HEALTH TECHNOLOGY ASSESSMENT OF HOSPITAL TECHNOLOGY: COST-UTILITY ANALYSIS OF MODERN RADIATION THERAPIES

Doctoral (Ph.D.) thesis

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1. INTRODUCTION

The purpose of health technology assessment is to support decision-making in healthcare at policy level by providing reliable information on the medical, economic and societal consequences of implementing health technologies or interventions within the health system.

The thesis evaluates the use of modern radiation therapies in the treatment of localized prostate cancer. The aim of the dissertation was to assess a technology that is used for treatment of a common disease. The curative radiation of prostate cancer is relevant from the perspective of public health and it imposes significant financial burden, therefore the evaluation of new radiation methods can provide valuable inputs for healthcare decision makers.

Prostate cancer is one of the most common tumorous diseases among male population in developed countries. Definitive radiation therapy is an accepted curative treatment for localized prostate cancer. The histological and biological features of prostate adenocarcinoma requires to provide high doses of radiation in order to achieve effective tumour control. Several randomized clinical trials have proved that higher doses will significantly decrease the risk of prostate-specific morbidity and mortality.

The necessity of providing escalated doses has led to a greater need for using state-of-the-art radiation technologies. Such technologies include intensity modulated radiation therapy (IMRT) with image guided radiation therapy (IGRT), which can warrant the prevention of severe irradiation toxicities when using high doses for radiation. One of the most common uses of IMRT is for the treatment of prostate cancer. It is obvious that the need for adapting new methods and achieving more favourable results in the care of prostate cancer patients is justifiable in Hungary.

Until now, conventional dose three-dimensional conformal radiation therapy (3DCRT) was considered as the standard of care in Hungary, therefore in our analysis this conventional therapeutic method was compared to the modern, dose-escalated IMRT. Recent developments in radiation therapy, imaging and irradiation planning have made it possible to provide shorter treatment schedules at higher doses. A specific biological characteristic of prostate adenocarcinoma is its low alpha/beta ratio (approximately 1.5), which led us to predict an advantageous radiobiological effect of higher doses per fraction.

Hypofractionation could be an alternative method of dose escalation in the radiotherapy of prostate cancer, considering the increased biological effectiveness of higher single doses and the special biological properties of this cancer site. Several clinical studies and reviews have analysed this type of biological dose escalation strategy and have found excellent clinical results without the higher risk of radiotherapy side effects. Therefore, our analysis was extended by including "hypofractionated" IMRT (HF-IMRT) as an additional alternative.

2. AIMS OF THE THESIS

The thesis intends to answer the question whether it is cost-effective to reimburse the use of modern radiation technologies in the treatment of localized prostate cancer.

The aims in this thesis were:

- To compare the clinical effectiveness – progression-free survival – of modern radiation therapies (dose escalated IMRT and HF-IMRT) and conformal radiotherapy (conventional dose 3DCRT) in the treatment of localised prostate cancer (Chapter 4.),
- To compare the probability of adverse effects of modern radiation therapies and conventional radiotherapy in the treatment of localised prostate cancer (Chapter 4.),
- To determine the resource use and costs of conventionally fractionated 3DCRT, normal and hypofractionated IMRT in the treatment of localized prostate cancer from the perspective of the healthcare provider and to compare the actual cost with the official reimbursement fee (Chapter 5.),
- To determine the health gains (QALY) and lifetime costs of the radiotherapeutic alternatives (Chapter 6.),
- To determine the incremental cost-effectiveness ratio of IMRT and HF-IMRT versus 3DCRT with the use of an economic model (Chapter 6.),
- To evaluate the effect of uncertain model parameters on costs and QALYs with the use of one-way deterministic and probabilistic sensitivity analysis (Chapter 6.),
- To appraise whether the HTA methodology that is mainly used for the evaluation of drugs in Hungary is applicable for the assessment of medical devices used in hospitals (Chapter 6.).

3. DETAILED ANALYSIS

3.1. META-ANALYSIS OF THE SIDE-EFFECT PROFILES OF MODERN RADIATION THERAPIES FOR PATIENTS WITH PROSTATE CANCER.

One of the most relevant focus of recent developments in radiotherapy technology was the adequate irradiation of prostate cancer. The aim of this research was to analyse the clinical effectiveness and safety of normo- and hypofractionated high dose intensity-modulated radiotherapy.

Clinical studies were retrieved through systematic literature search in Medline (PubMed) and Scopus databases. Clinical effectiveness was analysed descriptively while evidence regarding the adverse effects was synthetized with meta-analytical methods. The reviewed outcomes were progression-free survival (PFS) and radiation toxicity rates. The comparator was three-dimensional conformal radiation therapy.

We identified 13 relevant literature. Dose-escalated IMRT significantly increased the probability of PFS in the intermediate and high risk patient groups. Based on the reviewed randomized clinical trials (RCTs) hypofractionation showed an increase in the probability of PFS, however the difference compared to IMRT was not statistically significant.

The use of high dose IMRT resulted in no difference in severe genitourinary (acute $p=0.9$; late $p=0.95$) and moderate or severe gastrointestinal (acute: N/A; late: $p=0.08$) toxicities compared to 3DCRT. The risk ratio of moderate acute (RR 1.39, 95% CI 1.09-1.78; $p=0.008$) and late genitourinary toxicities (RR 1.48, 95% CI 1.26-1.75; $p<0,00001$) was significantly higher. There was no difference in hypo- and normofractionated IMRT regarding severe genitourinary (acute: N/A; late: $p=0.73$) and moderate or severe gastrointestinal (acute: $p=0.73$; late: $p=0.55$) toxicities, the risk of late moderate genitourinary toxicities was higher when hypofractionation scheme was used (RR 1.39 (1.00, 1.94); $p=0.05$).

1. Table: High dose IMRT vs. Conventional dose 3DCRT

Outcome	Number of studies	Number of patients	Random effect RR (95% KI)	p value
Acute GI ≥ grade 2	3	2 219	1,02 (0,47, 2,19)	0,97
Acute GI ≥ grade 3	0	0	not estimable	-
Acute GU ≥ grade 2	3	2 271	1,39 (1,09, 1,78)	0,008
Acute GU ≥ grade 3	2	700	1,08 (0,32, 3,68)	0,9
Late GI ≥ grade 2	4	3 636	0,67 (0,38, 1,20)	0,17
Late GI ≥ grade 3	3	2 219	0,54 (0,28, 1,07)	0,08
Late GU ≥ grade 2	4	3 688	1,48 (1,26, 1,75)	<0,00001
Late GU ≥ grade 3	3	2 271	0,99 (0,66, 1,48)	0,95

Source: self-edited

2. Table: Hypofractionated vs. Normofractionated high dose IMRT

Outcome	Number of studies	Number of patients	Random effect RR (95% KI)	p value
Acute GI ≥ grade 2	2	557	1,25 (0,36, 4,33)	0,73
Acute GU ≥ grade 2	2	557	0,85 (0,61, 1,18)	0,32
Late GI ≥ grade 2	4	1 132	0,91 (0,66, 1,25)	0,55
Late GI ≥ grade 3	0	0	not estimable	-
Late GU ≥ grade 2	4	1 132	1,39 (1,00, 1,94)	0,05
Late GU ≥ grade 3	2	661	1,28 (0,31, 5,19)	0,73

Source: self-edited

The use of normo- and hypofractionated high dose radiation therapy with intensity modulation and image guidance proved to be effective regarding tumour control. The probability of the development of severe adverse events requiring hospital care is low and shows no difference compared to the currently used method (3DCRT). However the higher risk of moderate genitourinary adverse events require an extensive clinical risk estimation when using HF-IMRT. Due to the relatively low number of published studies, further research should be made to better clarify the appropriate role of hypofractionation in the treatment of prostate cancer, where the benefits deriving from the shorter treatment protocol should also be considered.

3.2. A MICROCOSTING STUDY OF RADIATION THERAPY OF LOCALIZED PROSTATE CANCER

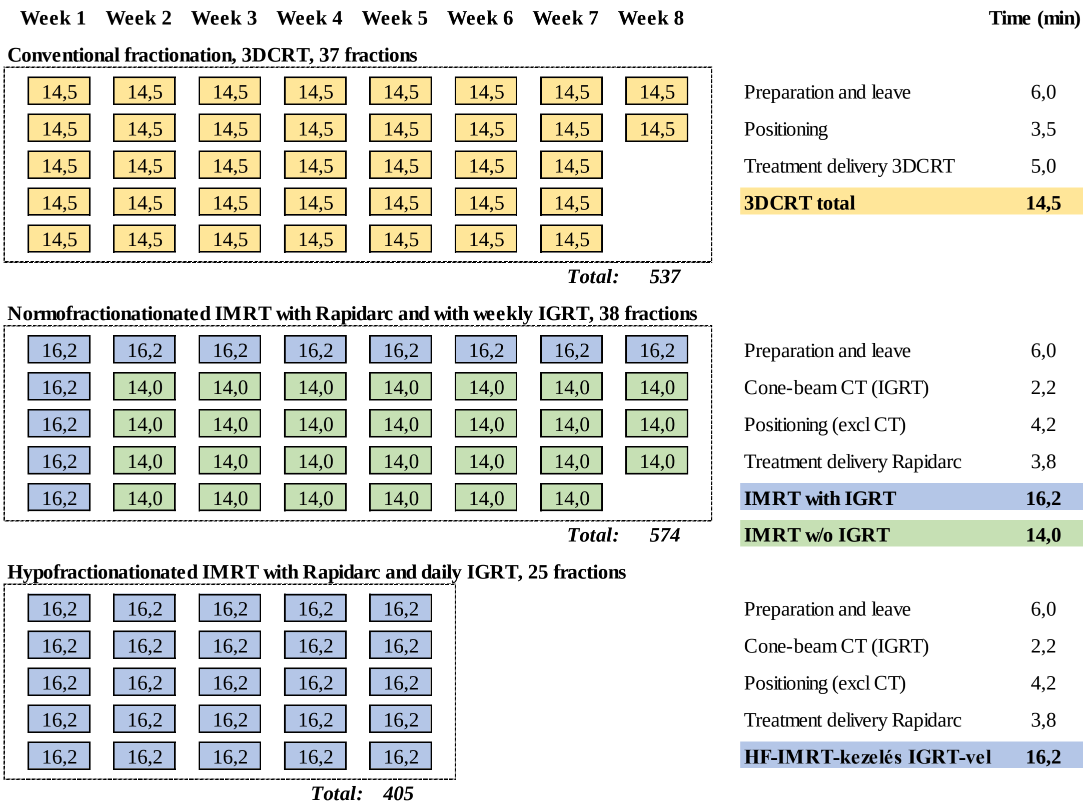
Development of radiation technology provides new opportunities for the treatment of prostate cancer, but little is known about the costs of novel technologies. The aim of this analysis was to compare the costs of conventional three-dimensional radiation therapy (3DCRT) to normal and hypofractionated intensity-modulated radiation therapy (IMRT and HF-IMRT) for the treatment of localized prostate cancer.

Detailed cost-calculation was conducted with the use of microcosting methods at the Oncology Centre of the University of Pécs. The calculation was performed from the perspective of the health care provider. Irradiation time was assessed from the data of 100 fractions delivered for 20 patients. Unit cost for each component was calculated according to actual costs retrieved from the accounting system of the University of Pécs. In the calculation of treatment delivery costs the number of fractions considered for 3DCRT, IMRT and HF-IMRT were 37, 39 and 25 respectively. We took the cost of capital into account.

Average treatment delivery times were 14.5 minutes for three-dimensional radiation therapy, 16.2 minutes for intensity-modulated radiation therapy with image-guided and 14 minutes without image-guided method. Estimated mean cost of patients undergoing conventional three-dimensional radiation therapy, normal and hypofractionated intensity-modulated radiation therapy were 619 000 HUF, 933 000 HUF and 692 000 HUF, respectively.

Modern radiation therapies (IMRT and HF-IMRT) are more expensive than the conventional radiotherapy (3DCRT) from the perspective of the healthcare providers.

1. Figure: Fractionation scheems



Source: self-edited

3. Table: Cost of radiation treatment in HUF

Nr.	Cost item	3DCRT	IMRT	HF-IMRT
1	Consultation	4 025	4 025	4 025
2	Supplementary diagnostics	37 509	37 509	37 509
3	CT simulation	8 515	8 515	8 515
4	Contouring	3 800	3 800	3 800
5	Planning and plan verification	4 250	24 070	24 070
6	Positioning and treatment	194 481	322 660	232 284
7	Weekly visit	12 075	12 075	6 900
8=1+…+7	**Total direct cost**	**264 655**	**412 654**	**317 103**
9	Overheads	240 741	266 625	193 160
10	Cost of capital	113 738	253 236	181 386
11=8+9+10	**Total cost of treatment**	**619 135**	**932 515**	**691 649**

Source: self-edited

3.3. Cost-utility analysis of intensity-modulated radiation therapy with normal and hypofractionated schemes for the treatment of localized prostate cancer

The aim of our analysis was to compare the cost-effectiveness of high dose intensity-modulated radiation therapy (IMRT) and hypofractionated intensity-modulated radiation therapy (HF-IMRT) versus conventional dose three-dimensional radiation therapy (3DCRT) for the treatment of localized prostate cancer.

A Markov model was constructed to calculate the incremental quality-adjusted life years and costs. Transition probabilities and adverse events were derived from the evidence synthesis presented in Chapter 4. Utilities were identified through targeted literature search. Results of the microcosting analysis in Chapter 5. were applied to calculate cost vectors. The cost of post-radiotherapy patient monitoring was determined based on the Hungarian guidelines on prostate cancer disease management.

Resource use of managing moderate adverse effects (bowel problems, urinary incontinence) and severe complications requiring hospital admission (rectal bleeding, urethral surgery) were determined based on retrospective analysis of hospital information system data at the University of Pécs and interviews held with urologists and internal medicine specialists.

The expected mean lifetime cost of patients undergoing 3DCRT, IMRT and HF-IMRT were 2212 thousand forints, 2111 thousand forints and 1860 thousand forints respectively. The expected quality-adjusted life years (QALYs) were 5.753 for 3DCRT, 5.956 for IMRT and 5.957 for HF-IMRT. Compared to 3DCRT, both IMRT and HF-IMRT resulted in more health gains at a lower cost.

4. Table: Result of the base-case analysis, cost data in HUF

Item	**3DCRT**	**IMRT**	**HF-IMRT**	**Difference IMRT - 3DCRT**	**Difference HF-IMRT - 3DCRT**
Radiation treatment cost	651 424	948 253	694 329	296 829	42 905
Post-radiation cost	70 461	80 217	80 217	9 756	9 756
Toxicity cost	22 364	19 361	22 732	-3 003	367
Hormone therapy cost	766 076	473 421	473 421	-292 655	-292 655
Chemotherapy cost	552 777	335 585	335 585	-217 192	-217 192
Cost of death	39 897	34 251	34 251	-5 646	-5 646
Total cost	**2 102 999**	**1 891 089**	**1 640 535**	**-211 910**	**-462 464**
Total cost (discounted 3,7%)	**2 212 488**	**2 110 737**	**1 859 923**	**-101 751**	**-352 565**
QALY (discounted 3,7%)	**5,753**	**5,956**	**5,957**	**0,203**	**0,204**
ICER				**-501 820 dominant**	**-1 730 266 dominant**

Source: self-edited

The sensitivity analysis by risk groups concludes that IMRT and HF-IMRT are cost effective in all subgroups. However if we reduce the probability of 10 years PFS by 10% concerning the new techniques and consequently decrease the difference in efficacy regarding tumour control, IMRT would no longer be cost effective for the treatment of patients in low risk group at a threshold of 6,18 million forints (two times of GDP per capita in Hungary), while HF-IMRT would still remain cost-effective.

The probabilistic sensitivity analyses quantified that IMRT had a 92% probability of being dominant (more health gain and lower costs) and 99% probability of being cost-effective, while HF-IMRT had a 99% probability of being dominant and cost-effective.

It can be concluded that high-dose IMRT is not only cost-effective compared to the conventional dose 3DCRT but, when used with a hypofractionation scheme, it has great cost-saving potential for the public payer and may improve access to radiation therapy for patients.

4. SUMMARY OF CONCLUSIONS

This thesis evaluated the cost-effectiveness of a health technology - the radiotherapy of prostate cancer – used in hospital environment. The analysis was based on local cost data and on the results of a mainly self-developed Markov-model.

We concluded that the use of normo- and hypofractionated high dose radiation therapy with intensity modulation and image guidance proved to be clinically effective compared to the conventional dose radiotherapy. We also found that the probability of severe adverse events requiring hospital care is relatively low and shows no difference compared to the conventional method (3DCRT).

The application of novel technologies at healthcare providers is usually more expensive. In order to measure the real costs of such new technologies, we assessed the incurring costs of using IMRT and HF-IMRT compared to 3DCRT in a Hungarian Oncology Centre based on real-world data. We found that the use of IMRT is one and a half times more expensive than 3DCRT (933 thousand forints vs. 619 thousand forints). The more advanced HF-IMRT exceeds the cost of 3DCRT only by 12% (692 thousand forints vs. 619 thousand forints).

In line with our preliminary expectations the use of state of art technologies are more expensive than the conventionally used techniques, however the difference in case of HF-IMRT is not large. When comparing the reimbursement fees of IMRT and 3DCRT we found no difference (it is 1086 thousand forints in both cases). Consequently the healthcare providers in Hungary are driven in a disadvantageous situation when using the more advanced and more expensive technology. Although the cost of HF-IMRT is not drastically higher, the reimbursement is lower compared to 3DCRT (814 thousand forints vs. 1086 thousand forints) due to the shortened treatment protocol used for hypofractionation, therefore oncology centres have disincentive to use HF-IMRT in Hungary.

The higher treatment costs of IMRT and HF-IMRT is primarily due to more intense utilization of medical resources in planning and treatment delivery and the higher capital costs of IMRT and IGRT. However, the cost-utility analysis showed that the higher radiation treatment costs are compensated by significant saving in the drug costs due to less patients receiving hormone- and chemotherapy. In case of HF-IMRT the cost per fraction is higher than for normal IMRT (27,7 thousand forints vs 23,9 thousand forints), since higher doses require to use IGRT more often, slightly stretching the length of average treatment delivery time (from 14.9 minutes to 16.2 minutes). In respect of HF-IMRT we considered a moderate hypofractionation scheme (25 instead of 35-40 fractions). However, due to the reduced number of fractions total radiation treatment costs are almost equal with conventional 3DCRT. Furthermore the increased efficacy due to the higher doses offers savings in drug spending, similarly to normal IMRT. A less quantifiable benefit of the lower number of fractions is freeing up equipment capacity, which allows at least 10% increase in the number of patients, thus improving the equal access to care.

In Hungary, IMRT technique has not yet been widely spread. Due to the risk of developing toxicities the total dose of radiation treatment delivered with 3DCRT technique does not reach the dose levels (≥74 Gy) recommended in international guidelines. The delivery of higher doses may be put into practice with new techniques such as IMRT and IGRT. Therefore in our analysis we examined whether it is worth to apply IMRT with a low level of expected toxicity risk to deliver higher doses and extend the progression-free period in localized prostate cancer patients. In accordance with this approach in our analysis our base-case assumption was a scenario where the risk of developing moderate and severe toxicities is low with the use of any of the techniques (3DCRT, IMRT and HF-IMRT). However, in case of IMRT and HF-IMRT this requirement can also be met with higher total doses, hence more favourable tumour control can be achieved.

In our analyses we assessed the efficacy, the cost and cost-effectiveness of an expensive medical technology. With the presented microcosting analysis and the model-based cost-utility analysis we also verified that HTA methodology is applicable for the assessment of medical devices used in hospitals.

5. NOVEL FINDINGS AND PRACTICAL APPLICATIONS

Novel findings

Results presented in this thesis include several novel findings which are summarized according to the following:

1. High dose **IMRT and HF-IMRT are more effective** than the conventionally used 3DCRT, which is the standard of care in Hungary. Treatment can be **delivered safely** with the use of IMRT and IGRT.
2. We determined the **resource use and cost** of normofractionated 3DCRT and IMRT for localized prostate cancer. We also estimated the cost vectors of the hypofractionated intervention, which is expected to be introduced in Hungary in clinical trials in the near future. The use of the **new techniques is more expensive** for the healthcare providers.
3. **IMRT and HF-IMRT proved to be cost-effective** in Hungary in comparison with 3DCRT in the treatment of localized prostate cancer, taking local healthcare provider's cost-structure and clinical practice into account for the treatment of localized prostate cancer. However, the cost-effectiveness for the treatment of **low risk patients is more uncertain** due to the lower advantage in tumour control and higher treatment costs.
4. IMRT and HF-IMRT are not only cost-effective but also provide a **great cost saving potential for the Hungarian health care system** due to the decreased expenses on medicines. Savings could be realized in the pharmaceutical budget.
5. The current healthcare **financial system does not make a distinction** between the reimbursement of standard treatment and modern procedures. The use of the more costly interventions (IMRT and HF-IMRT) generates loss for the hospitals and **hinders the deployment of the cost-effective alternative**.
6. Methods of **health technology assessment are appropriate** to support healthcare financial and development policy decisions **regarding medical technologies used in hospitals**.

Practical application

We would like to highlight the following conclusions regarding the practical application of our work:

1. We verified that the recent **development of radiation therapy infrastructure was beneficial for the society**, since the progression-free survival of patients and quality of life can be improved and the new interventions are cost-effective.
2. Our analysis also revealed that the use of novel technologies is financially disadvantageous for the hospitals and that this negative incentive can only be resolved through developing new reimbursement codes and fees encouraging providers to use the cost-effective treatments. The microcosting analysis, presented in this thesis and also published in a national scientific journal, can be an **appropriate basis for the National Health Insurance Fund to detect this financial anomaly** and to change the financial methods and reimbursement fees.
3. The methods and results of our cost-utility analysis were published in international journal, in order to confirm that **modern therapeutic techniques** which are cost-effective in Western Europe and in USA may **economically be beneficial to adopt in a Central-Eastern European countries,** where the utilization of cost saving potentials is crucial.
4. The results presented in our thesis can **contribute to evidence based decision-making** in healthcare, which can increase the effectiveness of resource-allocation and may improve the access to radiation therapies by increasing the capacity of the radiation facility and quality of life for patients. Methods applied in this thesis can evidently be used for the assessment of other medical technologies.

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