The burden of renal cell cancer: A retrospective longitudinal study on occurrence, outcomes and cost using an administrative claims database

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ABSTRACT

Objective: To assess the burden of renal cell carcinoma (RCC) in epidemiologic and economic terms.

Methods: Retrospective, naturalistic longitudinal study on the occurrence, outcomes and cost of RCC using an administrative database. We selected residents of Friuli-Venezia-Giulia (FVG), a North-eastern Region of Italy, who had a RCC first hospital admission during the period 2000–2004, and we followed them up until: 30th June 2005, death or transfers. Direct medical costs were quantified in the perspective of FVG Regional Health Service.

Results: We enrolled 1358 patients (63% male), the 18.8% presenting a metastatic-stage, leading to a crude incidence of 23/100,000 person-years. During the follow-up, 76% of the metastatic patients and 21% of the non-metastatic patients died. Total health care costs per-patient over the maximum of follow-up were 16,090 € for the localised stage group and 17,656 € in the metastatic-stage group.

Discussion: RCC imposes a significant epidemiologic and economic burden to the health-care-system and the society.

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1. Introduction and scope

The measurement of the burden of disease is a topic of perennial interest to public health researchers and policy makers. These measures are used to describe the general state of health of the population and to establish public health goals, to compare national health status and the performance of health systems across countries, to assess the allocation of health care and health research resources across disease categories, and to evaluate the potential costs and benefits of public health interventions.

Traditional measures of disease burden are well established, although the acquisition of data to synthesise these measures is still far from optimal in many national, regional and local jurisdictions. Core measures include disease-specific incidence, prevalence, mortality and, in some cases, years of potential life lost. These parameters tend to be relatively straightforward, unidimensional and ‘objective’, whereas newer, more conjectural measures tend to incorporate an...
evaluative component. These include such measures as the cost of illness (COI), where the evaluative components are the economic cost associated with treating illness (also called cost of care) and the economic value attributed to the loss of health and life. The COI methodology, established by Rice et al., has long been accepted as a descriptive measure of the burden of disease. COI estimates typically include three main elements: direct cost, morbidity cost and mortality cost. Often direct cost is measured by expenditures for medical procedures and services provided for the treatment and care for the disease: this is also called cost of care; morbidity cost is measured by lost income due to the work disability and absenteeism associated with the disease entity and mortality cost is measured as lost income associated with premature death.

The estimation of the direct medical costs for specific diseases is, increasingly, an important area of health services research. Policy makers need cost estimates to rationally allocate health care resources at a time when the main objectives, in many countries, are to contain costs as well as to improve the quality and quantity of care. The rigorous estimation of the direct medical costs can inform consideration of the cost effectiveness of alternative policies and interventions. Until fairly recently, most estimates of the direct medical costs fell within the type of ‘cost-of-illness’ studies, which tend aggregate expenditures per annum per disease category.

There has been an increasing demand for more detailed disease-specific estimates of the direct medical costs derived from patient-level longitudinal expenditures that occur over the entire course of life of a diseased individual. Such data can be used to build several policy-relevant indicators, e.g. the long-term cost from diagnosis until death, the cost per person-year lived with a disease, and the costs for the initial, continuing and terminal phases of cancer care. These phase-specific costs can be used to assess the efficiency, i.e. cost to effect ratio, of alternative treatments and disease management programmes.

Long-term costs are useful in assessing the cost effectiveness of preventive strategies. Costs per person-year can be used to adjust capitation rates and budgets on the basis of risk, and also to assess the ‘burden’ of a disease when setting broad priorities for research and public health programmes.

Renal cell carcinoma (RCC) is diagnosed in more than 120,000 patients in Europe and USA every year and causes about 60,000 deaths. It represents about 85% of kidney cancer which accounts for about 3% of all adult malignancies, RCC is the most lethal of the urologic cancers. Patients are often first diagnosed when already in advanced stages of the disease, with 40–50% of them having unrespectable or metastatic form of the disease.

Despite recent advances in treatment options with the emergence of new experimental therapies, the prognosis for long-term survival remains low, with or without therapy: the 5-year survival rate for patients with stage IV renal cell carcinoma (around 1/3 of total patients) ranges from 5% to 10% and a further 20–30% of patients with initially localised disease relapse after nephrectomy.

Treatment options for patients with localised stage cancer include: radical or partial nephrectomy, radiofrequency ablation and cryosurgery, all of which frequently lead to cure. However, patients with advanced RCC historically have had limited treatment options, considering the limited effectiveness and the associated severe side-effects of cytokine immunotherapy and chemotherapy.

For about 25 years, immunotherapy with interferon-α (IFN-α) and interleukin 2 (IL-2) has represented the basis of the treatment for metastatic RCC. During the last 3 years there has been a dramatic increase in treatment options, as four new drugs have received regulatory approval: sorafenib, sunitinib, temsirolimus and bevacizumab.

Despite the growing importance of RCC, data on its economic burden are sparse and rare.

Kidney cancer imposes a significant burden on health care systems due to: advanced diagnostic radiological test, high cost of treatment that often involves in surgery, hospitalisation, regular surveillance and visits to assess recurrence. This study is aimed to evaluating simultaneously frequency of occurrence, outcomes and cost of care of RCC, thus providing empiric evidence on the burden of RCC.

2. Methods

2.1. Techniques

To this end a retrospective, longitudinal, naturalistic study based on the claims of individuals enrolled in the Friuli Venezia Giulia (FVG) administrative database was performed.

FVG Regional Health Authority (RHA) is in charge of universal healthcare coverage of all the residents of FVG, a region of approximately 1.2 million inhabitants in the north-eastern Italy.

The analysis was carried out from the perspective of FVG Regional Health Service.

For the purpose of this study, hospital admissions, outpatient care, drug prescriptions and mortality databases were used and patients were identified followed longitudinally by means of an alphanumeric code that univocally identifies each enrollee of the FVG-RHA.

2.2. Study population

The source population for this study were FVG residents between 1996 and 2006. Membership to the study population was the occurrence of the first hospital admission event with diagnosis of RCC (ICD9 code 189) during the period between 1st January 2000 and 31st December 2004. The date of RCC diagnosis was considered as the index date, i.e. the date of inclusion in the study population. In order to be able to identify incident cases and to follow them up, individuals with diagnosis of cancer (ICD9 code 140–239) in the years 1996–1999 and patients coming from other Regions were excluded from our analysis.

2.3. Observation period

Enrolled patients were followed up starting from index date up to the occurrence of 30th June 2005, death, or withdrawal from the RHA (i.e. transfer out of the Region), whichever come first.

Therefore, the individual length of follow-up was variable.
2.4. **Data collection and quantification of cost**

Demographic characteristics (age and gender) were collected at baseline, whilst information on vital status, outpatient care, drug prescription and hospital admission were collected during the follow-up period.

Diagnosis related group (DRG) charges\(^{14}\) were applied to estimate the cost of hospitalisations and drug prescriptions information were obtained from the pharmaceutical database that includes every prescription dispensed to outpatients by the community pharmacies. Drug therapies were quantified using market prices reported by the Italian National Therapeutic Formulary.\(^{15}\)

Outpatient care database, including visits, diagnostic and laboratory tests, was used to quantify resources absorption whilst costs were calculated by means of ambulatory tariffs.\(^{16}\)

Survival and costs analyses were performed considering the presence or the absence of metastases. The disease was considered at the metastatic-stage at diagnosis if the patient had a hospital admission recording metastases (ICD-9 CM 196.xx, 197.xx, 198.xx) within a time window of 60 d (i.e. either before or after) from the index date.

The crude incidence was calculated as the rate between new cases and person time expressed as 100,000 person-years.

All costs are expressed in Euros of 2005 and have been calculated as the sum of all claims related to RCCs incident subjects recorded after the index date.

Costs expressed as Euros per patient and further described as the cost of the first year (i.e. 365 d from the index date) and as total cost (i.e. all the follow-up period), because these can be used for short and long-term planning needs of Health Authorities.

2.5. **Statistical analysis**

Estimates of central tendency expressed by using means and frequencies, and standard deviation was used as a measure of dispersion

Kaplan–Meier estimates of survival according to the presence or absence of metastases were compared with the use of a log-rank test. Univariate and multivariate analyses of survival with the use of the Cox proportional hazards method were performed to obtain the hazard ratios for death and associated 95% confidence intervals for the comparison between patients with and without metastases.

Point and interval estimates of differences between cases with or without metastases were assessed resorting to a bootstrap technique with 5000 samples. Mean costs differences were subsequently estimated fitting a linear least squares regression model adjusting for age and sex.

All analyses were performed using SPSS versions 15.0 software (SPSS, Chicago, IL).

3. **Results**

During the study period (January 2000–December 2004) 1358 patients with diagnosis of RCC were enrolled (63% male), the 18.8% of which presenting with a metastatic-stage (mRCC), leading to a crude incidence of 23/100,000 person-years.

Subjects with and without metastases were, on average, 69.9 and 66.8 years old, respectively, with a difference statistically significant (Table 1).

During the period of observation, 195 subjects in the metastatic group died (76%) and 240 (21%) subjects in the group without metastases.

As compared with RCC patients, mRCC patients had an increased risk of death (hazard ratio 5.8, 95% confidence interval 4.79–7.04; \(P < 0.0001\)). After adjustment for age and sex, the hazard ratio associated with metastases was not significantly affected by any of the baseline characteristics examined (Table 1).

The risk of death was significantly higher amongst metastatic-stage patients with a median survival of about 6 months (Fig. 1).

Total health care costs per patients over the maximum of follow-up were 16,090 Euro for the localised stage group and 17,656 Euro in the metastatic-stage group (Table 2).

Inpatient payments were 11,424 Euro (71%) for RCC patients and 14,238 Euro (81%) for mRCC patients. Ambulatory and diagnostic payments per patients were 2946 Euro (18%) and 1986 Euro (11%) for RCC and mRCC patients, respectively.

The cost per patient related to the first year after diagnosis for subjects with and without metastases was 13,692 and 10,502 Euro, respectively, with a mean difference of 3363 Euro after adjusting for age and sex (Table 3). Considering subsequent years, differences between the two groups raised to 5900 Euro.

The vast majority of the total costs estimated either in the first year after diagnosis and during the entire follow-up can be attributed to hospital care (Tables 2 and 3).

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### Table 1 – Population characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>With metastases</th>
<th>Without metastases</th>
<th>Difference/OR/(95% CI)</th>
<th>Difference/OR/(95% CI)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69.8</td>
<td>66.7</td>
<td>-3.1 (-4.63/-1.46)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>156</td>
<td>700</td>
<td>1.12 (0.84/1.47)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>100</td>
<td>402</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of follow-up (d)</td>
<td>382.14</td>
<td>857.81</td>
<td>475.66 (409.57/541.56)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0.76</td>
<td>0.21</td>
<td>5.8 (4.79/7.04)(^b)</td>
<td>5.5 (4.52–6.64)(^b)</td>
</tr>
</tbody>
</table>

\(^a\) Adjusted for age and sex.

\(^b\) Hazard ratio.
4. Discussion

This is the first study to assess occurrence, cost and outcomes of RCC in the third party payer’s perspective in Italy and one of the few ever performed.

Results from our study show that, due to the large number of hospitalisations and the high mortality, the epidemiologic and socioeconomic burden to the healthcare-system and to the society of RCC is high.

![Kaplan-Meier survival curves of individuals with diagnosis of RCC with and without metastases.](image)

**Table 2 – Cost per patient during entire follow-up period**

<table>
<thead>
<tr>
<th>Variable</th>
<th>With metastases (N = 256)</th>
<th>W/O metastases (N = 1102)</th>
<th>Difference (95% CI)</th>
<th>Difference (IC 95%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of hospitalisation</td>
<td>14238.30</td>
<td>11424.69</td>
<td>2813.61 (1112.47/4514.76)</td>
<td>2928.97 (1326.35/4531.58)</td>
</tr>
<tr>
<td>Cost of drugs</td>
<td>1431.34</td>
<td>1719.29</td>
<td>-287.96 (-673.42/97.51)</td>
<td>-285.62 (-663.53/92.29)</td>
</tr>
<tr>
<td>Cost for outpatient care</td>
<td>1986.38</td>
<td>2946.36</td>
<td>-959.99 (-1744.41/-175.56)</td>
<td>-817.14 (-1560.39/-73.89)</td>
</tr>
<tr>
<td>Total health care cost</td>
<td>17656.02</td>
<td>16090.35</td>
<td>1565.67 (-664.21/3795.55)</td>
<td>1826.20 (-223.72/3876.12)</td>
</tr>
</tbody>
</table>

a Adjusted for age and sex.

**Table 3 – Cost per patient in the first year of follow-up**

<table>
<thead>
<tr>
<th>Variable</th>
<th>With Metastases (N = 256)</th>
<th>W/O metastases (N = 1102)</th>
<th>Difference (95% CI)</th>
<th>Difference (IC 95%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of hospitalisation</td>
<td>11670.12</td>
<td>8859.47</td>
<td>2810.65 (1681.76/3939.54)</td>
<td>2920.42 (1872.69/3968.15)</td>
</tr>
<tr>
<td>Cost of drugs</td>
<td>875.38</td>
<td>597.52</td>
<td>277.86 (27.62/528.09)</td>
<td>283.28 (24.09/542.47)</td>
</tr>
<tr>
<td>Cost for outpatient care</td>
<td>1147.18</td>
<td>1045.36</td>
<td>101.83 (-229.11/432.76)</td>
<td>159.59 (-160.55/479.73)</td>
</tr>
<tr>
<td>Total health care cost</td>
<td>13692.68</td>
<td>10502.34</td>
<td>3190.34 (1857.88/4522.79)</td>
<td>3363.29 (2172.48/4554.11)</td>
</tr>
</tbody>
</table>

a Adjusted for age and sex.
The natural history of the disease requires a great absorption of resources in the early phases after diagnosis, which is true for patients with metastatic and without metastases at diagnosis, and in the late stages of the disease. Given the latter is more common for mRCC than for RCC, especially in the first year after diagnosis, this fact could explain the higher costs incurred by mRCC patients than RCC patients in the first year of follow-up. The cost of mRCC is in fact concentrated into a very short time window, given the often rapid and fatal evolution of the disease, whereas the cost of RCC is spread over a longer period of time in light of its more favourable survival. Once referred to a homogeneous time basis (e.g. one month), RCC patient costs are consistently lower than those for mRCC as the latter die earlier than the localised stage patients. To put figures into perspective, the 17,656 Euro of total healthcare cost of an incident non-metastatic RCC individual are related to an average follow-up of almost 12.5 months (i.e. 382 d): therefore, the average monthly cost is approximately 1400 Euro per patients per month. In contrast, the 16,090 Euro of total healthcare cost of an incident non-metastatic RCC individual are related to an average follow-up of 28.5 months (i.e. 857 d); consequently the average monthly cost is approximately 560 Euro per patients per month. Therefore, it is both true that the cost per unit of time (e.g. month) of mRCC is much (2.5 times) higher than non-mRCC, and that, because of limited survival, the overall cost is only slightly (10%) superior.

Hospital care represents the most important component of health care resources utilisation for RCC. In fact, considering the entire follow-up period, hospitalisation account for the 71% and 81% in the localised and metastatic-stage group, respectively. This is mainly represented by surgical procedures, which remain the standard of care for most stages of the disease.

Despite the evidence we presented is based on more than 5 years observation of a source population of 1.2 million subjects, with a study population of more than 1300 subjects and measurements of real practice, actual resources absorption and cost directly borne by the third party payer, our study has potential limitations.

First, direct costs other than those for hospitalisation, drug therapy and diagnostic test could not be measured as they are not reimbursed by the third party payer. This is likely to cause an underestimate, though probably marginal, of the total burden of care for RCC, as costs associated with the consumption of nursing or other resources for personal care were not available.

A second limit is the absence of information on indirect cost, i.e. productivity loss, as well as intangible consequences, such as health related quality of life impairment. This is likely again to lead to an underestimate of the total burden. Anyway, the impact of indirect cost on society is likely to be of modest economic value, as indirect costs are expected to represent around 10% of total cost; because of the age at onset, most patients are likely to be already retired when the disease is diagnosed.

Despite conservative, the results of this study exhibit a considerable economic impact of RCC in FVG Region. Interventions able to prevent the presence of metastases at the time of diagnosis have the potential to yield medical but also considerable economic benefits.

Evidence from this study will be potentially beneficial to estimate preventive strategies as well as different established and new therapies, particularly in the metastatic and advanced phase of the disease, in which several new therapies have recently become available.

**Conflict of interest statement**

This study is part of a collaboration between the Pharmaceutical Services Unit, Health General Directorate, Friuli Venezia Giulia Regional Health Authority and CIRFF, Center of Pharmacoeconomics, Federico II University of Naples. Fondazione Charta provided technical statistical assistance for data analysis. The authors declare that this paper has not been reported or published elsewhere and that they have no competing interests.

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