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Original Article

Cost-effectiveness of hypofractionated versus conventional radiotherapy in patients with intermediate-risk prostate cancer: An ancillary study of the PROstate fractionated irradiation trial – PROFIT

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ABSTRACT

Purpose: To evaluate the cost-effectiveness of moderate Hypofractionated Radiotherapy (H-RT) compared to Conventional Radiotherapy (C-RT) for intermediate-risk prostate caner (PCa).

Methods: A prospective randomized clinical trial including 222 patients from six French cancer centers was conducted as an ancillary study of the international PROstate Fractionated Irradiation Trial (PROFIT). We carried-out a cost-effectiveness analysis (CEA) from the payer's perspective, with a time horizon of 48 months.

Patients assigned to the H-RT arm received 6000 cGy in 20 fractions over 4 weeks, or 7800 cGy in 39 fractions over 7 to 8 weeks in the C-RT arm. Patients completed quality of life (QoL) questionnaire: Expanded Prostate Cancer Index Composite (EPIC) at baseline, 24 and 48 months, which were mapped to obtain a EuroQol five-dimensional questionnaire (EQ-5D) equivalent to generate Quality Adjusted Life Years (QALY).

We assessed differences in QALYs and costs between the two arms with Generalized Linear Models (GLMs). Costs, estimated in euro (€) 2020, were combined with QALYs to estimate the Incremental Cost-effectiveness ratio (ICER) with non-parametric bootstrap.

Results: Total costs per patien were lower in the H-RT arm compared to the C-RT arm €3,062 (95 % CI: 2,368 to 3,754) versus €4,285 (95 % CI: 3,355 to 5,215), ($p < 0.05$). QALY were marginally higher in the H-RT arm, however this difference was not significant: 0.044 (95 % CI: − 0.016 to 0.099).

Conclusions: Treating localized prostate cancer with moderate H-RT could reduce national health insurance spending. Adopting such a treatment with an updated reimbursement tariff would result in improving resource allocation in RT management.

Intensity Modulated Radiation Therapy (IMRT) with Image Guided Radiation Therapy (IGRT) for the treatment of prostate cancer (PCa) enables dose escalations without increasing side effects [1]. The latest systematic review comparing hypofractionated RT (H-RT), with conventional fractionated RT (C-RT) to treat prostate cancers (PCa) included 10 studies with 8,278 men. It concluded that moderate H-RT has similar oncological outcomes with little or no increase in toxicity [1]. Moderate H-RT stands as a strong recommendation for intermediate-risk PCa in the 2021 EAU-EANM-ESTRO-ESUR-SIOG guidelines [2], based on its comparable effectiveness to C-RT without increasing toxicity [1], nor altering patients' Quality of life (QoL) [3–7]. In addition, H-RT might be considered as a cost saving option [8] and improve availability of RT treatments, addressing supply shortages and disparities in access that have been observed in many European countries [9]. However, robust health economics evidence is needed to support the use of H-RT as a strategy yielding to improved patient reported outcomes, such as health-related QoL (HRQoL) per euro spent [9]. To our

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knowledge, among the few cost-effectiveness analysis (CEA) carried out on H-RT versus C-RT for PCa which estimated costs per HRQoL from clinical trials, none of them was made in Europe [8,10–14].

Hence, we aimed to conduct a CEA with real-world data based on the PROstate Fractionated Irradiation Trial (PROFIT) multicenter international phase III trial [15]. The PROFIT trial included 1,206 men with intermediate-risk PCa, and showed that H-RT was non-inferior to C-RT in terms of biochemical-clinical failure (BCF) whilst not being associated with increased late toxicity [15].

The present paper reports on the cost-effectiveness of H-RT versus C-RT assessing costs and HRQoL differentials within the PROFIT trial of French patients with intermediate-risk PCa.

Materials and Methods

Overview of the study

A French multicenter randomized clinical trial was conducted as an ancillary study of PROFIT. Inclusion and exclusion criteria are detailed elsewhere [15]. All patients signed written consent to participate in the study that the Ethics Committee (CPP-OUEST IV18/10) approved on 5 July 2010. Random assignment was stratified by the use of neoadjuvant hormone therapy and risk of seminal vesicle invasion [15]. The delineation and dosimetric constraints on the Clinical Target Volume (CTV) and organs at risk were based on the European Organisation for Research and Treatment of Cancer (EORTC) delineation guidelines [16].

Patients were treated using "step and shoot" IMRT (7 static beams) or dynamic arc therapy with daily IGRT (using gold fiducial markers implanted in the prostate with kV, MV-CT or ultrasound IGRT) and bladder and rectal preparation protocol. Participants were recruited between December 2011 and January 2016. Patients assigned to the H-RT arm received 6000 cGy in 20 fractions over 4 weeks, or 7800 cGy in 39 fractions over 7 to 8 weeks in the C-RT arm.

Cost-effectiveness analysis

We conducted a cost-effectiveness analysis (CEA), of which aim is to help decision makers choose strategies that have highest health outcomes given the resources available. Among outcome measures, the Quality-Adjusted Life Year (QALY) is the most commonly used. In this metrics, we capture both the gains in health-related quality-of-life (HRQoL) and the increased life expectancy attributable to an intervention. Preference based measure (PBM) instruments are used to measure HRQoL that are linked to a utility value to estimate QALY [17] (See below in 2.4).

To compare the cost-effectiveness of the two strategies, we estimated the differences in mean total cost (ΔC) and mean QALY (ΔE) of the intervention strategy (i.e H-RT) versus the C-RT. We derived the Incremental cost-effectiveness ratio (ICER) by dividing ΔC by ΔE as follows:

$$\text{ICER} = \frac{\Delta C}{\Delta E} = \frac{Costs\ of\ H-RT\ -\ Costs\ of\ C-RT}{QALYs\ of\ H-RT\ -\ QALYs\ of\ C-RT} \quad (1)$$

In the scenario where the incremental cost of intervention strategy is negative and the incremental effectiveness is positive, the intervention is cost saving or dominant.

From the ICER (1), we can derive the cost-effectiveness decision rule. A decision–maker would consider an intervention worthwhile if its ICER is less than the maximum value the society is willing to pay for a year in full health (or one QALY). As done in previous studies [18], we selected a €50,000 willingness to pay which is a common threshold used in similar wealthy societies to value health gains.

We used individual French patient data including their QoL to perform the CEA from the national health insurance system (NHIS) perspective [19]. The analysis had a time horizon of four years. We applied a 2.5 % discounting rate to the costs and HRQoL [19].

Resource use and costs

We assumed variations in resource use that comprised transportation, visits to general practitioners (GPs) and specialists, diagnostic tests and procedures, imaging, and inpatient stays due to serious adverse events (SAE) i.e., SAE grades 3 and 4 according to the Radiation Therapy Oncology Group (RTOG) criteria [20]. We considered the resource use for each fraction of RT to be identical in the two arms, in terms of planning stages and treatment delivery. The type of linear accelerators for the two arms were comparable ($p = 0.48$).

We estimated transportation use for RT sessions and other medical direct travel from patients' home address to cancer center and mode of transport they used (Table 1).

We counted visits to GPs as well as to specialists, i.e., urologists, gastroenterologists, oncologists, sexologists and cardiologists (only for check-up prior hormone therapy). For radiation oncologist visits, we included only those following end of RT.

Diagnostics tests and procedures included those related to PCa follow up and toxicity, and all unit costs were obtained from the NHIS classifications (Table 1). Inpatient stays were collected from each inclusion center and proximity hospital in which patients were admitted for SAE imputed to treatment. Resource use was retrieved from the hospital Diagnosis-Related Group (DRG) database.

To estimate total costs per patient, we assigned unit costs to resource use for each activity above described. Total costs per patient (i.e., costs that vary between H-RT and C-RT) equate costs of transports + costs of diagnostic tests and procedures + costs of visits to GPs and specialists + costs of inpatient stays, for each patient. We reported the costs during and after the treatment period. All costs were estimated in euro 2020.

Health outcomes

HRQoL was assessed using the Expanded Prostate Cancer Index Composite (EPIC-50) questionnaire, a 50-item measure that evaluates function and bother in bowel, sexual, hormonal and urinary domains [21]. All patients were offered to complete the paper questionnaire at baseline, at 24-, 48-months post-randomization.

EPIC questionnaire can be used in combination with a PBM generic instrument such as the EuroQol five-dimension questionnaire (EQ-5D) that measures more global elements of HRQoL including five dimensions i.e. mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. With the EQ-5D-3L questionnaire, patients report for each dimension their level of health on a 1 to 3 Likert scale, from no problems (1) to extreme problems (3) and some problems (2). Patients' health states are converted into a range of values from zero to one. Zero (0) means the worst health equivalent in value to death, and one (1) represents a state of full health [22]. As recommended by the international professional society for health economics and outcomes research (IPSOR) [23] we mapped EPIC questionnaire with EQ-5D-3L to provide a health state related utility value to estimate QALY [24]. We used the mapping algorithms developed for PCa by Khairnar *et al.* [25].

Statistical analysis

We estimated cost differences between the two arms using a generalized linear model (GLM), with a log link function and gamma distribution. Adjustment variables included age, center of

Table 1
Resource used, unit costs and sources.

Resource	Unit cost	Source
Medical visits		
General practitioner	€ 25	CCAM French classification of medical procedures[1]
Specialists	€ 30	CCAM French classification of medical procedures
Diagnostic tests and procedures		
Blood test	€11.07; €23.16; €34.23	NBAM French classification for biology[2]
Urine test	€17.55	NBAM French classification for biology
CT scan	€99.62; €124.89; €161.31	CCAM French classification of medical procedures
Echography	€47.7; €52.45; €75.6	CCAM French classification of medical procedures
Endoscopy	€261.78; €288.23; €377.24	CCAM French classification of medical procedures
Inpatient stays	Various	French DRG reference costs
Transports		
Taxi	€0.10/108.696 meters/round trip € 7.30 basic fee €26.15 for 1 hour waiting time	National Health Insurance (NHIS) fee
Light medical vehicle	€1.02/km (First 3 kms excluded) € 12.97 basic fee short trip compensation (€0.87-€6.57)	National Health Insurance (NHIS) fee
Ambulance	€2.32 /km (First 3kms excluded) € 55.09 € basic fee short trip compensation (€2.83-€7.91)	National Health Insurance (NHIS) fee
Car	0.3 € / km	National Health Insurance (NHIS) fee
Public transports	2.2 € / single trip	Average regional public transport fee

All unit costs were estimated in €2020. [1]Unit costs for medical visits, imaging, tests and procedures were obtained from the French classification of medical procedures (Classification Commune des Actes Médicaux CCAM), and their national related prices. [2]For laboratory tests, we used their nomenclature (Codages des Actes Biologiques, NBAM) and their unit costs included a procedure fee plus a lump sum. The differences in unit costs reflect the variation in procedure details; for example, "Abdominal, pelvic and thoracic computed tomography", "Abdominal and pelvic computed tomography", and "thoracic computed tomography" cost €99.62, €124.89, and €161.31 respectively.

inclusion (as random effect), baseline clinical characteristics and patient average transportation distance (km).

We compared baseline characteristics of patients responding to EPIC questionnaires at baseline and up to 48-month follow-up with those who had incomplete data. EPIC-50 between-group score differences were estimated 99 % CI and tested with ANOVA for baseline, 24 and 48-months. Score changes from baseline were used to account for pre-existing health conditions and post-RT evolution of QoL. To check if incomplete data were missing at random, we tested the association with baseline characteristics for EPIC scores, and utility values from mapping algorithm at each follow-up. We imputed missing EQ-5D-3L data with subject's previously or subsequently observed values. [26].

We estimated QALY differences between treatment groups by adjusting baseline utility in a GLM with an identity link and Gauss distribution [27]. Other covariates adjusted for the QALY were the same as those used for the costs. We conducted a sensitivity analysis to check whether the between-group difference of baseline utilities had any influence on the incremental QALY estimation [27].

To evaluate the uncertainty associated with costs, QALYs and ICERs, non-parametric bootstraps based on non-imputed and non-adjusted costs and QALYs were performed. We produced a cost-effectiveness plane and a cost-effectiveness acceptability curve (CEAC) to present our results. We reported bias-corrected and accelerated (BCa) bootstrap 95 % confidence intervals for mean and incremental costs and QALYs.

We estimated frequencies of Genitourinary (GU) and Gastrointestinal (GI) toxicity grades. We evaluated adverse events (AE) Risk Ratio (RR) for Grade 2 to 4 with 95 % CI and compared between two arms using χ^2 and Fisher's exact test.

All statistical analyzes were made on SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata Special Edition 13.1 (StataCorp, College Station, Texas, USA).

Results

Two hundred and thirty-two patients were screened for eligibility of which 10 were excluded (Supplementary Fig. 1).

Clinical characteristics were comparable except the prostate specific antigen (PSA) level and the respiratory clinical history that differed significantly between arms (Supplementary Table 1).

Early GI and GU toxicities were similar in both arms in which there were only 3 to 4 % of grade $\geq$ 3 GU. We observed no significant difference in late GI or GU toxicities, despite slightly more grade 4 GU toxicity in the H-RT and relatively less inpatient stays associated with SAE (Supplementary Table 2).

We observed statistically significant differences in mean kilometers per patient and their related costs between arms (Supplementary Table 3). Transport costs during RT period for C-RT were almost twice these for H-RT ($p < 0.001$). Car was the first mode of transport (Supplementary Table 4).

There was no significant difference between arms in mean number of visits to GPs and specialists, clinical tests and procedures and inpatient stays nor in their associated costs during and post treatment periods.

Total costs per patient were €4,285 (95 % CI: €3,355 – €5,215) for C-RT and €3,062 (95 % CI: €2,368 - €3,756) for H-RT ($p < 0.05$) (Table 2). The cost difference was observed during RT period ($p < 0.001$) and was mainly due to transportation costs (Fig. 1). Costs through the post-RT period marked no difference between treatment groups, with comparable medical costs for AE and monitoring.

Of the 222 patients, 54 (46.6 %) in the C-RT arm and 47 (44.3 %) in the H-RT arm had complete answers of EPIC questionnaires up to 48-months. Baseline characteristics for respondents were not significantly different from those of patients with incomplete data (Supplementary Table 5). Overall, the H-RT arm had significantly higher scores for the urinary domain and urinary function subscale at baseline. At each follow-up, EPIC scores and change scores were not statistically different (Supplementary Fig. 2).

The utility values for the EQ-5D-3L are presented in Table 3. Respondents in the H-RT arm had a slightly higher utility at baseline; such an advantage remained at Month-24 and 48. There were no significant differences in mean utilities at any point of follow-up. The proportion of missing data was statistically comparable in both arms; the probability of patients having missing data did

Table 2
Total costs per patient for conventional RT (C-RT) and hypofractionated RT (H-RT), in €2020.

Resource use	C-RT Mean (SD)	H-RT Mean (SD)	*P* value
Transportation	2944 (3072)	1754 (1902)	<0.01
Diagnostic tests & procedures	622 (631)	628 (578)	NS
Inpatient stays	432 (3621)	387 (2891)	NS
Medical visits	287 (126)	293 (119)	NS
Total costs (CI 95 %)*	**4,285 (3,355–5,215)**	**3,062 (2,368–3,756)**	<0.05

*95% confidence interval (CI): based on bias-corrected and accelerated (BCa) bootstrap with 1,000 iterations, excluding (25/1000)2.5% values at either end of the estimated distribution.

not depend on baseline characteristics at any point except at Month-24 for center of inclusion (Supplementary Table 6).

The incremental analysis between the two arms is shown in Table 4. With -€1,223 (95 % CI: - €2,373 to - €73) difference in average total costs and 0.044 QALYs gained (95 % CI: −0.016 to 0.099), the H-RT was the dominant strategy i.e. cheaper and with higher QALYs.

The major source of uncertainty in our CEA was related to QALYs, for which the difference was not statistically significant between arms, and remained robust across sensitivity analysis (Supplementary Table 7).

The cost-effectiveness plane shows the bootstrapped samples of the ICER, which had a lower cost for the H-RT arm than for the C-RT (Fig. 2). The majority of bootstrapped ICERs in the southeast quadrant, with higher QALYs and lower costs, made the H-RT a dominant and cost-effective strategy when compared to the C-RT for these samples (Supplementary Fig. 3).

Discussion

Cost is a major limitation of the accessibility to curative PCa radiotherapy in several countries. Hypofractionation may therefore reduce this cost but data based on randomized clinical studies are scarce. We therefore estimated the cost-effectiveness of using the moderate H-RT for patients with intermediate-risk PCa treated in a prospective randomized phase 3 clinical trial and found that it saved money and improved QoL. When exploring uncertainty using bootstrap samples, about 99 % of the ICER pairs had a lower cost in H-RT compared to the C-RT, and 93 % had a higher QALY. With a WTP of €50,000/QALY, an estimated value we previously used [18], the probability of the H-RT to be cost-effective was 97.8 %.

H-RT had significantly lower total costs, mainly due to cost reduction during the treatment period. For the post-RT period, costs marked no statistical difference between arms, which mirrors the statistically comparable incidence of all toxicity related AE [15]. Halving the number of fractions does not halve the costs that were supposed to vary, because both regimens have similar costs for medical visits, tests and inpatient stays. Those results remained robust when changing the actual to the hypothetical endpoint of RT and after adjusting for covariates. H-RT saved 29 % of average total costs compared to C-RT. Our findings are in line with the H-RT cost-containment effect previously demonstrated [28], and when late toxicity management costs were included [8]. Of note, due to the focus of CEA on RT–related-effects only, costs associated with recurrent PCa and palliative care were excluded.

The Mapping EPIC to EQ-5D-3L utilities, recommended for economic evaluations by national and international agencies [19,23], made it possible to estimate utility values. Our EPIC scores were statistically comparable with those from the mapping algorithm cohort model [25] (Supplementary Table 8), suggesting that our utility values from the mapping are reliable. The differential QALY we estimated might have been influenced by the between-group difference of baseline utilities, which we accounted for it in our estimation [27]. Previous studies focusing only on patient reported outcomes and/or HRQoL between the two treatment regimens in low-intermediate-risk PCa reported no substantial differences [3–7]. Overall, with moderate H-RT being clinically non-inferior to C-RT [15], significantly less costly than C-RT and without worse QALY, the results of our CEA show that H-RT is a dominant strategy

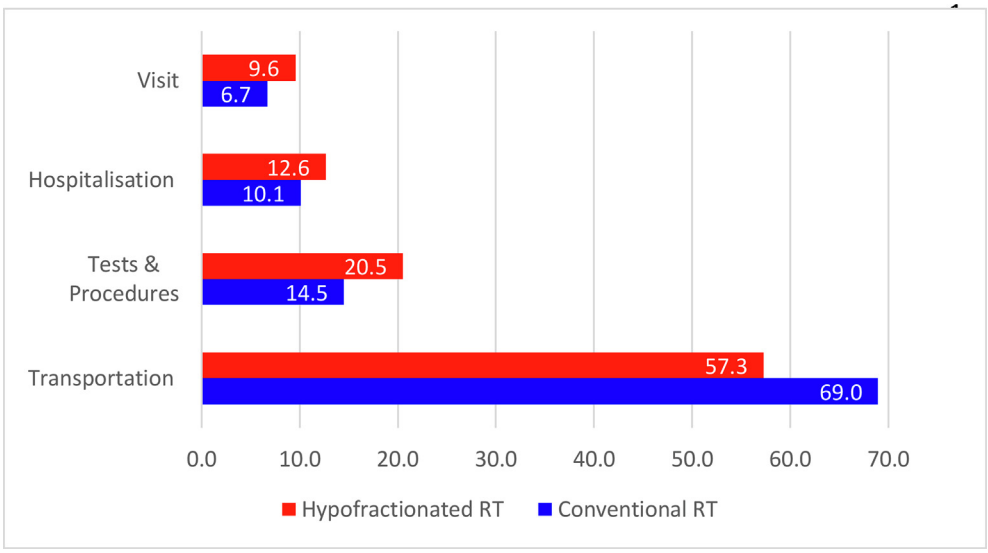

Fig. 1. Breakdown of costs per type of resource use in C-RT and H-RT*. *C-RT: Conventional RT, H-RT: hypofractionated RT.

Table 3
EQ-5D utility values generated from EPIC score mapping.

EQ-5D	C-RT* N = 116	H-RT* N = 106	Difference (95 % CI *)	p-value
Baseline				
N (%)	81 (70)	67 (63)		
Mean (SD)	0.902 (0.07)	0.912 (0.07)	0.010 (-0.013 to 0.032)	0.29
24 months				
N (%)	42 (36)	36 (34)		
Mean (SD)	0.900 (0.061)	0.904 (0.073)	0.004 (-0.026 to 0.032)	0.38
48 months				
N (%)	43 (37)	41 (39)		
Mean (SD)	0.897(0.07)	0.901 (0.09)	0.004 (-0.032 to 0.036)	0.41

*C-RT: Conventional RT, H-RT: hypofractionated RT; 95% confidence interval (CI): based on bias-corrected and accelerated (BCa) bootstrap with 1,000 iterations.

Table 4
Incremental cost-effectiveness results for the two treatment arms.

	Costs € (95 %CI)	IC	QALY (95 % CI *)	IQ	CE
C-RT*	4,285 (3,355 to 5,215)	–	3.252 (3.210 to 3.295)	–	
H-RT*	3,062 (2,368 to 3,756)	− 1,223 (−2,373 to −73)	3.297 (3.253 to 3.340)	0.044 (−0.016 to 0.099)	H-RT dominant

*IC: Incremental Costs; IQ: Incremental QALY; CE: Cost-effectiveness; C-RT: Conventional RT, H-RT: hypofractionated RT; 95% confidence interval (CI): based on bias-corrected and accelerated (BCa) bootstrap with 1,000 iterations.

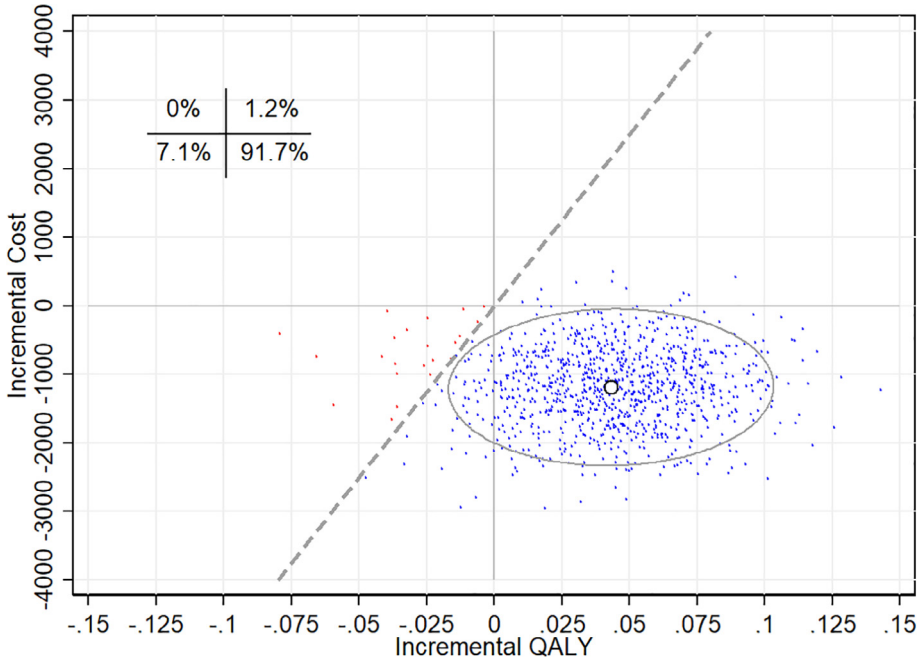

Fig. 2. Cost-effectiveness plane. Cost-effectiveness plane with 1.000 bootstrap iterations incremental cost-effectiveness ratio (ICER) between C-RT and H-RT. Blue dots represent cost-effective iterations. The circle represents the 95% confidence ellipse. About 92% of iterations are in the south-east quadrant, meaning that H-RT is with lower cost and higher effectiveness. When adding a willingness to pay (WTP) of €50 000, represented by the straight line, about 98% of iterations are under that line and therefore cost-effective.

for the treatment of patients with intermediate-risk PCa. Our CEA supports the 2021 EAU-EANM-ESTRO-ESUR-SIOG guidelines [2].

Despite the high burden of PCa, economic evaluations are scarce [9]. To our knowledge, this is the first European study exploring the cost-effectiveness of H-RT compared to C-RT, based on longitudinal real-world data on costs and HRQoL from a clinical trial [8,10,11,13,14]. We estimated only direct medical and non-medical costs reimbursed by the NHIS. We acknowledge that the cost difference between the two arms was underestimated. A societal perspective would have made it possible to estimate indirect costs associated with the RT, such as the opportunity cost of the time patients spend during RT treatment and in travelling. One should keep in mind that our evaluation was made from the French system perspective. This could also be applied to other OECD countries that have the same coverage scheme for patient transport to hospital such as Belgium, Germany, Japan, Korea and the UK. However, globally not all healthcare systems pay for travel expenses to radiation oncology center, which thus represent individual out of pocket expenses and indirect costs, instead. This should be considered carefully before generalizing our findings.

Notwithstanding the strengths of our study, which reports long-term real-world data on QoL, there were challenges. In particular,

not all participants were able to provide sufficient information to generate an EPIC-50 score and consequently derive EQ-5D-3L utilities. However, we found that QoL data were missing completely at random (MCAR) and regardless of treatment allocation and baseline characteristics. This makes MCAR data unlikely to affect QALY differences and to bias our findings. It is worth noting that consistent with previous studies, high levels of missing data in PCa patients QoL did not affect significantly their final results [3,4,6].

The precision of the HRQoL measures might be considered insufficient. Notably, the EQ-5D-3L do not cover all important dimensions of EPIC-50 [24]. Although this could have been limiting, our final scores estimated in the H-RT and C-RT arms did not differ from those of the literature [3–7]. Interestingly, physician-reported outcomes late GI and GU toxicities were comparable between arms. Using patients reported QoL is becoming of growing interest not only to get their view on treatment outcomes with similar efficacy [29] but also to value the treatments as done in European countries [30].

Our study shows that, in France using H-RT for intermediate-risk PCa would decrease costs supported by the NHIS and improve resource allocation, addressing both the optimal means of treatment delivery, and the associated patient outcomes [28]. Reimbursement mechanisms are one of the policy tools that help stimulate healthcare innovations and performance [31]. In European countries as well as elsewhere, hospitals are reimbursed based on DRGs. However, radiotherapy comes under separate payment schemes such as in England, Estonia and France [30,32]. RT is paid on a fee-for-service basis which financially incentivises the longer fractionated regimen and impacts clinical practices and hospital revenue [30,32]. In France, to stimulate the implementation of the H-RT for intermediate-risk of PCa, some reimbursement arrangements with tariffs reflecting the most cost-effective RT are critical. In addition, shortening the procedure duration, H-RT enables more patients to benefit from RT. This might help solve radiotherapy underutilisation observed across Europe due to factors such as geographic distance to RT facility, treatment delays, and reimbursement barriers [33]. Ultimately, this rises the question of the policy perspective of using economic evaluation. To allocate public resource efficiently, decision makers would incentivize H-RT, which in return reduce RT fees and hospital revenue. Without adjustment, such competing interests might delay the H-RT tariff negotiation on the NHIS agenda.

Conclusion

For intermediate-risk PCa, H-RT is cost-effective compared to C-RT. Adopting H-RT optimizes means of treatment delivery, improves access to radiation and enhance patient convenience. This first clinical trial-based CEA of H-RT for PCa conducted in Europe found additional evidence to support the shift towards H-RT in France. Improving resource allocation and making hospitals adopt the cost-effective strategy should stimulate reimbursement policy changes.

Authorship

Author contributions: ZHOU K and Supiot S had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Catton C., Martin J., Supiot S., Bellanger M., Perrocheau G., Zhou K.

Acquisition of data: Supiot S., Catton C. Magné N., De Brisson de la Roche G., Latorzeff I., Pommier P., Créhange G., Paumier A., Bera G.

Analysis and interpretation of data: Zhou K., Bellanger M., Renouf M.

Drafting of the manuscript: Bellanger M., Zhou K, Renouf M.

Critical revision of the manuscript for important intellectual content: Bellanger M., Renouf M., Catton C., Martin J., Supiot S., Zhou K.

Statistical analysis: Zhou K.

Obtaining funding: Supiot S., Perrocheau G.

Other: None.

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CRediT authorship contribution statement

K. Zhou: . **M. Renouf:** . **G. Perrocheau:** . **N. Magné:** . **I. Latorzeff:** . **P. Pommier:** . **G. Créhange:** . **A. Paumier:** . **G. Bera:** . **J. Martin:** . **C. Catton:** . **M. Bellanger:** Supervision. **S. Supiot:** Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.06.014.

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