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Long-term costs and survival of prostate cancer; a population based study

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Abstract

Purpose: There is a rising interest in measuring the societal burden of malignancies including prostate cancer. However, population-based studies reporting incidence costs of prostate cancer in the long-term are lacking in Europe. The objectives of the study is to analyse the long-term costs and survival of prostate cancer patients treated by radical prostatectomy (RP) or conservative management (nRP).

Methods: A retrospective claims data analysis of the National Health Insurance Found Administration of Hungary between 01.01.2002 and 31.10.2013 was carried out. Annual incidence costs related to prostate cancer and overall survival were calculated for a cohort of patients diagnosed between 2002 and 2005.

Results: Altogether 17,642 patients were selected, 2,185 (12%) of them have undergone RP. The annual incidence rate ranged between 4,177-4,736 cases. Mean age of RP and nRP patients were 59.4 (SD 5.9) and 71.0 (8.4) years, respectively. The mean survival time of the RP patients was significantly longer compared to nRP patients both in the total sample (11.2 vs. 7.4 years;

p<0.001) and in the subgroup <70 years (11.3 vs 8.8 years; p<0.001). At the end of the 12-year follow-up, RP patients had a higher (0.83 vs 0.68), while nRP patients had a slightly lower (0.35 vs. 38) probability of being alive compared with the age-matched general male population. The long-term cumulative costs of the RP and nRP patients amounted to €4,448 and €8,616. Main driver of the cost difference was high drug cost in the nRP group.

Conclusions: To our knowledge, this study applied the longest time-window in reporting population-based incidence costs in Europe. We found that RP patients not only lived longer, but they had significantly lower total long-term costs than nRP patients. Therefore radical prostatectomy is a cost-effective strategy in prostate cancer.

Key words: prostate cancer, cost-of-illness, administrative claims, survival, radical prostatectomy

Introduction

In Europe, prostate cancer is the most common malignancy among men (96.0 cases per 100,000) followed by lung (68.3 cases per 100,000) and colorectal cancer (55.7 cases per 100,000), and the third leading cause of cancer deaths (19.3 deaths per 100,000) [1,2]. The majority (55%) of incident cases of prostate cancer occur over the age of 70 years [3]. In Hungary, the number of incident cases for the year 2011 ranged between 3,419 and 4,117 based on the data of the National Health Insurance Fund Administration (NHIFA) and of the National Cancer Registry [4,5].

There is a rising interest in measuring the societal burden of malignancies due to limited resources and cost escalation in the healthcare sector. Incidence costs of diseases are reported less frequently than prevalence-based average annual costs. Although prevalence-based cost

studies are helpful in estimating the costs of prostate cancer at a given time point, they provide little insight in the long-term costs associated with incident cases. In the US, one study using the SEER-Medicare database, reported the incidence and life-time costs of prostate cancer in the past 20 years [6]. No such study has been identified from Europe according to a systematic review on the costs of prostate cancer by Rencz et al. [7]. Their literature search, however, was closed in 2013. Since then, only one population-based cost study by Laudicella et al. has reported incidence costs of prostate cancer over a 9-year period (3 years observation and 6 years projections) for England [8]. Incidence costs in prostate cancer have not been investigated in Hungary, so far only data on average annual costs were reported [9,4].

Newly diagnosed patients aged over 70 years are more likely to receive conservative, non-radical prostatectomy (nRP) treatment due to various reasons including the increased risk of complications [10]. The majority of the patients undergoing radical prostatectomy (RP) are under the age of 70 years [11,12]. Nevertheless, there is a shortage of data on the cost consequences of RP in the long-term. Therefore, our study aims to analyse and compare the long-term costs and survival of the RP and nRP patients from a payer perspective.

Methods

We analysed the claims data of the NHIFA between January 1st, 2001 and December 31st, 2013. NHIFA is a single health insurer in Hungary covering the whole population of the country (approximately 10 million people) across all types of care (primary, secondary care, pharmaceutical claims, etc.). Male patients over the age of 30 years were selected in multiple steps based on international classification codes (ICD-10) for prostate cancer (C61 - Malignant neoplasm of prostate or D07.5 - Carcinoma in situ of other and unspecified genital organs,

prostate or D40.0 - Neoplasm of uncertain or unknown behaviour of male genital organs, prostate) and having prostate biopsy and androgen-deprivation therapy, or radical prostatectomy, or radiotherapy [13].

Disease duration was calculated as the time between the date of the first occurrence of the ICD code of prostate cancer in a patient's claim records and the date of death or the study endpoint. The following data were collected: date of birth and death, date of first occurrence of ICD code for prostate cancer, date of diagnosis of bone metastases and the date of radical prostatectomy. Moreover, prostate cancer-related healthcare utilisation and expenses were collected including outpatient visits, hospital admissions and the use of the following prescription drugs: buserelin, leuprorelin, goserelin, triptorelin, flutamid, nilutamid, bicalutamid, abiraterone, degarelix and cabazitaxel.

A cohort of patients diagnosed with prostate cancer between 2002 and 2005 was selected from the NHIFA database. Patients diagnosed with prostate cancer in 2001 were excluded in order to guarantee that only new cases without medical history of prostate cancer are involved. In order to have the longest possible period without the need for censoring, patients diagnosed after 2005 were also excluded. Observational period varied between 8-11 years.

Cost calculation

Reimbursement data from the NHIFA were used to estimate the cost associated with prostate cancer. In Hungary, active inpatient care is reimbursed through the diagnosis-related groups (DRG) system, while outpatient services are funded on an activity basis. Data about direct medical costs were obtained directly from the administrative claims database. All prostate cancer-related (ICD C.61) health care services covered by NHIFA were captured including outpatient visits, laboratory tests, diagnostic imaging, hospitalisation, radiation therapy and prescription drug costs. Costs from the date of diagnosis to date of death or to 31 October, 2013

were considered. For each year after diagnosis, total incidence costs included only those patients who survived the year before. Average exchange rate of EUR/HUF = 296.92 was applied, and nominal costs were reported.

Survival analysis

Kaplan–Meier survival analysis for all-cause mortality were conducted in order to compare different subgroups of patients with PC. Differences between survival curves were tested by log-rank test. The Cox proportional hazards model was used for multivariate analysis to assess the relationship between PC and variables. Variables that proved significant in the univariate analysis were included in a forward stepwise multivariate Cox proportional hazards model in order to identify independent predictors in the overall PC population. P values of <0.05 were considered to indicate statistical significance. All analyses were conducted using R version 3.1.3.

Results

Epidemiology

During the study period, a total of 50,380 patients with prostate cancer were identified from the database (Figure 1). Patients diagnosed before January 1st, 2002 and after December 31st, 2005 were excluded (n=32,738) and the remaining cohort of 17,642 patients diagnosed between 2002 and 2005 were analysed. Their mean (SD) age at diagnosis was 69.5 (9.0) years and half of the patients were older than 70 years. Altogether 2,185 (12%) patients went through RP. These patients were typically diagnosed at a younger age than nRP patients (59.4 vs. 71.0; p<0.001). The overall mortality rate was 5.6-fold (95% CI: 5.0-6.4) higher among nRP patients.

Bone metastasis occurred in 1,380 (7.8%) patients. The average age at diagnosis was marginally different between the patient groups with and without bone metastasis (68.7 vs. 69.6; $p<0.001$). The overall mortality was 1.3-fold (95% CI: 1.20-1.31) higher in patients who developed bone metastasis.

Survival

Mean survival time of RP patients was significantly longer than that of nRP patients (11.2 vs. 7.4 years; $p<0.001$) (Figure 2). Controlling for the age at diagnosis and bone metastasis, radical prostatectomy had the most significant effect on mortality hazard (Table 2). RP patients had a 6.6 times lower mortality hazard compared to nRP patients. Patients younger than the age of 70 years indicated a similar mortality hazard, but the difference between the survival times was still significant (11.3 vs 8.8 years; $p<0.001$) and the mortality hazard was 5.8 times lower.

Costs

Table 3 summarizes the annual and cumulative long-term costs of the patients. The mean total cumulative costs for the whole study population were €8,100 (SD 7,192). The main cost drivers were drugs (77%) and costs of hospitalization (including surgery) (19%). RP patients had significantly lower long-term total costs compared with nRP patients (€4,448 vs. €8,616).

Discussion

Principal findings

In this study, we estimated the long-term total costs of prostate cancer in the RP and nRP patients and the overall survival in these two groups of patients using an insurance claims database in Hungary covering approximately 10 million people. To our best knowledge, this is

the second study in the literature estimating long-term incidence costs of prostate cancer in Europe.

The overall long-term costs were almost twice as high in nRP group compared with the RP group; a surprising finding given that survival was shorter in nRP group. Our results showed that prescription drugs accounted for the majority of costs in nRP group (79%). Mean drug costs were almost 3.5-fold higher in nRP group (€6,829) than in RP group (€2,013). In the RP group, inpatient hospital stay (45%) and drug costs (45%) were responsible for the majority of costs. Mean inpatient hospital stay costs were 1.5 times higher in RP (€2,022) than in nRP groups (€1,433). These results demonstrate that the cost differences could be mainly explained by higher drug costs in the RP group.

Comparison with other studies reporting long-term incidence costs

In the US, analysing the SEER-Medicare data Stokes et al. estimated that the aggregated life-time incidence costs of prostate cancer patients diagnosed in 2008 was as high as $34,432 [6]. Only patients older than 65 years were included in their analysis. Using survival estimation and claims data, they developed a phase-base model to predict life-time costs. In a population based study from the UK, Laudicella et al. reported that the total costs of prostate cancer patients aged under and over 65 years for a 9 years period mounted to £18,056 and £26,806, respectively [8]. In this study, cost data of the first 3 years were based on observation of a population-based cohort and costs of year 4 to 9 were estimated according to the hospital's activity-based cost projection from a different cohort. However none of these studies reported costs by intervention types.

Comparison with other Hungarian cost-of-illness studies in prostate diseases

Although two prior studies estimated the costs of prostate cancer treatment in Hungary, long-term costs of prostate cancer have not been scrutinized so far [9,4]. In addition, these two studies failed to capture cost consequences of radical prostatectomy. Both studies have reported average annual costs of prostate cancer based on the NHIFA's administrative database. In 2005, 2008 and 2011 the average annual costs of prostate cancer were €3,336, €4,194 and €3,014 per case, respectively (due to the different exchange rates, the original reported results were converted) [4]. According to an official report by the NHIFA, prostate cancer-related average annual direct costs represented €11,114 in 2007, and €12,798 in 2010 [9]. Comparing with costs of other prostate diseases, total annual per patient cost of pharmacologically treated benign prostatic hyperplasia patients was merely €877 (SD €1,829) in Hungary [14]. However, a direct comparison between incidence long-term costs of a cohort and average annual costs of prevalent cases is pointless because of the methodological differences.

Survival

Our results showed that RP patients lived on average four years longer than nRP patients ($p<0.001$). Although RP patients were younger at the time of diagnosis and the majority of radical prostatectomy occurred under the age of 70 years, the differences in life-expectancy were independent of the age. In the subgroup of patients younger than 70 years, life-expectancy of RP patients was also significantly longer (2.5 years). In recently published studies, radical prostatectomy was associated with reduced risk of mortality compared both to watchful waiting (RR=0.56) and to androgen deprivation therapy (RR=0.33)[15-17]. Radical prostatectomy is a common treatment for patients with lower stage of prostate cancer and a good life-expectancy. Thus, our data might be a result of selecting patients with lower stage disease. However, the NHIFA database contains no data on disease severity, so the staging could not be included in the analysis as an explanatory variable.

In our study, at the end of the 12-year study period, the probability of being alive (Kaplan-Meier survival estimate) was 0.83 and 0.35 for the RP and nRP patient groups. These data indicate that the RP patients had a higher probability of being alive at the end of the 12-year observation period than the age-matched general male population (0.83 vs. 0.68) [18]. In contrast, the nRP patients had a slightly lower probability of being alive compared with the age-matched general male population (0.35 vs. 0.38) [18]. RP patients might be diagnosed at an early stage of the disease and have a better life-expectancy. In addition, there are evidences that patients diagnosed at early-stage PC might have higher socioeconomic status and better access to health care services compared to patients diagnosed at distant-stage [19]. We assume this explain the longer life expectancy of this patient population compared with the general male population.

Limitation

This study has several limitations. First, this was a retrospective administrative claims database analysis; thus, the amount of clinical information available (e.g., tumor stage, grading, disease severity, therapeutic indication) is limited. This would be needed to stratify the sample by risk groups and conduct a more detailed analysis [20,21]. Furthermore, patients treated conservatively by choice or by disease status might be different regarding both survival and costs, but these groups could not be differentiated based on retrospective claims data. Claim database did not contain information on cause of death, only occurrence of death was recorded. Cause specific survival estimation would be more accurate when comparing subgroups among prostate cancer patients. Secondly, in administrative healthcare database studies that using ICD codes misclassification of claims might occur. However, besides ICD codes, exclusively codes of prostate cancer-related interventions were used for the patient selection, which is a strength

of our analysis. Thirdly, costs of primary care were excluded from this study, because prostate cancer-related primary care costs were not available in the NHIFA database due to reimbursement techniques, such as capitation. Fourthly, the simple mean was used for estimating the costs for the cohort of patients. Estimates based on the mean may bias the costs downward because costs occurred after the observed follow-up are equated to zero.

Conclusions

Using insurance claims database between 2002 and 2013 our study has the longest time-window in Europe analysing incidence total long-term costs and survival of RP and nRP prostate cancer patients. We found that RP patients lived longer. Beside longer survival, cumulative long-term costs were lower in RP group compared to nRP group. Most of the difference was attributable to higher drug costs in nRP group. Compared to conservative therapy, RP is a cost-effective treatment strategy in prostate cancer.

Although it has been already proved that radical prostatectomy provides better overall survival in patients with prostate cancer, there is very few data on financial benefits. Thus, our results showed that find the disease in early, curative stadium has not only medical but also financial advantage.

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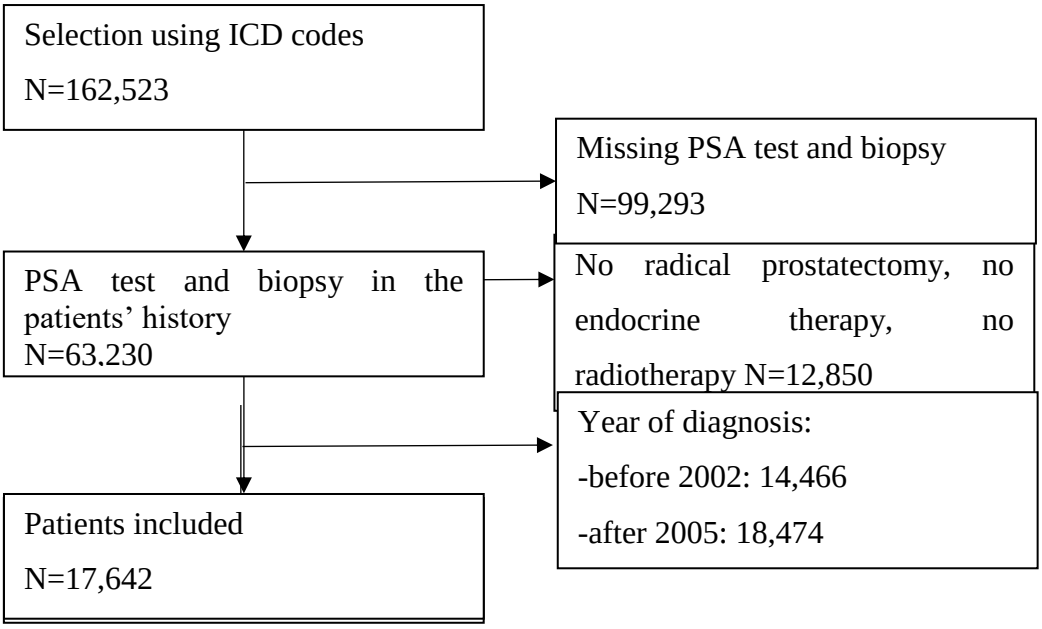
Tables and Figures

Figure 1 Selection process



ICD= International Classification of Diseases, PSA= prostate-specific antigen

Table 1 Main characteristics of patients

Variables	Patient with prostate cancer	Patients having radical prostatectomy (RP)	Patients without prostatectomy (nRP)
Number of patients	17,642	2,185	15,457
Age at diagnosis (year), mean (SD)	69.5 (9.0)	59.4 (5.9)	71.0 (8.4)
Died, % (n)	52.3% (9,221)	10.3% (226)	57.9% (8,955)
Bone metastasis, % (n)	7.8% (1,380)	5.1% (111)	8.2% (1,269)
Survival (year), mean (SD)	7.8 (4.3)	11.2 (1.9)	7.4 (4.3)
Mean time between diagnosis and radical prostatectomy or endocrine treatment (year), mean (SD)	2.4 (3.1)	4.3 (3.3)	2.2 (3.0)
Received endocrine treatment	92.8% (16,366)	44.3% (967)	99.2% (15,339)
Number of patients with survival time			
< 1 year	6.4% (1,131)	0.0% (1)	7.3% (1,130)
1-5 years	24.8% (4,372)	3.2% (70)	28.3% (4,372)
5< years	68.8% (12,139)	96.8% (2,114)	64.9% (10,025)

Table 2 Uni- and multivariate survival analysis, Cox proportional-hazards model

Variable	**N**	**Survival (years)**	**Univariate Hazard ratio (95% CI)**	**p**	**Multivariate Hazard ratio (95% CI)**	**p**
Age at diagnosis						
<70 years	8,428	9.3	2.93 (2.81-3.06)	<0.001	2.39 (2.28-2.49)	<0.001
≥70 years	9,214	6.3				
Having bone metastasis						
no	16,262	7.9	1.32 (1.23-1.42)	<0.001	1.44 (1.34-1.54)	<0.001
yes	1,380	7.2				
Radical prostatectomy						
no	15,457	7.4	0.12 (0.11-0.14)	<0.001	0.15 (0.13-0.17)	<0.001
yes	2,185	11.2				
Long-term costs						
below the median	8,821	7.0	0.70 (0.67-0.72)	<0.001	0.50 (0.48-0.52)	<0.001
over the median	8,821	8.7				

Table 3 Yearly and long-term incidence cost of prostate cancer (in €)

Year from diagnosis	N		Outpatient		Inpatient		Drug		CT		Total	
	no RP	RP	no RP	RP	no RP	RP	no RP	RP	no RP	RP	no RP	RP
Year 0*	15,457	2,185	22 (48)	12 (40)	180 (423)	166 (407)	484 (668)	73 (286)	8 (36)	10 (37)	693 (928)	261 (625)
Year 1	14,939	2,185	31 (57)	16 (47)	226 (713)	212 (554)	986 (1 074)	169 (614)	11 (46)	12 (43)	1,254 (1,422)	408 (961)
Year 2	13,639	2,178	29 (57)	14 (36)	167 (764)	123 (424)	887 (1 067)	202 (721)	9 (43)	10 (42)	1,092 (1,413)	349 (924)
Year 3	12,366	2,164	29 (59)	17 (40)	147 (862)	138 (562)	814 (1 045)	210 (682)	8 (42)	12 (52)	998 (1,453)	377 (969)
Year 4	11,337	2,139	27 (56)	19 (46)	136 (844)	152 (597)	754 (1 007)	224 (710)	9 (45)	16 (56)	926 (1,412)	412 (1,004)
Year 5	10,440	2,126	25 (54)	23 (50)	119 (763)	183 (662)	715 (979)	231 (661)	8 (42)	20 (65)	867 (1,341)	456 (1,038)
Year 6	9,626	2,105	24 (55)	27 (62)	111 (729)	223 (796)	675 (934)	233 (599)	9 (45)	21 (69)	820 (1,284)	505 (1,118)
Year 7	8,816	2,077	22 (58)	31 (72)	112 (728)	239 (773)	573 (853)	232 (594)	9 (47)	22 (64)	717 (1,229)	523 (1,098)
Year 8	8,038	2,049	21 (54)	29 (55)	101 (691)	248 (837)	457 (746)	211 (543)	10 (47)	25 (70)	588 (1,123)	514 (1,084)
Year 9	5,633	1,483	15 (53)	22 (52)	68 (551)	178 (688)	284 (608)	136 (468)	7 (42)	17 (57)	374 (918)	353 (936)
Year 10	3,532	938	9 (42)	14 (40)	46 (480)	120 (711)	139 (391)	66 (269)	5 (36)	11 (47)	200 (706)	210 (848)
Year 11	1,686	430	4 (33)	7 (46)	20 (297)	41 (313)	61 (286)	26 (157)	2 (19)	5 (31)	86 (469)	79 (428)
Cumulative	15,457	2,185	259 (285)	233 (238)	1,433 (3,101)	2,022 (2,455)	6,829 (6,137)	2,013 (4,337)	96 (231)	180 (269)	8,616 (7,237)	4,448 (5,701)

Cost data were collected in calendar years unit. * Length of year 0 might vary between 0-365 days.

nRP= patients without prostatectomy; RP= patients having radical prostatectomy

Figure 2 Kaplan-Meier survival analysis for all-cause mortality