Original paper

Comparative cost-effectiveness of focal and total salvage ^{125}I brachytherapy for recurrent prostate cancer after primary radiotherapy

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Abstract

Purpose: Focal salvage (FS) iodine 125 (^{125}I) brachytherapy could be an effective treatment for locally radiorecurrent prostate cancer (PCa). Toxicity is often reduced compared to total salvage (TS) while cancer control can be maintained, which could increase cost-effectiveness. The current study estimates the incremental cost per quality-adjusted life year (QALY) of FS compared to TS.

Material and methods: A decision analytic Markov model was developed, which compares costs and QALYs associated with FS and TS. A 3-year time horizon was adopted with six month cycles, with a hospital perspective on costs. Probabilities for genitourinary (GU) and gastrointestinal (GI) toxicity and their impact on health-related quality of life (SF-36) were derived from clinical studies in the University Medical Center Utrecht (UMCU). Probabilistic sensitivity analysis, using 10,000 Monte Carlo simulations, was performed to quantify the joint decision uncertainty up to the recommended maximum willingness-to-pay threshold of €80,000/QALY.

Results: Focal salvage dominates TS as it results in less severe toxicity and lower treatment costs. Decision uncertainty is small, with a 97-100% probability for FS to be cost-effective compared to TS (€0-€80,000/QALY). Half of the difference in costs between FS and TS was explained by higher treatment costs of TS, the other half by higher incidence of severe toxicity. One-way sensitivity analyses show that model outcomes are most sensitive to utilities and probabilities for severe toxicity.

Conclusions: Focal salvage ^{125}I brachytherapy dominates TS, as it has lower treatment costs and leads to less toxicity in our center. Larger comparative studies with longer follow-up are necessary to assess the exact influence on (biochemical disease free) survival and toxicity.

J Contemp Brachytherapy 2016; 8, 6: 484–491
DOI: 10.5114/jcb.2016.64808

Key words: brachytherapy, cost-effectiveness, focal salvage, ^{125}I, prostate cancer, whole-gland salvage.

Purpose

Biochemical recurrences after primary radiotherapy can be common, from up to 50% in older cohorts to still approximately 15-40% at 10 years in dose-escalation trials, depending on pre-treatment risk factors [1,2,3,4]. Recurrences are often thought to be confined to the prostate at the site of the primary dominant index lesion [5,6,7]. These recurrences might be eligible for a second curative ablation, called salvage [8,9]. One commonly employed salvage strategy after primary radiotherapy is iodine 125 (^{125}I) brachytherapy. Salvage brachytherapy is commonly directed at the entire prostate, since accurate determination of the exact recurrent location is difficult. This can lead to damage to the surrounding organs (rectum, bladder neck, prostatic urethra) with a combined average of grade 3 gastrointestinal (GI) and genitourinary (GU) toxicity in 10-30% of patients [8,9,10]. However, some series report very low (0%) severe toxicity rates, especially when using high-dose-rate (HDR) brachytherapy [11,12]. These complications should be resolved with invasive interventions, which pose a significant burden to the patient and are associated with high costs. Increased accuracy in detecting organ confined recurrences and excluding distant metastases has made focal salvage (FS) possible [13,14,15]. This approach targets only the recurrent tumor, thereby, potentially limiting severe toxicity rates. The first FS series show promising results with usually

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Received: 06.09.2016
Accepted: 06.12.2016
Published: 30.12.2016

≤ 5% grade 3 toxicity and cancer control rates comparable to total salvage (TS) [15,16,17,18,19,20]. In the University Medical Center Utrecht (UMCU), two cohort studies of FS [19] and TS [10] ^{125}I brachytherapy have been performed. These studies have shown differences in severe GI and GU toxicity rates in favor of FS, while cancer control is maintained, possibly leading to a difference in cost-effectiveness between the two modalities. Therefore, the objective of this study was to evaluate the comparative cost-effectiveness of FS and TS using ^{125}I brachytherapy in patients with recurrent PCa after primary radiotherapy. In addition, this first early cost-effectiveness analysis can identify specific areas of uncertainty, which drive cost-effectiveness, so that these endpoints can be incorporated in future (randomized) trials comparing salvage strategies directly.

Material and methods

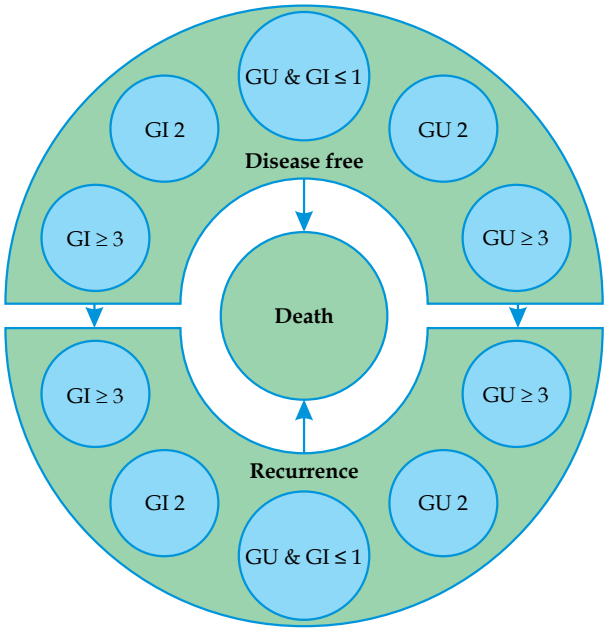
Data analysis was permitted by the institutional review board of the University Medical Center Utrecht (UMCU). The informed consent requirement was waived for this study. A decision analytic Markov model was developed to simulate the medical course of a cohort of 69-year-old men treated with FS or TS ^{125}I brachytherapy for recurrent prostate cancer after primary external beam radiotherapy or brachytherapy (Figure 1). In Markov modeling, hypothetical cohorts of patients may transit between mutually exclusive and exhaustive health states at fixed time increments for a certain time. These health states are associated with different costs and health-related quality of life (HRQoL). Our model comprises three states: a disease-free state (DFS) for patients with no evidence of disease, a biochemical recurrence (BCR) state for recurrences defined according to the Phoenix definition (PSA nadir + 2 ng/ml), and death. After treatment with FS or TS, all patients enter the model in DFS from where they may move to BCR or death (Figure 1). Within DFS or BCR, patients may experience mild to no toxicity (≤ grade 1), moderate (grade 2), and severe (grade 3) GU and GI toxicity, each with their associated costs and impact on health related-quality of life. A distinction was made between acute (≤ 6 months) and late (> 6 months) toxicity. Late moderate toxicity was assumed to be chronic. Severe toxicity was assumed to become chronic moderate toxicity after treatment. The model considers a 3-year time horizon with 6-month cycles. A hospital perspective on costs was adopted, meaning that costs of FS and TS brachytherapy were included, as well as costs for treating toxicity and patient follow-up. Health-related quality of life was expressed in quality-adjusted life-years (QALYs).

Model inputs

The transition possibility from DFS to BCR and probabilities for toxicities were derived from two cohorts from the University Medical Center Utrecht (UMCU) [10,19]. Twenty patients were treated with FS and 31 patients with TS brachytherapy. Seven patients (35%) in the FS group and 11 (36%) in the TS group received ^{125}I brachytherapy as primary treatment. All other patients were treated with EBRT/IMRT with doses ranging from 66 (TS patients) to 70-76 Gy (FS patients).

In these studies, cancer-specific mortality was zero after three years. Therefore, transition probabilities from DFS to death and BCR to death were assumed to be equal (Table 1). These probabilities were derived from age- and sex-adjusted population mortality statistics [21]. GU and GI toxicity were measured using the common terminology criteria for adverse events version 4.0 (CTCAE-4) [22]. Toxicity incidence at 3 and 12 months was used as probability of acute and late toxicity, respectively. In the TS cohort, 1 patient suffered from acute grade 3 GU toxicity (urethral stricture), and 7 patients from late grade 3 GU toxicity (1 recto-vesical fistula, 1 recto-prostatic fistula, 5 urethral strictures). A total of 2 patients had late severe (grade 3) GI toxicity (recto-vesical and rectourethral fistula). One patient from the focal salvage cohort had a urethral stricture (Table 1). For toxicity rates of zero, a probability of 1% was taken, since sensitivity analysis does not allow a lower border of zero. Erectile dysfunction was not considered in this model because no reliable numbers were available and its impact on costs and HRQoL was uncertain.

Data inputs for HRQoL after salvage brachytherapy were also derived from the UMCU cohort studies. Individual patient HRQoL data as measured with the SF-36 at 1, 6, and 36 months after treatment were recalculated to their corresponding EQ-5D values in order to allow usage as utilities in the health economic model [23]. Next, the individual recalculated data was mapped to individual patient severity scores to estimate average utility decrements associated with ≥ grade 2 GU and GI toxicity. No distinction regarding utilities was made between grade 2 and grade 3 toxicity, since grade 3 usually recedes to grade 2 soon after treatment. However, in costs, this distinction was made since interventions for grade 3 toxicity



GU – genitourinary toxicity, GI – gastro-intestinal toxicity

Fig. 1. Decision analytic Markov-model

are associated with considerably higher costs in comparison to grade 2. Utilities are listed in Table 1. Resource use and unit costs for diagnostics, hospital inpatient stay, staff (including medical, nursing, and support staff), materials, and overhead costs for all treatments were gathered from the UMCU financial administration (Table 2). Resource use regarding management of toxicity was estimated from hospital data and through expert opinion. It was assumed that patients with recurrent prostate cancer received intermittent androgen deprivation therapy (ADT) after an average of one year after biochemical recurrence. In line with the national guidelines for costing in economic evaluations [24], medication costs were taken from the national drug cost registry, which includes costs of all approved drugs in the Netherlands [25]. Costs and QALYs were discounted by 4% and 1.5% in accordance with the national guidelines [24]. All costs are expressed in 2014 euros.

Model analysis

The model's primary outcome measure is incremental cost per QALY gained with either FS or TS, and is evaluated against the prevailing national cost-effectiveness threshold of €80,000/QALY. The model was first analyzed deterministically, using the point estimates for each parameter as model input. In order to assess the robustness of model outcomes against changes in specific input parameters, one-way sensitivity analyses were performed by varying single input parameters to the lower and upper bound of their 95% confidence intervals. A probabilistic sensitivity analysis was performed using 10,000 Monte Carlo simulations to quantify the joint decision uncertainty surrounding the model output. In order to do so, distributions were fitted to every input parameter. Beta-distributions were fitted to probability and utility parameters, as these are continuous parameters with values constrained between zero and one. Costs were assumed gamma distributed. The parameters of the beta and gamma distributions were solved using analytic methods-of-moments fitting, which involves equating the mean and standard error (SE) observed in the trial data to the expressions for the mean and SE of the distribution. For those cost parameters, on which no information regarding the SE was available, an SE of 20% of the mean was assumed, which is generally accepted as a rule of thumb in health economics. Costs derived from the drug cost registry were not varied. The results were evaluated against a range of willingness to pay thresholds (from €0/QALY to €80,000/QALY) and presented as cost-effectiveness acceptability curves, indicating the probability that a treatment is cost-effective, given a specific cost/QALY-threshold.

Results

Focal salvage brachytherapy results in an increase in QALYs (i.e. +0.15 QALYs) and lower expected costs compared to TS brachytherapy (i.e. –€2451) (Table 3). Total salvage is therefore dominated by FS. Half of the difference in costs can be explained by the higher initial treatment costs of TS, the other half by a higher incidence of toxicity in TS. The difference in QALYs in these cohorts is determined only by a higher incidence of toxicities (and associated lower utilities) in TS. One-way sensitivity analyses show that model outcomes are most sensitive to utility

Table 1. Transition probabilities, toxicity probabilities, and utilities for focal salvage and total salvage ^{125}I brachytherapy

	Focal salvage			Total salvage		
	Base case	Lower bound	Upper bound	Base case	Lower bound	Upper bound
Transition probabilities						
pDFS to BCR	0.156	0.071	0.276	0.245	0.143	0.316
pDeath	0.015	Not varied		0.015	Not varied	
Probability toxicity						
Acute GU2	15.0%	3.2%	33.7%	52%	34%	69%
Acute GI2	1.0%	0.0%	7.7%	10%	0%	22%
Late GU2	1.0%	0.0%	7.7%	29%	15%	46%
Late GI2	1.0%	0.0%	7.7%	3%	0%	12%
Acute GU3	1.0%	0.0%	7.7%	3%	0%	12%
Acute GI3	1.0%	0.0%	7.7%	1%	0%	6%
Late GU3	5.0%	0.1%	18.0%	23%	10%	39%
Late GI3	1.0%	0.0%	7.7%	6%	1%	17%
Utilities						
DFS & BCR ≤ 12 months	0.948	0.864	0.993	0.948	0.864	0.993
DFS & BCR > 12 months	0.924	0.853	0.973	0.924	0.853	0.973
Toxicity ≥ grade 2	0.828	0.682	0.935	0.828	0.682	0.935

DFS – disease free state, BCR – biochemical recurrence, GU2 – CTCAE genitourinary toxicity grade 2, GI2 – CTCAE gastrointestinal toxicity grade 2, GU3 – CTCAE genitourinary toxicity grade 3, GI3 – CTCAE gastrointestinal toxicity grade 3

Table 2. Resource use and cost inputs used in the study

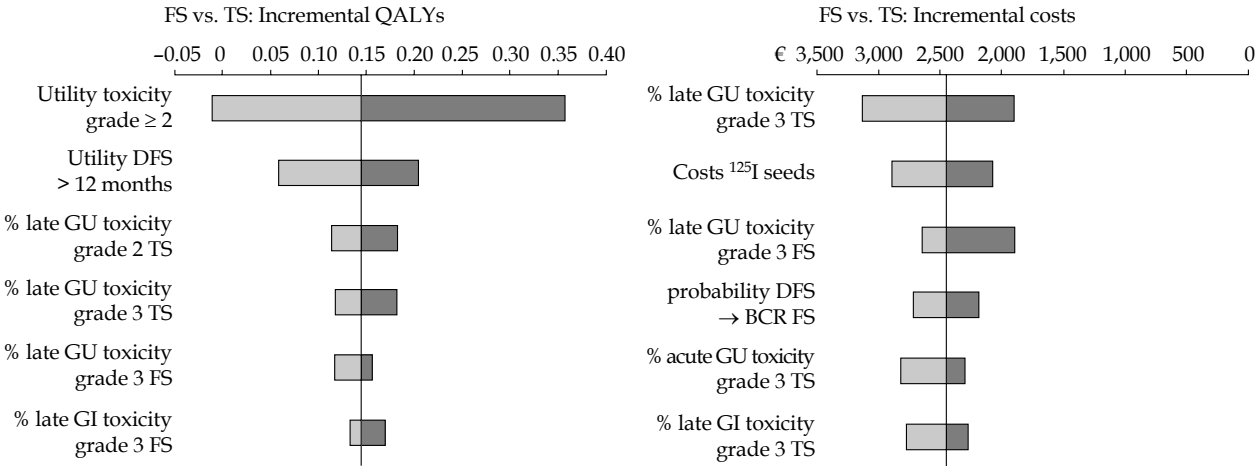
Costs	Proportion of patients	Frequency	Unit cost (€)	Total (€)
Diagnostic multiparametric MRI, including radiologic evaluation	100%	1	400.00	400.00 once
Diagnostic PET, including radiologic evaluation	100%	1	1000.00	1000.00 once
Procedure cost FS & TS				7220.00 once
TRUS		1	355.00	
Histology biopsy		1	280.00	
OR cost		1	6585.00	
Seeds and needles FS				1544.00 once
Seeds		32	45.80	
Needles		9	8.75	
Seeds and needles TS				2659.00 once
Seeds		55	45.80	
Needles		16	8.75	
Follow-up first year FS &TS				813.00/year
PSA		4	5.00	
Urology consultation		4	88.75	
Radiology consultation		4	109.50	
Follow-up year 2 and 3 FS & TS				300.00/year
PSA		4	5.00	
Urology consultation		2	79.00	
Radiology consultation		2	61.00	
Intermittent hormonal treatment				915.00/year
LHRH agonists	57%		1003.00/year	
LHRH antagonists	10%		1458.00/year	
Anti-androgen	33%		597.00/year	
GU grade 3 toxicity				4394.00 once
Urodynamic examination	100%	1	100.00	
Artificial sphincter	20%	1	6443.00	
Laser therapy	50%	1	1315.00	
Urinary catheter	50%	1	152.00	
Hyperbaric O_2	30%	30	173.00	
TUR-prostate	10%	1	2600.00	
Blood transfusion	10%	1	545.00	
In-hospital day	80%	1	500.00	
GI grade 3 toxicity				3047.00 once
Flexible sigmoidoscopy	100%	1	527.00	
Laser therapy	50%	1	1315.00	
Blood transfusion	10%	1	545.00	
Hyperbaric O_2	30%	30	173.00	
In-hospital day	50%	1	500.00	
Grade 3 GU & GI				287.00/year
Incontinence materials				
GU grade 2 toxicity 0-6 months				175.00/half year
Tamsulosine, Solifenacine, Prednisolon, Diclofenac				
GU grade 2 toxicity 7-12 months				42.00/half year
Tamsulosine				
GI grade 2 toxicity 0-6 months				22.00/half year
Volcolon, Prednisolon, Diclofenac				

FS – focal salvage, TS – total salvage, LHRH – luteinizing hormone-releasing hormone, TUR – transurethral resection, GU – genitourinary, GI – gastrointestinal

Table 3. Deterministic model results

Therapy	Costs	Incremental costs	QALYs	Incremental QALYs	Incremental cost/QALY
TS	€13,449		2.41		
FS	€10,998	–€2,451	2.56	0.15	Dominates TS

QALY – quality-adjusted life-year, FS – focal salvage, TS – total salvage



FS – focal salvage, TS – total salvage, QALY – quality-adjusted life-year, DFS – disease free state, GU – genitourinary, GI – gastro-intestinal, BCR – biochemical recurrence

Fig. 2. Results of the one-way sensitivity analysis, showing the parameters that have the most influence on incremental QALYs (**A**) and costs (**B**) of focal compared to total salvage, when the parameters are varied to the lower and upper bounds of their 95% confidence intervals

values and to the probabilities of severe (≥ grade 3) toxicity (Figure 2). Decision uncertainty between focal and total salvage, however, is small, with the probability of focal salvage to be cost-effective compared to total salvage ranging from 100% at a willingness-to-pay threshold of €0 to 97% at €80,000 (Figure 3).

Discussion

This study has provided a preliminary cost-effectiveness analysis comparing FS and TS ^{125}I brachytherapy. It shows that FS has a probability of 97-100% to be cost-effective compared to TS (at a WTP range of €0-€80,000 per QALY gained). The differences in costs between FS and TS can be explained by the higher initial treatment costs of TS and a higher incidence of severe toxicity associated with TS. These toxicities require expensive medical treatment and therefore lead to higher costs for TS compared to FS.

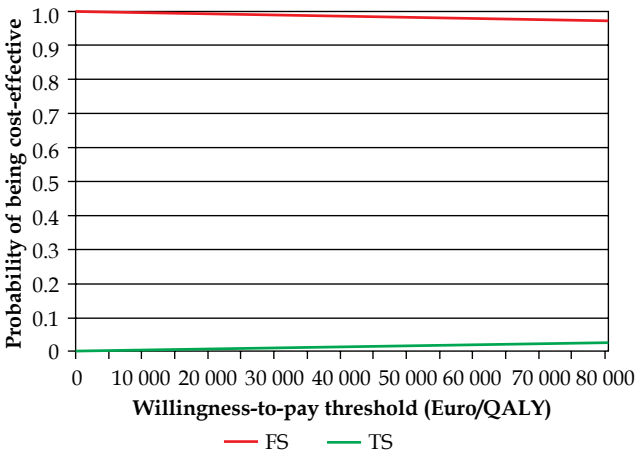


Fig. 3. Cost-effectiveness acceptability curve comparing focal salvage (FS) and total salvage (TS)

One-way sensitivity analyses show that the outcomes are most sensitive to the probabilities for severe toxicity. Caution must consequently be taken when comparing these results to the current outcomes of salvage series in the literature and when comparing future cost-effectiveness results in the salvage setting. Differences are visible in salvage brachytherapy research regarding toxicity: grade 3 GU and GI toxicity can vary between 0-47% and 0-24% in series, with an average of 17.0% and 5.6%, respectively [9]. The toxicity profiles from our series seem to be on the higher end compared with these estimates from the current (limited) evidence. This can be caused by higher doses to surrounding organs at risk and a high prostate D_{90}/V_{150} [26]. Dosimetry for 10 TS patients was available, showing a median D_{90} of 169.7 Gy (range: 153.8-199.6 Gy), and V_{150} of 68.5 Gy (range: 46.3-83.7 Gy). It is recommended to keep the D_{90} < 150 Gy [26]. In addition, recent dose restrictions based on a pooled analysis of TS ^{125}I brachytherapy patients (including 10 patients from this cohort) have been published for the rectal wall, urethra, and bladder base. TS patients often exceeded the found restrictions [27,28]. Thus, our cost effectiveness analysis may not apply to TS procedures that adhere to current dosimetric recommendations.

Because of the importance of severe toxicity rates in the definitive cost-effectiveness comparison, it could very well be that other FS strategies might obtain the same cost-effectiveness results. Furthermore, while a healthcare perspective was used in this analysis, it is reasonable to assume that a societal perspective, considering costs outside the hospital on the patient and society level, would increase FS cost-effectiveness even more, since severe toxicity can lead to drastic losses in functioning. Using data from one center on both costs and effects, ensured internal validity in the financial parameters associated with treatment, toxicity, and follow-up. However, differences in outcomes and associated costs are to be expected between centers performing salvage. Data for this analysis was obtained retrospectively, as randomized studies do not yet exist for salvage therapies. Despite the limited evidence currently available, the analyses show that the model outcomes are robust to changes in input parameters and decision uncertainty is very low. Nevertheless, uniform approaches to collect data on costs of treatment and toxicity should be incorporated into future randomized studies, in order to update cost-effectiveness estimations as new data becomes available [29]. Androgen deprivation therapy is generally used in case of a biochemical recurrence after primary radiation treatment. The question remains how this treatment relates to FS and TS regarding cost-effectiveness. Androgen deprivation therapy was not analyzed as a separate treatment option in the current study due to the short follow-up time and the fundamental difference in treatment objectives between ADT (a palliative treatment strategy) and salvage (a curative option). Especially the last point is important in cost-effectiveness research, since a palliative treatment strategy can decrease cost-effectiveness substantially in the long run, due to mortality differences compared to curatively intended treatments. Salvage could decrease the biochemical failure rates compared to ADT and consequently decrease mortality for a specified group of patients, thereby influencing cost-effectiveness. Also, biochemical failure rates after FS (and TS) may in future even further decrease if the selection of patient eligible for salvage improves. Cost-effectiveness of salvage compared to ADT is expected to improve when more adequate selection criteria become available for these patients.

Morbidity can also be significant with ADT, even though intermittent use has decreased this to an important extent [30]. Morbidity and survival data should once again be determined from randomized controlled trials, directly comparing ADT and salvage, since estimations from published literature leave a room for variation in treatment schedules (particularly regarding initiation of ADT and management of side-effects). A new cost-effectiveness analysis between FS/(TS) and ADT could provide some answers. However, because of the difference in treatment purposes, it is doubtful whether these groups of patients will ever directly be compared to each other in trials. It is questionable if patients eligible for curative salvage would be randomized to a palliative treatment strategy. It is also doubtful whether ADT will be supplied in addition to salvage treatment, since the principle goal of salvage is to postpone palliative ADT. Androgen deprivation therapy might potentially be used (neo) adjuvantly in the future in high risk subsets of patients eligible for salvage (e.g. T3 disease). Possible randomized trials could then be needed.

Today, another problem is the number of patients eligible for focal salvage. Numbers in this study were small (20 FS patients were compared to 31 TS patients). Salvage still constitutes a specialized treatment modality after primary radiotherapy failure and is performed only in specialized centers in the Netherlands. Furthermore, focal salvage is still in the experimental phase, as is reflected in the amount of literature available on the subject. This is especially clear in the ^{125}I brachytherapy setting, in which only four studies so far were published (with 12, 15, 20, and 25 patients, respectively) [17,19,31,32]. The effect of focal salvage regarding biochemical control and prostate cancer specific survival in the long run is still unknown, since multifocal disease might be present at the time of failure and subsequently during salvage treatment. Till now, there is no strong and significant data to support the hypothesis that FS is superior over TS in terms of cancer control. On the contrary, one would expect TS to increase cancer control, since possible multifocal disease is more adequately targeted. However, a recent review of observational studies suggests cancer control of FS to be approximately equal to established TS modalities [15]. Furthermore, the difference in cancer control in our cohorts was minor and did not substantially influence cost-effectiveness. On the other hand, it is to be expected that in the current era of increased IMRT use and even (partial) dose-escalation in the primary setting, secondary non-lethal tumor foci are increasingly and successfully treated. Afterwards, the primary index lesion might be the single focus to potentially recur and cause disease progression. If these lesions are detected and delineated correctly, FS would be ideal to ensure cancer control with a potentially significant decrease in treatment related toxicity, and successive increase in health-related quality of life. To achieve these results, a more uniformly applied, yet personalized selection approach for focal salvage is necessary. Imaging modalities, such as dynamic contrast enhanced, diffusion weighted MRI, MRI-spectroscopy, and PET-CT with various tracers are accurate in localizing recurrences and excluding metastatic disease [13,33,34]. In these cohorts, the selection was already improved for the FS group by using multiparametric-MRI and PET-CT in most patients, which could have led to a lower failure rate. For future salvage patients, workup must be uniform with all patients receiving the same local and metastatic diagnostic examination. Patients with multifocal disease would then be able to opt for TS and patients with a localized recurrence for FS. Therefore, costs associated with the diagnostic process will most probably even out between these types of salvage treatments. Other salvage methods such as HDR-brachytherapy might have a more favorable toxicity profile and lead to increased cancer control due to enhanced dosimetry over ^{125}I brachytherapy [35]. Therefore, trials between FS and TS should preferably focus on various ablation modalities.

This study shows that (further research on) FS can have an important impact on health outcomes and re-

duce costs of care. This year, for example, approximately 233,000 patients received a primary diagnosis of prostate cancer in the United States, of which 45% were treated with some form of radiotherapy [36]. With a recurrence rate of approximately 10%, 23%, and 43% after 8 years in the low, intermediate, and high risk groups, respectively, a substantial amount of patients has a recurrence restricted to the prostate and could be eligible for FS in the future [37]. Lastly, the willingness-to-pay threshold for one additional QALY is subject to ongoing debate. Some research suggests that societies' willingness-to-pay for an extra QALY is higher than €80,000 [38]. In the US for example, a WTP threshold of $100,000-200,000 is the norm, while in the UK a recent study formally calculated that the WTP should be as low as £17,000-18,000, in order to maximize the health benefits to be attained within the NHS budget. Research in the Netherlands is lacking on this subject [39]. Toxicity differences between FS and TS could be smaller than observed in these current cohorts. It might also be that TS will lead to less toxicity in future studies, due to improvements in application techniques, which increase tissue sparing. A higher willingness-to-pay threshold per QALY gained might still favor FS in the future.

Conclusions

This is the first single center study describing cost-effectiveness outcomes comparing FS and TS ^{125}I brachytherapy. There is a high probability (97-100%) that FS is cost-effective compared to total salvage because of reduction in treatment costs and severe toxicity at our center. The difference in cost-effectiveness between FS and TS is therefore substantial. Future directions for cost-effectiveness research in the (focal) salvage setting should focus mostly on toxicity outcomes and treatment costs. Trials between the modalities are necessary to provide robust data on differences in cancer control and toxicity. To guarantee more comparable results for the future, it is important to incorporate cost-related outcomes in clinical trials from the beginning.

Disclosure

Authors report no conflict of interest.

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