pinkawa, M., Berneking, V., König, L., Frank, D., Bretgeld, M., & Eble, M. J. (2017). Hydrogel injection reduces rectal toxicity after radiotherapy for localized prostate cancer. *Strahlentherapie Und Onkologie*, *193*(1), 22–28. Available from: https://doi.org/10.1007/s00066-016-1040-6

Pinkawa, M., Escobar Corral, N., Caffaro, M., Piroth, M. D., Holy, R., Djukic, V., … Eble, M. J. (2011). Application of a spacer gel to optimize three-dimensional conformal and intensity modulated radiotherapy for prostate cancer. *Radiotherapy and Oncology*, *100*(3), 436–441. Available from: https://doi.org/10.1016/j.radonc.2011.09.005

Prioriteringsutvalget. (1987). *Retningslinjer for prioriteringer innen norsk helsetjeneste*. Lønning. I. (Editor).

Rancati, T., Palorini, F., Cozzarini, C., Fiorino, C., & Valdagni, R. (2017). Understanding Urinary Toxicity after Radiotherapy for Prostate Cancer: First Steps Forward. *Tumori Journal*, *103*(5), 395–404. Available from: https://doi.org/10.5301/tj.5000681

Redmond, E. J., Dolbec, K. S., Fawaz, A. S., Flood, H. D., & Giri, S. K. (2018). Hospital burden of long-term genitourinary and gastrointestinal toxicity after radical radiotherapy for prostate cancer. *The Surgeon*, *16*(3), 171–175. Available from: https://doi.org/10.1016/j.surge.2017.08.003

Rucinski, A., Brons, S., Richter, D., Habl, G., Debus, J., Bert, C., … Jäkel, O. (2015). Ion therapy of prostate cancer: Daily rectal dose reduction by application of spacer gel. *Radiation Oncology*, *10*(1), 56. Available from: https://doi.org/10.1186/s13014-015-0348-1

Ruggieri, R., Naccarato, S., Stavrev, P., Stavreva, N., Fersino, S., Giaj Levra, N., … Alongi, F. (2015). Volumetric-modulated arc stereotactic body radiotherapy for prostate cancer: Dosimetric impact of an increased near-maximum target dose and of a rectal spacer. *The British Journal of Radiology*, *88*(1054), 20140736. Available from: https://doi.org/10.1259/bjr.20140736

Schörghofer, A., Drerup, M., Kunit, T., Lusuardi, L., Holzinger, J., Karner, J., … Wolf, F. (2019a). Rectum-spacer related acute toxicity – endoscopy results of 403 prostate cancer patients after implantation of gel or balloon spacers. *Radiation Oncology*, *14*(1), 47. Available from: https://doi.org/10.1186/s13014-019-1248-6

Sehn, J. K. (2018). *Recent Updates and Controversies*. 5. Science of medicine. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6139855/pdf/ms115_p0151.pdf

Shadad, A. K. (2013). Gastrointestinal radiation injury: Symptoms, risk factors and mechanisms. *World Journal of Gastroenterology*, *19*(2), 185. Available from: https://doi.org/10.3748/wjg.v19.i2.185

Siebert, U., Alagoz, O., Bayoumi, A. M., Jahn, B., Owens, D. K., Cohen, D. J., & Kuntz, K. M. (2012). State-Transition Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-3. *Value in Health*, *15*(6), 812–820. Available from: https://doi.org/10.1016/j.jval.2012.06.014

Solberg, A., Angelsen, A., Berge,V., Iversen, R., Klepp, O., Brennhovd, B., Johannessen, D., Nygård, Y., Larsen, K., Kvale, R. (2015). *Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av prostatakreft.* (7.utgave). Helsedirektoratet. Available from: https://www.helsedirektoratet.no/retningslinjer/prostatakreft-handlingsprogram/Prostatakreft%20%E2%80%93%20Nasjonalt%20handlingsprogram%20med%20retningslinjer%20for%20diagnostikk,%20behandling%20og%20oppf%C3%B8lging.pdf/_/attachment/inline/a0bb1696-5a09-4cd6-93da-05907e829974:b994ab8e4720 4ecbfa4560030b1f9c64cb7c598c/ Prostatakreft%20%E2%80%93%20Nasjonalt%20handlingsprogram%20med%20retningslinjer%20for%20diagnostikk,%20behandling%20og%20oppf%C3%B8lging.pdf

Song, D. Y., Herfarth, K. K., Uhl, M., Eble, M. J., Pinkawa, M., van Triest, B., … Ford, E. C. (2013). A Multi-institutional Clinical Trial of Rectal Dose Reduction via Injected Polyethylene-Glycol Hydrogel During Intensity Modulated Radiation Therapy for Prostate Cancer: Analysis of

Dosimetric Outcomes. *International Journal of Radiation Oncology*Biology*Physics*, *87*(1), 81–87. Available from: https://doi.org/10.1016/j.ijrobp.2012.12.019

Statistisk sentralbyrå. Statistics Norway. (2019). *Døde*. Available from: https://www.ssb.no/befolkning/statistikker/dode.

Statens legemiddelverk.(Edit.).(2018). *Retningslinjer for legemiddeløkonomiske analyser*. Helsedirektoratet. Avaliable from: https://legemiddelverket.no/Documents/ Offentlig% 20finansiering%20og%20pris/Dokumentasjon%20til%20metodevurdering/Retningslinjer%20151018.pdf

Stewart, S. T., Lenert, L., Bhatnagar, V., & Kaplan, R. M. (2005). Utilities For Prostate Cancer Health States in Men Aged 60 and Older. *Medical Care*, *43*(4), 9.

Sullivan, S. D., Mauskopf, J. A., Augustovski, F., Jaime Caro, J., Lee, K. M., Minchin, M., … Shau, W.-Y. (2014). Budget Impact Analysis—Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value in Health*, *17*(1), 5–14. Available from: https://doi.org/10.1016/j.jval.2013.08.2291

te Velde, B. L., Westhuyzen, J., Awad, N., Wood, M., & Shakespeare, T. P. (2017). Can a peri-rectal hydrogel spaceOAR programme for prostate cancer intensity-modulated radiotherapy be successfully implemented in a regional setting? *Journal of Medical Imaging and Radiation Oncology*, *61*(4), 528–533. Available from: https://doi.org/10.1111/1754-9485.12580

Trager, M., Greenberger, B., Harrison, A. S., Keller, J., & Den, R. B. (2018). SpaceOAR to improve dosimetric outcomes for monotherapy high-dose-rate prostate implantation in a patient with ulcerative colitis. *Journal of Contemporary Brachytherapy*, *10*(6), 577–582. Available from: https://doi.org/10.5114/jcb.2018.81001

The Norwegian Medicines Agency. Statens legemiddelverk. (2018). *Retningslinjer for legemiddeløkonomiske analyser*. Helsedirektoratet.

Uhl, M., Herfarth, K., Eble, M. J., Pinkawa, M., van Triest, B., Kalisvaart, R., … DeWeese, T. L. (2014). Absorbable hydrogel spacer use in men undergoing prostate cancer radiotherapy: 12 month toxicity and proctoscopy results of a prospective multicenter phase II trial. *Radiation Oncology*, *9*(1), 96. Available from: https://doi.org/10.1186/1748-717X-9-96

Uhl, M., van Triest, B., Eble, M. J., Weber, D. C., Herfarth, K., & De Weese, T. L. (2013). Low rectal toxicity after dose escalated IMRT treatment of prostate cancer using an absorbable hydrogel for increasing and maintaining space between the rectum and prostate: Results of a multi-institutional phase II trial. *Radiotherapy and Oncology*, *106*(2), 215–219. Available from: https://doi.org/10.1016/j.radonc.2012.11.009

van de Wetering, F. T., Verleye, L., Andreyev, H. J. N., Maher, J., Vlayen, J., Pieters, B. R., … Scholten, R. J. (2016). Non-surgical interventions for late rectal problems (proctopathy) of radiotherapy in people who have received radiotherapy to the pelvis. *Cochrane Database of Systematic Reviews*. Available from: https://doi.org/10.1002/14651858.CD003455.pub2

van der Wielen, G. J., Mulhall, J. P., & Incrocci, L. (2007). Erectile dysfunction after radiotherapy for prostate cancer and radiation dose to the penile structures: A critical review. *Radiotherapy and Oncology*, *84*(2), 107–113. Available from: https://doi.org/10.1016/j.radonc.2007.07.018

van Gysen, K., Kneebone, A., Alfieri, F., Guo, L., & Eade, T. (2014). Feasibility of and rectal dosimetry improvement with the use of SpaceOAR® hydrogel for dose-escalated prostate cancer radiotherapy: Spacer use in prostate radiotherapy. *Journal of Medical Imaging and Radiation Oncology*, n/a-n/a. Available from: https://doi.org/10.1111/1754-9485.12152

van Wijk, Y., Vanneste, B. G. L., Walsh, S., van der Meer, S., Ramaekers, B., van Elmpt, W., … Lambin, P. (2017). Development of a virtual spacer to support the decision for the placement of an implantable rectum spacer for prostate cancer radiotherapy: Comparison of dose, toxicity and cost-effectiveness. *Radiotherapy and Oncology*, *125*(1), 107–112. Available from: https://doi.org/10.1016/j.radonc.2017.07.026

Vanneste, B. G. L., Hoffmann, A. L., van Lin, E. N., Van De Voorde, L., Pinkawa, M., & Lambin, P. (2016). Who will benefit most from hydrogel rectum spacer implantation in prostate cancer radiotherapy? A model-based approach for patient selection. *Radiotherapy and Oncology*, *121*(1), 118–123. Available from: https://doi.org/10.1016/j.radonc.2016.08.026

Vanneste, B. G. L., Pijls-Johannesma, M., Van De Voorde, L., van Lin, E. N., van de Beek, K., van Loon, J., … Lambin, P. (2015). Spacers in radiotherapy treatment of prostate cancer: Is reduction of toxicity cost-effective? *Radiotherapy and Oncology*, *114*(2), 276–281. Available from: https://doi.org/10.1016/j.radonc.2015.01.005

Vranova, J., Vinakurau, S., Richter, J., Starec, M., Fiserova, A., & Rosina, J. (2011). The evolution of rectal and urinary toxicity and immune response in prostate cancer patients treated with two three-dimensional conformal radiotherapy techniques. *Radiation Oncology*, *6*(1), 87. Available from: https://doi.org/10.1186/1748-717X-6-87

Weber, D. C., Zilli, T., Vallee, J. P., Rouzaud, M., Miralbell, R., & Cozzi, L. (2012). Intensity Modulated Proton and Photon Therapy for Early Prostate Cancer With or Without Transperineal Injection of a Polyethylen Glycol Spacer: A Treatment Planning Comparison Study. *International Journal of Radiation Oncology*Biology*Physics*, *84*(3), e311–e318. Available from: https://doi.org/10.1016/j.ijrobp.2012.03.028

Weg, E. S., Pei, X., Kollmeier, M. A., McBride, S. M., & Zelefsky, M. J. (2019). Dose-Escalated Intensity Modulated Radiation Therapy for Prostate Cancer: 15-Year Outcomes Data. *Advances in Radiation Oncology*, *4*(3), 492–499. Available from: https://doi.org/10.1016/j.adro.2019.03.012

Whalley, D., Hruby, G., Alfieri, F., Kneebone, A., & Eade, T. (2016). SpaceOAR Hydrogel in Dose-escalated Prostate Cancer Radiotherapy: Rectal Dosimetry and Late Toxicity. *Clinical Oncology*, *28*(10), e148–e154. Available from: https://doi.org/10.1016/j.clon.2016.05.005

White, I. D., Wilson, J., Aslet, P., Baxter, A. B., Birtle, A., Challacombe, B., … Kirby, M. (2014). Development of UK guidance on the management of erectile dysfunction resulting from radical

radiotherapy and androgen deprivation therapy for prostate cancer. *International Journal of Clinical Practice*, *69*(1), 106-123. doi:10.1111/ijcp.12512

Wilton, L., Richardson, M., Keats, S., Legge, K., Hanlon, M.-C., Arumugam, S., … Martin, J. (2017). Rectal protection in prostate stereotactic radiotherapy: A retrospective exploratory analysis of two rectal displacement devices. *Journal of Medical Radiation Sciences*, *64*(4), 266–273. Available from: https://doi.org/10.1002/jmrs.238

Wolf, F., Gaisberger, C., Ziegler, I., Krenn, E., Scherer, P., Hruby, S., … Sedlmayer, F. (2015). Comparison of two different rectal spacers in prostate cancer external beam radiotherapy in terms of rectal sparing and volume consistency. *Radiotherapy and Oncology*, *116*(2), 221–225. Available from: https://doi.org/10.1016/j.radonc.2015.07.027

Zelefsky, M. J., Cowen, D., Fuks, Z., Shike, M., Burman, C., Jackson, A., … Leibel, S. A. (1999). Long term tolerance of high dose three-dimensional conformal radiotherapy in patients with localized prostate carcinoma. *Cancer*, *85*(11), 2460-2468. doi:10.1002/(sici)1097-0142(19990601)85:11<2460::aid-cncr23>3.0.co;2-n

Appendix

Table A1. Transition probabilities for the main analysis model, considering Standard Care.*

Probabilities from 0 - 3 months

Intermediate risk group		*High localized risk group*		*High locally advanced risk group*	
Transitions	***Value***	***Transitions***	***Value***	***Transitions***	***Value***
from grade 0+1 to grade 0+1	0,514	from "grade0+1" to "death"	0,001	from "grade0+1" to "death"	0,003
from grade 0+1 to GI grade 2	0,028	from "grade 0+1" to "GI grade 2"	0,028	from "grade 0+1" to "GI grade 2"	0,028
from grade 0+1 to GI grade 3	0,014	from "grade 0+1" to "GI grade 3"	0,014	from "grade 0+1" to "GI grade 3"	0,014
from grade 0+1 to GU grade 2	0,444	from "grade 0+1" to "GU grade 2"	0,444	from "grade 0+1" to "GU grade 2"	0,443
		from "grade 0+1" to "grade 0+1"	0,513	from "grade 0+1" to "grade 0+1"	0,512

Probabilities from 3 - 15 months

Intermediate risk group		*High localized risk group*		*High locally advanced risk group*	
Transitions	***Value***	***Transitions***	***Value***	***Transitions***	***Value***
from "grade0+1" to stay there	0,334	from "grade0+1" to stay there	0,367	from "grade0+1" to stay there	0,380
from "grade0+1" to "death"	0,003	from "grade0+1" to "death"	0,005	from "grade0+1" to "death"	0,006
from "grade 0+1" to "grade 0+1"	0,662	from "grade 0+1" to "grade 0+1"	0,629	from "grade 0+1" to "grade 0+1"	0,615
from "GU grade 2" to stay there	0,544	from "GU grade 2" to stay there	0,550	from "GU grade 2" to stay there	0,553
from "GU grade 2" to "GU grade 2"	0,024	from "GU grade 2" to " GU grade 2"	0,024	from "GU grade 2" to " GU grade 2"	0,024
from "GU grade 2" to "death"	0,003	from "GU grade 2" to "death"	0,005	from "GU grade 2" to "death"	0,006
from "GU grade 2" to "grade 0+1"	0,428	from "GU grade2" to "grade 0+1"	0,421	from "GU grade2" to "grade 0+1"	0,418
from "GI grade 2" to stay there	0,371	from "GI grade 2" to stay there	0,395	from "GI grade 2" to stay there	0,405
from "GI grade 2" to "grade 0+1"	0,624	from "GI grade 2" to "grade 0+1"	0,599	from "GI grade 2" to "grade 0+1"	0,588
from "GI grade 2" to "GI grade 3"	0,002	from "GI grade 2" to "GI grade 3"	0,002	from "GI grade 2" to "GI grade 3"	0,002
from "GI grade 2" to "death"	0,003	from "GI grade 2" to "death"	0,005	from "GI grade 2" to "death"	0,006
from "GI grade 3" to stay there	0,334	from "GI grade 3" to stay there	0,367	from "GI grade 3" to stay there	0,380
from "GI grade 3" to "death"	0,003	from "GI grade 3" to "death"	0,005	from "GI grade 3" to "death"	0,006
from "GI grade 3" to "GI grade 3"	0,662	from "GI grade 3" to "GI grade 3"	0,629	from "GI grade 3" to "GI grade 3"	0,615

Probabilities from 15 - 36 months

Intermediate risk group		*High localized risk group*		*High locally advanced risk group*	
Transitions	***Value***	***Transitions***	***Value***	***Transitions***	***Value***
from "grade 0+1" to stay there	0,710	from "grade 0+1" to stay there	0,713	from "grade 0+1" to stay there	0,716
from "grade 0+1" to "death"	0,004	from "grade 0+1" to "death"	0,005	from "grade 0+1" to "death"	0,006
from "grade 0+1" to "grade 0+1"	0,274	from "grade 0+1" to "grade 0+1"	0,271	from "grade 0+1" to "grade 0+1"	0,268
from "grade 0+1" to "GI grade 2"	0,007	from "grade 0+1" to "GI grade 2"	0,006	from "grade 0+1" to "GI grade 2"	0,006
from "grade 0+1" to "GU grade 2"	0,005	from "grade 0+1" to "GU grade 2"	0,004	from "grade 0+1" to "GU grade 2"	0,004
from "GI grade 3" to stay there	0,597	from "GI grade 3" to stay there	0,621	from "GI grade 3" to stay there	0,628
from "GI grade 3" to "GI grade 2"	0,399	from "GI grade 3" to "GI grade 2"	0,374	from "GI grade 3" to "GI grade 2"	0,366
from "GI grade 3" to "death"	0,004	from "GI grade 3" to "death"	0,005	from "GI grade 3" to "death"	0,006
from "GU grade 2" to stay there	0,597	from "GU grade 2" to stay there	0,621	from "GU grade 2" to stay there	0,628
from "GU grade 2" to "GU grade 2"	0,399	from "GU grade 2" to "GU grade 2"	0,374	from "GU grade 2" to "GU grade 2"	0,366
from "GU grade 2" to "death"	0,004	from "GU grade 2" to "death"	0,005	from "GU grade 2" to "death"	0,006
from "GI grade 2" to stay there	0,597	from "GI grade 2" to stay there	0,621	from "GI grade 2" to stay there	0,628
from "GI grade 2" to "GI grade 2"	0,399	from "GI grade 2" to "GI grade 2"	0,374	from "GI grade 2" to "GI grade 2"	0,366
from "GI grade 2" to "death"	0,004	from "GI grade 2" to "death"	0,005	from "GI grade 2" to "death"	0,006

**Dirichlet distribution was used for all transition probabilities in this table*