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Resource use and costs of newly diagnosed cancer initial medical care

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Summary. *Aims:* Assessment of direct medical costs of cancer diagnosis and treatment for newly diagnosed cancer patients; analysis of patterns of medical service utilization; description of costs according to ICD-10 diagnosis, age and stage at diagnosis; identification of major cost drivers; description of cost of terminal stage patients at the end of life. *Material and methods:* A retrospective, bottom-up database analysis was conducted on insurance claims and cancer registries. A payer's perspective and six-month time span were adopted. *Results:* Duration of observation was 170+/-106 days (CI95%;164-176). A total of 1222 newly diagnosed cancer patients consumed on average € 6,837 (standard deviation [SD] € 24,523, range € 1-€ 438,042) per patient, in the first half year of treatment. Out of 151 deceased patients the mean survival time from diagnosis was 75+/-109 days (CI95%; 57-92). The mean cost of care was € 6,949 (SD € 36,414) per patient. Pharmaceuticals with monoclonal antibodies, in particular, were dominant among cost domains. The combined budget impact of this patient cohort was € 8,154,214 or € 6,837 per patient. *Conclusion:* The cost differentials of initial oncology diagnostics and treatment are substantial among major ICD-10 malignancy groups. The deceased - mostly late diagnosed, advanced stage patients - cost approximately twice in terms of terminal care compared to survivors, bearing in mind their short survival time. Evidence-based resource allocation in line with market demand for services will remain a key challenge in the provision of more effective and less costly oncology care in the Balkans.

Key words: cancer incidence and cost, newly diagnosed, resource use patterns, retrospective, database, oncology, Serbia

«Uso di risorse e costi per terapie iniziali per un nuovo cancro diagnosticato»

Riassunto. *Scopo:* Valutazione dei costi medicali diretti per diagnosi e terapie di pazienti con nuove diagnosi di cancro; analisi dei tipi di servizi medici utilizzati; descrizione dei costi in base alla diagnosi ICD-10, all'età ed allo stadio al momento della diagnosi; identificazione dei principali fattori di costo; discriminazione dei costi

Ethical Committee Approval: The study was conducted in line with The Declaration of Helsinki and was approved by the regional Ethics Committee of the Kragujevac University Clinical Center, Serbia. Decision number 01-5978 issued on 28.05.2013.

per pazienti a stadio terminale fino al termine della loro vita. *Materiali e Metodi:* È stata condotta un'analisi retrospettiva e crescente dei database relativi ai crediti assicurativi e a registri del cancro. Sono stati considerati la prospettiva del pagante e 6 mesi come lasso di tempo. *Risultati:* La durata dell'osservazione è stata di 170+/-106 giorni (CI 95%; 164-176). Per un totale di 1222 pazienti con nuova diagnosi di cancro sono stati spesi in media € 6.837 (Deviazione Standard [SD] € 24.523 range € 1-€ 438,042) per paziente nella prima metà di un anno di trattamento. Di 151 pazienti deceduti, il tempo medio di sopravvivenza dal momento della diagnosi è stato di 75+/-109 giorni (CI 95% ; 57-92). Il costo medio per le loro cure è stato di € 6.949 ([SD] € 36.414) per paziente. In particolare, i farmaci con anticorpo monoclonale sono stati predominanti tra le varie voci di costo. L'impatto del bilancio combinato di questa coorte di pazienti è stato di € 8.154,214 o € 6.837 per paziente. *Conclusione:* I differenziali di costo della diagnostica oncologica iniziale e del trattamento sono sostanziali tra i gruppi ICD-10 a maggiore malignità. I pazienti deceduti, quelli con diagnosi tardiva e quelli con stadio avanzato, presentano approssimativamente costi due volte superiori in termini di cure allo stadio terminale se paragonati ai sopravvissuti, tenendo conto del loro periodo di sopravvivenza. L'allocazione delle risorse in base alla domanda del mercato relativa ai servizi, resterà una sfida cruciale nella fornitura di una più efficace e meno costosa cura oncologica nei Balcani.

Parole chiave: costi ed incidenza del cancro, nuove diagnosi, tipologia di uso delle risorse, retrospettiva, banca dati, oncologia, Serbia

Introduction

Considering the clinical complexity of cancer treatment, the unpredictability of its outcomes and high related costs, the observed healthcare expenditure is crossing the line of affordability in many health systems today (1). Bearing in mind that the population of European nations is aging, cancer will likely remain high in the health policy agenda in the long run (2). Implementation of efficient cost containment strategies in order to decrease its budget impact but sustain quality of medical care is certainly a growing need (3). It will remain difficult to establish priorities without field assessment as to the exact size and structure of the financial burden of malignant disorders (4). The burden of major illnesses including cancer could be regarded as preventable by risk factor reduction, as recently conducted in Serbia (5). The cancers most frequently targeted by national health polices worldwide are breast, lung, colorectal, cervical, prostate, gastric carcinoma and malignant melanoma, as being the ones most susceptible to prevention measures. Some regional health economic assessments have already been undertaken on cervical cancer screening in Slovenia (6), Bulgaria and Romania (7).

Well established electronic registries have existed in high income Western European countries for decades. Even the most prosperous economies among the post-2004 EU members still experience substantial difficulties in creating and maintaining electronic healthcare databases (8). With respect to middle income Eastern European economies (9), there is a significant gap in knowledge on regional cancer economics and its budget impact to the national healthcare systems, and papers on this issue are few and far between (10). Resource use attributed to the initial phase of oncological care following tumor diagnosis remains a hot topic worldwide (11).

The legacy of Serbia's recent history entails a quite unique cancer rate in the population. Among other contributing factors, the proximity of Chernobyl (12), ecological disasters following military conflicts in the 1990s (13), post-war syndromes and unhealthy lifestyles are frequently cited as the causes of the rising cancer incidence rates in some malignant neoplasms, as opposed to trends seen in the majority of EU populations (14).

Even more important, this largest healthcare market of the Western Balkans has entered societal transition from socialism to capitalism with a substantial,

one decade long delay, compared to most post-2004 EU members. Post-socialist countries share the common heritage of a hospital-oriented health system establishment, management practice and financing traditions (15). Modernization of the healthcare system has proceeded at the same pace too. Getting familiar with the major cost drivers and utilization patterns of medical services in cancer as a major "prosperity disease" would lay the groundwork for more informed health policy strategies in the region.

The aims of our study were an in-depth assessment and comparison of the direct medical costs of newly diagnosed cancer diagnosis and treatment (imaging and laboratory diagnostic procedures, hospital admission, physician consultations, prescription drugs, radiation therapy, surgical procedures, rehabilitation etc.) across an array of malignant disorders, observing a large cohort of patients with diverse morbidities.

Research questions of interest were: the pioneering attempt in the Balkans region to establish detailed patterns of oncology medical service consumption; description of costs by age at diagnosis, incidence by diagnosis; stage distribution at diagnosis; insight into mortality rates up to two years after diagnosis and ICD-10 standardized mortality; identification of major cost drivers in cancer patients and description of medical care costs among terminal stage patients.

Materials and methods

Study design

A retrospective study design was chosen as the most feasible way of addressing the above research questions (16). This study was conducted as an in depth, retrospective, bottom-up analysis of service consumption patterns, including expenses related to cancer diagnosis and other demographic and clinical variables, from the payer's perspective. Most Eastern European health systems still have one single, large, state-owned Health Insurance Fund in charge of financing most public and part of private health care. This Payer's perspective was adopted in this study. After the significant societal transformation process going on in the region since 1989, citizens' out-of-pocket expenditure has become a growing contributor to health care funding (17). Unfortunately, to measure the out-of-pocket expenses and the indirect lost productivity related lay beyond the scope and available budget of this study. Regardless of this weakness, the Payer's perspective adopted still faithfully reflects the vast majority of costs accrued and the key issue of regional affordability of cancer medical care.

Setting

Serbia's typical upper-middle income Eastern European health system is funded by one core state-owned Fund in charge of most public health care. It still has high rates of hospital beds per 1000 inhabitants and remnants of a heavy, hospital-based, Soviet influenced system (15). The authors observed the central urban region of Sumadija (297,000 population) during the period 01.01.2010-31.12.2011. It hosts several secondary care hospitals and one large university tertiary care facility (1297 beds). Cancer prevalence and incidence rates in this region are comparable to the national average (14). The authors had at their disposal the prevalence-based insurance claims registry of the The Republican Health Insurance Fund of Serbia and the incidence-based Oncology Registry of The "Batut" Public Health Institute of Serbia.

The patients observed had received their initial cytostatic; surgical and/or radiation treatment according to the Oncologists' Committee recommendation, following clinically confirmed diagnosis and malignancy stage and grade determination (18). Resource use and costs were assessed for these initial few months of disease with the observation period ranging from one quarter to six months on average.

The research questions were defined in July 2012. Negotiations with National institutions managing Boards, aimed at providing access to data, began in August 2012. The Faculty of Medical Sciences of the University of Kragujevac, Serbia, officially requested access to the registries on regional patients with cancer at two Republican-level institutions. First to cooperate was the Republican Health Insurance Fund of Serbia, followed by the Public Health Institute "Batut" of Serbia, whose central region branch office provided the data. Collection of data from the data-providing

registries (insurance claims + epidemiological / clinical data) took place from September 2012. The study was in compliance with Data Privacy legislation in Serbia and was supported by the regional Institute of Public Health and Serbian Academy of Sciences and Arts. All information allowing personal identification of patients was removed from the database, and the data handled were anonymous throughout the study.

Data

The target population of the study were patients from Central Serbia newly diagnosed with malignant disorders (ICD-10) over the two-year period (2010-2011). The data were obtained through two main sources of evidence. Firstly, consumption of medical services and costs was extracted from The Republic Fund of Health Insurance, the Republic of Serbia (19) database of insurance claims regarding cancer patients from the aforementioned territory. These patient files were prevalence based and consisted of 8,375 cases in 2010 and 8,680 cases in 2011. Due to the rather limited yearly contribution of new (approx. 1,600) and deceased (approx. 300) cases, the number of patients suffering from any form of cancer in the region was estimated at 8,500 per year (20). Secondly, the oncology registry of morbidity and mortality provided by the Institute of Public Health of Serbia "Dr Milan Jovanovic Batut" (14) was used as a complementary source of clinical and epidemiological evidence. These data were incidence-based and consisted of all newly diagnosed cases of cancer: 1,602 in 2010 and 1,655 in 2011 (3,257 patients in total), out of whom 466 (14 %) died before the end of 2011. The final study database was based on record linkage between the two main data sources relying on newly diagnosed (incidence) cases only. After exclusion of all patients treated elsewhere whose files were thus incomplete, the study focused on 1,222 cases diagnosed with cancer between 1st January 2010 and 31st December 2011, out of which 151 died in their first year from diagnosis. For each single file, basic demographics, diagnosis, tumor histology, clinical stage at diagnosis, medical resource use, related costs, and time and cause of death (where applicable) were assessed. All types of malignant tumor behavior were observed in selected patients.

Data analysis

Microcosting and resource use analyses were performed on insurance claims to meet the previously defined objectives. This study was population-based. The authors analyzed each single case's consumption of medical services along with multiple hospital admissions and primary care visits. Official pricelists of the Health Insurance Fund at the time of service provision were applied. Discharge invoices delivered to the insurance offices included the exact kind and number of laboratory and imaging diagnostic examinations, physician consultations, pharmaceuticals consumption, surgical services provided and radiation therapy protocols administered. Thus close insight into attending oncologists' prescription habits, patterns of care and direct medical costs became possible. The cost of care was estimated in order to assess cost-of-illness for major malignant diseases together with the most substantial expected budget impact. For all statistical procedures, $p<0.05$ was considered as significant. The influence of patients' age, tumor stage at diagnosis and the presence of metastasis on the total direct medical cost of care and the length of survival was tested using Spearman's rank correlation coefficient, the Kruskal-Wallis and Mann-Whitney test, respectively. The correlation of patients' age with the incidence of particular ICD-10 malignancy groups, as well as the correlation of tumor type or stage with the frequency of hospital admissions and physician consultations, were examined by the Kruskal-Wallis test. Statistical analyses were performed with Statistica version 7.1 (21).

Results

The study sample consisted of 1222 cancer patients (52% male), with a median age of 64 years (range 12-90). Primary tumor locality according to ICD-10 diagnostic groups is presented in detail in Figure 1. Out of those, locally advanced disease (stages 0, I and II) and metastatic cancer (stages III and IV) were present in 138 and 246 patients, respectively. The majority (n=838) of patients had no precise staging information. During the study period, 151 patients died. The

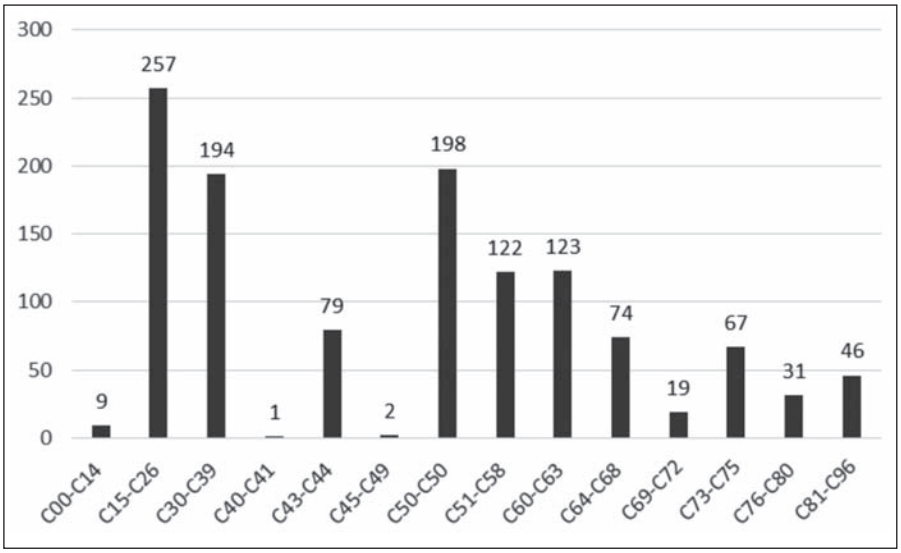

Figure 1. ICD-10 diagnosis structure of the sample (primary tumor site locality).

***Legend : Malignant neoplasm grouping according to ICD-10 :**
C00-C75 Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, hematopoietic and related tissue
C00-C14 Malignant neoplasms of lip, oral cavity and pharynx
C15-C26 Malignant neoplasms of digestive organs
C30-C39 Malignant neoplasms of respiratory and intrathoracic organs
C40-C41 Malignant neoplasms of bone and articular cartilage
C43-C44 Melanoma and other malignant neoplasms of skin
C45-C49 Malignant neoplasms of mesothelial and soft tissue
C50-C50 Malignant neoplasm of breast
C51-C58 Malignant neoplasms of female genital organs
C60-C63 Malignant neoplasms of male genital organs
C64-C68 Malignant neoplasms of urinary tract
C69-C72 Malignant neoplasms of eye, brain and other parts of central nervous system
C73-C75 Malignant neoplasms of thyroid and other endocrine glands
C76-C80 Malignant neoplasms of ill-defined, secondary and unspecified sites
C81-C96 Malignant neoplasms, stated or presumed to be primary, of lymphoid, hematopoietic and related tissue
C97-C97 Malignant neoplasms of independent (primary) multiple sites

length of survival within the first year from diagnosis, the top five morbidity causes, as well as the most frequent mortality causes and metastatic tumor localities, are shown in Table 1.

Duration of observation varied depending on the diagnosis date 0.47±0.29 years) or 170±106 days (1-363) (mean ± [SD]. The total financial value of medical services provided for all study subjects during their initial phase diagnostics and treatment was € 8,354,808. Primary care accounted for € 18,531 (2%), hospital outpatient care for € 723,469 (9%) and hospital inpatient care for € 7,446,029 (89%). Average costs per patient were € 6,837±€ 24,523; (€ 1-€ 438,042). On average outpatients saw their attending physician (oncologist) 8.14±19.70 times and had 7.31±31.47 inpatient physician consultations. Patients were subject to an average of 0.32±2.38 surgical treatments of primary tumor site or metastatic localisations (Table 2).

There were 151 deceased patients. Their average survival time from the first cancer diagnosis was 75±109 days (6-489). The costs for the deceased of € 6,949±€ 36,414 per patient, accrued within 2.5 months on average compared to 6 months among survivors. These cost of terminal care was thus approximately twice as high as the mean initial costs of oncology care for survivors. The worst survival rates were observed among patien suffering from malignant neo-

Table 1. Patients' demographic profile and medical background.

	Survivors		Deceased		Total	
Total Sample	1071	88%	151	12%	1222	100%
Age at diagnosis (mean±StDev; CI95)	63±12	(62-64) 63	67±10	(66-69) 67	63±12	(63-64) 64
Median Sex (male/female)	540/530		96/54			636/585
Length of observation/survival within 01.01.2010-31.12.2011 time span (days) (N;CI95%)	179±106	(162-196)	75±109	(57±92)	170±106	164-176
Stage at diagnosis						
Carcinoma "in situ" (intraepithelial lesion)	12	1%	0	0%	12	1%
Cancer localized within primary tissue/organ of origin	62	6%	2	1%	64	5%
Locally advanced malignancy	56	5%	6	4%	62	5%
Locally advanced malignancy (spreading to the nearby lymph nodes)	68	6%	8	5%	76	6%
Presence of distant metastasis	102	10%	68	45%	170	14%
Unstaged Malignancies	771	72%	67	44%	838	69%
Top five morbidity causes (ICD-10)						
C50.9 (Malignant neoplasm of breast, unspecified)	168	16%	12	8%	180	15%
C61 (Malignant neoplasm of prostate)	113	11%	10	7%	123	10%
C20 (Malignant neoplasm of rectum)	80	7%	10	7%	90	7%
C34.9 (Malignant neoplasm of bronchus or lung, unspecified)	70	7%	42	28%	112	9%
C73 (Malignant neoplasm of thyroid gland)	66	6%	1	1%	67	5%
Top five mortality causes (ICD-10)						
C34.9 (Malignant neoplasm of bronchus or lung, unspecified)	N/A	N/A	42	28%	42	28%
C50.9 (Malignant neoplasm of breast, unspecified)	N/A	N/A	12	8%	12	8%
C61.9 (Malignant neoplasm of prostate, unspecified)	N/A	N/A	10	7%	10	7%
C20.9 (Malignant neoplasm of rectum, unspecified)	N/A	N/A	10	7%	10	7%
C80.9 (Malignant neoplasm, without specification of site, unspecified)	N/A	N/A	9	6%	9	6%
Top five metastatic tumor localities (ICD-10)						
Intrahepatic bile duct	33	3%	21	14%	54	4%
Axillary and upper limb lymph nodes	42	4%	0	0%	42	3%
Brain, unspecified	12	1%	11	7%	23	2%
Lymph node, unspecified	17	2%	2	1%	19	2%
Bronchus or lung, unspecified	6	1%	9	6%	15	1%

Table 2. Costs attributed to the main ICD-10 malignancy groups– mean cost per patient observed, rounded to full Euro 2011 values.

M±SD per patient; (Min-Max); CI95%	Age at diagnosis	N° (%)	Primary Care Costs (€)	Hospital Outpatient Costs (€)	Hospital Inpatient Costs (€)	Total Costs per Patient (€)	Average duration of observation (Days)
C00-C14 Malignant neoplasms of lip, oral cavity and pharynx	64±9 (55-85)	8 (1%) 29-81	31±72 (0-207)	202±373 (0-895) 0-461	555±730 (0-2120) 49-1061	789±624 (123-2120) 356-1222	131
C15-C26 Malignant neoplasms of digestive organs	67±10 (32-90)	257 21%	134±273 (0-1952) 0-3477	457±911 (0-5973) 346-568	5031±27563 (0-438042) 1661-8401	5622±27664 (70-438042) 2240-9004	176
C30-C39 Malignant neoplasms of respiratory and intrathoracic organs	65±6 (12-84)	196 16% 41-89	65±175 (0-1191) 9-43	26±123 (0-1280) 1710-2528	2119±2919 (0-16683) 1801-2621	2211±2929 (2-16684)	173
C40-C41 Malignant neoplasms of bone and articular cartilage	78	1 0%	0	0	64	64	224
C43-C44 Melanoma and other malignant neoplasms of skin	69± 11 (41-88)	77 6%	6±10 (0-67) 4-8	21±129 (0-1105) 0-50	377±484 (0-2238) 269-485	403±493 (187-2238) 293-513	166
C45-C49 Malignant neoplasms of mesothelial and soft tissue	59±6 (56-66)	3 0%	0 (0-0) 0	6±11 (0-19) 0-18	721±226 (460-872) 465-977	727±231 (460-872) 465-989	102
C50-C50 Malignant neoplasm of breast	59±12 (28-88)	198 16%	155± 262 (0-1373) 118-192	95±304 (0-1801) 53-137	17,205±27,053 (0-154,134) 13,437-20,973	17,456±27,149 (6-154,170) 13,675-21,237	186
C51-C58 Malignant neoplasms of female genital organs	58±12 (32-85)	122 10%	120 ± 197 (0-869) 85-155	107 ± 261 (0-1,858) 61-153	2,033±3,133 (0-12576) 1,477-2,589	2,260±3,275 (2-13,234) 1,679-2,841	171
C60-C63 Malignant neoplasms of male genital organs	72±8 (53-88)	123 10% 503-695	599± 542 (0-2,889) 3,196-4,312	3,754±3,157 (0-14,879) 3,188-15,196	9,192±33,972 (0-376,721) 7,264-19,826	13,545± 35,544 (174-393,765)	207
C64-C68 Malignant neoplasms of urinary tract	65±10 (32-83)	74 6%	82±157 (0-1,007) 46-118	244±352 (0-1,858) 164-324	501±987 (0-4,567) 276-726	827±1,051 (2-4,990) 587-1,067	168
C69-C72 Malignant neoplasms of eye, brain and other parts of central nervous system	58±14 (21-80)	19 2%	22±81 (0-353) -14-58	5±19 (0-83) -4-14	24,507±100,152 (0-438,042) -20,527-69,540	24,534±100,145 (9-438,042) -20,496-65,564	196
C73-C75 Malignant neoplasms of thyroid and other endocrine glands	53±12 (21-75)	67 5%	93±350 (0-2,876) 9-177	1,196±1,251 (0-7,752) 897-1,495	2124±1634 (0-6,385) 1,733-2,515	3,413±2,389 (78-10,628) 2,841-3,985	200

(continued)

Table 2. Costs attributed to the main ICD-10 malignancy groups– mean cost per patient observed, rounded to full Euro 2011 values.

M±SD per patient; (Min-Max); CI95%	Age at diagnosis	N° (%)	Primary Care Costs (€)	Hospital Outpatient Costs (€)	Hospital Inpatient Costs (€)	Total Costs per Patient (€)	Average duration of observation (Days)
C76-C80 Malignant neoplasms of ill-defined, secondary and unspecified sites	65±9 (50-82)	31 3%	129±454 (0-2,383) -31-289	30±151 (0-841) -23-83	788±3,254 (0-18,120) -357-1,933	947±3,333 (3-18,257) -226-2,120	199
C81-C96 Malignant neoplasms, stated or presumed to be primary, of lymphoid, hematopoietic and related tissue	62±13 (16-82)	45 4%	33±152 (0-1,007) -11-77	98±209 (0-913) 37-159	5,488±11,221 (0-47,773) 2,210-8,766	5,619±11,191 (4-47,901) 2,349-8,889	174
C97-C97 Malignant neoplasms of independent (primary) multiple sites	70	1 0%	0	407	236	643	151

plasms of the thyroid and other endocrine glands, malignant melanoma, female genital organs, and malignant neoplasm without specification of site (Figure 2).

Within primary care, the most financially demanding services were physician consultations and "all other services" (these account for services not directly targeted at oncology care such as screening, general lab tests, etc.), which contributed 34% and 34%, respectively, to all primary care expenditure. In the hospital outpatient setting, the most expensive were radiotherapy procedures, accounting for 53% of the allocated sum, followed by 23% spent on nuclear medicine diagnosis and treatment. In the hospital, 33% of the budget was used for monoclonal antibody therapy, while the second most costly medical service included antineoplastic agents and immunosuppressants with 17% participation (Figure 3).

Analysis of the overall cost distribution revealed that pharmaceuticals, general oncology related medical care and teleradiotherapy procedures were the highest

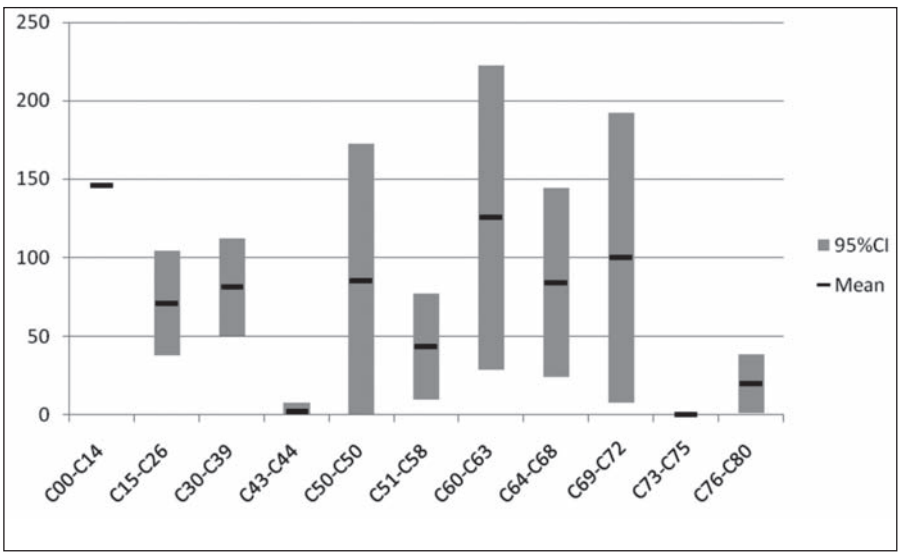

Figure 2. Survival among deceased patients expressed in days across main ICD-10 malignancy groups (mean ± 95% CI) (survivors within observation period excluded from figure).

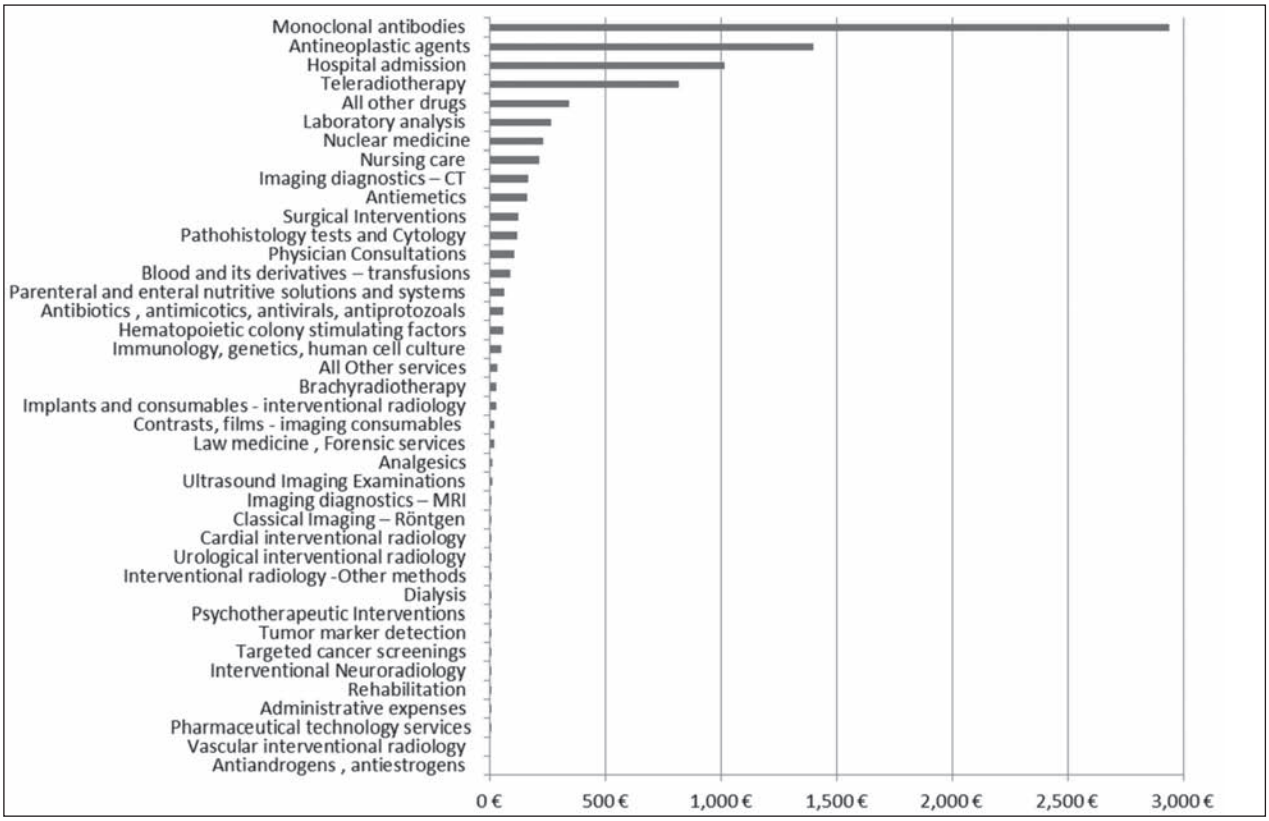

Figure 3. Average costs per patient / per service group *(primary, outpatient and inpatient care presented together).

budget impact medical services, i.e. 27% and 18% of the total budget, respectively (Figure 3).

The distribution of costs attributed to the main ICD-10 diagnostic groups and the detailed direct medical cost matrix across components, are presented in Tables 2-4, respectively. The top five most expensive to treat ICD-10 groups were C69-C72 (mostly brain tumours); C50-C50 (breast); C60-C63 (male genital, mostly prostate cancer); C73-C75 (thyroid and other endocrine glands); C15-C26 (mostly colorectal carcinoma) in declining order of appearance, while the hospital budget impact of the group was considered (Figure 4).

Costs differed by tumor stage at diagnosis. Early stages (Stages 0, I and II observed together) consumed on average € 4,291 while advanced stages, metastatic cancer (Stages IV and V observed together) consumed a total of € 7,934 per patient (Table 4). The combined budget impact of early stage cancer in this sample amounted to the € 592,124 while the advanced stage cancer value was € 1,951,785.

The frequency of outpatient physician consultations was 8.14±19.70 while the number of inpatient physician consultations (mostly attending oncologists) was 7.31±31.47 per patient. Patients received on average 0.32±2.38 outpatient surgical treatments, while there were 124.86±427.73 classical biochemistry-hematology lab analyses and 3.11±7.87 CT imaging examinations per patient. Selected resource use patterns for some services are given in Table 5.

There was no influence by patients' age at diagnosis on the total direct medical cost of care (p=0.81), but a higher age at diagnosis significantly decreased the length of survival (p=-0.16, p=0.047). Neither the total direct medical cost of care (p=0.49), nor the length of survival of those patient who died (p=1.00), were affected by the tumor stage at diagnosis. Similarly, tumor stage did not correlate with the frequency of physician consultations (p=0.17). The frequency of physician consultations differed significantly with regard to the ICD-10 diagnostic group (H=415.86, p<0.0001),

Table 3. Cost matrix of initial phase oncological care - mean cost per patient observed, rounded to full Euro 2011 values.

M ± SD per patient; Min-Max 95%CI	Primary care	Hospital Outpatient	Hospital Inpatient	Total Cost	Total Cost per service group
General - Oncology related medical care					**€ 1,234,465**
Hospital Admission	N/A	N/A	833±2,857 0-55,349	833±2,857 0-55,349	1,017,823
Physician Consultations	51±101 0-1,223	42±105 0-997	32±88 0-1,165	124±214 0-2,220	151,655
Clinical Pharmacology/ Pharmacist services	N/A	0±5 0-177	0±0 0-0	0±5 0-177	248
Rehabilitation services	0	1±11 0	0±11 0-345	0-345	698
Dialysis	N/A	0±2 0	0±2 0-22	0-22	391
Psychotherapy	0±2 0-41	0	0±0 0-2	0±2 0-41	385
Administrative expenses	0	0±1 0	0±1 0-7	0-7	181
All other services (social care , transport, counseling, epidemiological measures...etc.)	51±191 0-2,055	0±3 0-66	0±8 0-228	52±191 0-2,071	63,086
Pharmaceuticals					**€ 4,738,208**
Antineoplastic agents and immunosuppressants	0±1 0-26	0±0 0-2	1,054±5,162 0-101,775	1,054±5,162 1,054±5,162	1,288,196
Monoclonal antibodies	N/A	0	2,026±12,980 0-221,708	2,026±12,980 0-221,708	2,476,113
Analgesic NSAIDs, opioids, others - pain control medicines	1±2 0-23	0±0 0-0	7±23 0-460	8±23 0-460	9,332
Antibiotics, antimicotics, antiviral and antiprotozoal drugs	0±1 0-20	0±3 0-116	64±184 0-1,710	64±185 0-1,710	78,035
Antiemetics	0±0 0-3	0±0 0-0	119±540 0-10,239	119±540 0-10,239	145,856
Parenteral and enteral nutritive solutions and systems	1±4 0-78	1±17 0-533	58±172 0-2,216	60±173 0-2,216	73,269
Hematopoietic colony stimulating factors	N/A	0	42±302 0-5,874	42±302 0-5874	51,760
Antiandrogens , antiestrogens – therapy of steroid dependent carcinoma	N/A	0±1 0	0±1 0-44	0-44	44
Blood and its derivatives – transfusions	N/A	1±4 0-55	73±278 0-4,130	74±278 0-4,130	90,445
All other drugs	2±28 0-978	5±19 0-310	423±1,309 0-17,227	430±1,313 0-17,227	525,157

(continued)

Table 3. Cost matrix of initial phase oncological care - mean cost per patient observed, rounded to full Euro 2011 values.

M ± SD per patient; Min-Max 95%CI	Primary care	Hospital Outpatient	Hospital Inpatient	Total Cost	Total Cost per service group
Laboratory Analysis					**€ 468,789**
Classical Biochemistry and Hematology	17±44 0-402	21±83 0-769	193±633 0-10,700	231±645 0-10,700	281,865
Targeted cancer prevention screenings	0±2 0-31	0±0 0-3	0±0 0-7	0±2 0-34	542
Tumor marker detection		2±9	0±2	0±2	
Pathohistology tests and cytology examinations	0 0±1 0-13	0-98 2±11 0-102	0-27 98±409 0-7,524	0-27 100±410 0-7,524	253 121,990
Immunodiagnostics, genetics, cell culture techniques	N/A	12±64 0-750	27±133 0-2,877	39±158 0-2,877	48,114
Law medicine and Forensic services	N/A	1±6 0-104	12±53 0-954	13±53 0-955	16,025
Surgery					**€ 408,438**
Surgical Interventions	20±65 0-811	1±3 0-47	94±310 0-5,487	115±320 0-5,487	140,535
Nursing care and consumables	4±20 0-282	6±20 0-290	209±618 0-10,912	219±622 0-10,912	267,902
Imaging diagnostics					**€ 564,452**
Classical Imaging diagnostics – Röntgen	1±3 0-35	0±1 0-13	4±12 0-155	4±12 0-159	5,421
Contrasts, films and consumables intended for imaging diagnostics service provision	0	3±12 0-129	16±35 0-571	19±38 0-571	23,431
Ultrasound Imaging Examinations	1±3 0-33	2±6 0-63	0	7±22 0-298	8,801
CT Imaging diagnostics	N/A	43±172 0-2,128	117±296 0-3,357	160±348 0-3,357	195,031
Magnet Resonance Imaging	N/A	2±11 0-148	4±14 0-145	5±18 0-148	6,270
Nuclear medicine diagnostics and treatment	N/A	137±409 0-256	130±638 0-10,498	266±839 0-10,498	325,498
Interventional Radiology					**€ 32,138**
Interventional Neuroradiology services (both diagnostic and treatment)	N/A	0	0±6 0-197	0±6 0-197	197
Cardial interventional radiology	N/A	0±0 0-5	4±19 0-311	3±19 0-311	3,415
Urological interventional radiology	N/A	0±2 0-42	1±6 0-62	1±6 0-62	1,683

(continued)

Table 3. Cost matrix of initial phase oncological care - mean cost per patient observed, rounded to full Euro 2011 values.

M ± SD per patient; Min-Max 95%CI	Primary care	Hospital Outpatient	Hospital Inpatient	Total Cost	Total Cost per service group
Vascular interventional radiology	N/A	0±11 0	0±11 0-261	0-261	522
Interventional radiology -Other methods (biopsies, cyst punctuations, nonvascular int. etc)	N/A	0±1 0-33	0±6 0-138	0±6 0-138	385
Implants and consumables used in interventional radiology services (stents, tools etc.)	N/A	1±10 0-278	20±61 0-929	21±63 0-929	25,936
Radiation Treatment					**€ 906,797**
Teleradiotherapy Procedures in Oncology	N/A	315±1,080 0-11,600	410±1,673 0-29,332	725±2,167 0-32,593	885,998
Brachyradiotherapy (intracavitary) Procedures in Oncology	N/A	17±207 0	17±207 0-4,538	0-4,538	20,799
Total Costs	92±321 (0-2889) 74-111	502±1,578 (0-14,879) 413-590	7,926±24,176 (0-438,042) 6,571-9,282	6,837-24,523 (1-438042) 5462-8212	**€ 8,154,214**

with the maximum need for consultations reported for malignant neoplasms of male genital organs and digestive organs, respectively. The presence of metastasis did not affect the total direct medical cost of care (p=0.78) or the length of survival (p=0.08). There was no difference observed between patients diagnosed with locally advanced disease and with metastasis in terms of cost of oncological medical care (p=0.42), laboratory analyses (p=0.22), imaging diagnostics (p=0.92), interventional radiology (p=0.59), surgery (p=0.43), radiation treatment (p=0.29) or pharmaceuticals (p=0.41). Cost differentials among primary, hospital outpatient and hospital inpatient care are presented in Figure 5.

Discussion

The results presented point to substantial differences in cost per patient among the main ICD-10 malignancy groups as well as between early and advanced stage carcinoma. One recently published preparatory pilot study on cancer expenditure in Serbia reported a continuing rise in the overall financial burden of cancer care (by almost one third in domestic currency) in the 2007-2010 time span (22). The results of the current study essentially confirm the hypothesis of far more expensive cancer medical care compared to the other main "prosperity" diseases in Serbia (23-26). High out-of-pocket expenses mostly covering outpatient drug acquisition (27), complementary and alternative medicine treatments (28) and informal payments, pose some well-known serious issues of access equity and affordability among lower income citizens (29). These out-of-pocket expenses largely remain uncovered by average citizen's insurance package both in Serbia and elsewhere in the region (17).

Two particularly sensitive issues are the impact of patient age (30) and tumor clinical stage at diagnosis (31) on the overall long-term cost of care. Our results showed there were no higher overall costs of care for the elderly than for younger age groups (Spearman, p=0.81; Mann Whitney comparison of total costs 1st-4th vs 5th - 9th life decade, p=0.36). This finding should be taken cautiously due to the fact that we observed initial care in most patients on average over the first six months after the cancer diagnosis date. More advanced stages of malignant disease at initial detection were clearly associated with higher costs of care and

Table 4. Cost comparison dependent on tumor clinical stage upon detection - mean cost per patient observed, rounded to full Euro 2011 values.

M ± SD per patient; (Min-Max); 95% CI	Locally Advanced Malignancy (Stages 0, I and II)	Metastatic Malignancy (Stages III and IV)	Total Sample (inclusive of unstaged patients)
Oncology Nursing Care	829±1,567 (0-12,588) 568-1,090	1,151±3,816 (0-56,427) 674-1,628	1,023±3,003 (0-56,427) 855-1,191
Laboratory Analysis	291±585 (0-3,472) 193-389	417±1,304 (0-18,862) 254-580	371±1,045 (0-18,862) 312-430
Imaging Diagnostics	359±576 (0-2,780) 263-455	308±513 (0-2,780) 244-372	462±965 (0-13,471) 408-516
Interventional Radiology	29±79 (0-577) 28-42	26±89 (0-1,243) 15-37	25±79 (0-1,243) 21-29
Surgery	294±591 (0-2,719) 95-393	364±1,165 (0-16,399) 218-510	334±919 (0-16,399) 282-386
Radiation Treatment	556±1,167 (0-7,968) 361-751	666±2,231 (0-29,332) 520-812	742±2,180 (0-32,593) 620-864
Pharmaceuticals	2,042±6,849 (0-49,735) 899-3,185	5,197±22,677 (0-313,930) 2,363-8,031	3,877±18,106 (0-313,930) 2,862-4,892
Mean Total Cost per Patient	4,396±9,457 (2-61,907) 2,818-5,974	8,129±30,854 (1-438,042) 4,273-11,985	6,837±24,522 (1-438,042) 5,462-8,212
Total Cost (population observed)	€ 592,124	€ 1,951,785	€ 8,154,214

poor prognosis (32). Our mean values, consistently with previous findings, showed that Stages 0, I and II exhibited substantially lower average costs of initial phase care than Stage IV and V detected patients. Nevertheless this differential turned out to be statistically insignificant. This is in contrast with the strong correlation reported for colon and breast cancer by (33). These findings could be explained by the great malignancy diversity and rather limited time horizon of the study. Approximately 88 % of patients who survived in the first year after diagnosis is slightly above the broad projections for first-year survival elsewhere in Europe, such as 67 % in men and 77 % for women, reported in Switzerland (34).True survival rates in the Balkans probably lag behind high income EU countries. This distorted view is created by the fact that due to administrative delay in database updating, many deaths happening early in 2012, and therefore though referring to 2011 diseased patients, were actually not recorded punctually.

If we observe the cost structure reported, we notice the clear dominance of pharmaceuticals, oncology medical care and radiation therapy in the direct medical cost structure of our patient cohort. Radiation treatment due to its demanding cost of supply and huge budget impact is a particularly hot topic among low and middle income countries' policy makers (35). Radiation therapy procedures' cost-effectiveness can be properly assessed in a well designed setting (36) and in many of these proved to give satisfactory value

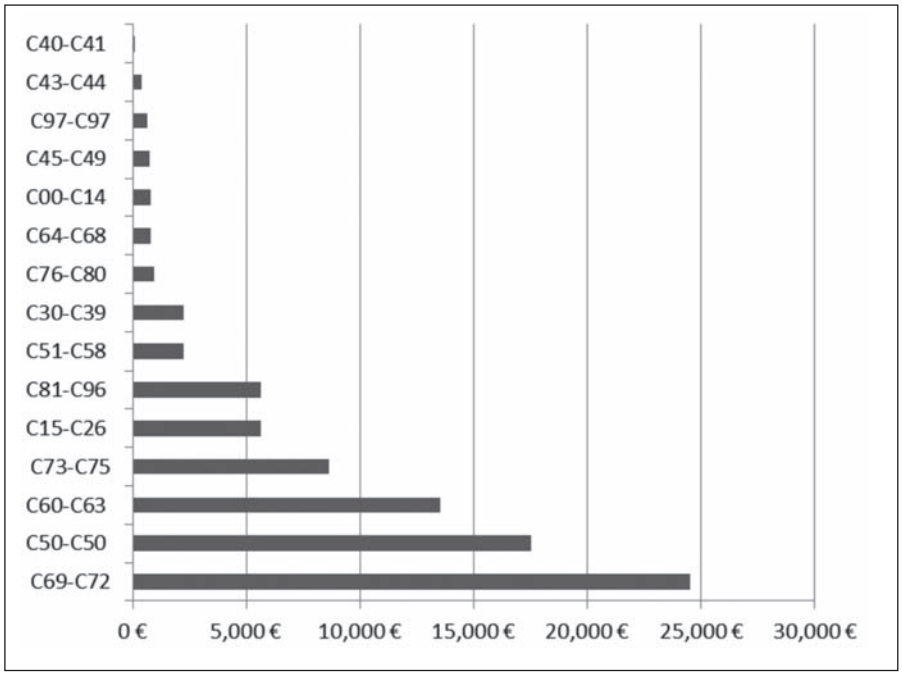

Figure 4. Cost matrix for main ICD-10 malignancy groups (mean cost per patient presented.

Table 5. Resource use patterns - unit consumption of selected services.

Medical Service	M ± SD per patient/year; (Min-Max)
Inpatient Physician Consultations (Oncologist)	7,31±31,47 (0,00-534,00)
Outpatient examinations by attending physician (Oncologist)	8,14±19,70 (0,00-284,01)
Clinical Pharmacologist Consultations	0,00±0,10 (0,00-2,00)
Psychiatrist Consultation	0,00±0,06 (0,00-1,00)
Classical Biochemistry and Hematology	124,86±427,73 (0,00-7837,00)
Targeted cancer prevention screenings	0,01±0,09 (0,00-2,00)
Immunodiagnostics, genetics, cell culture techniques	1,56±6,03 (0,00-102,00)
Surgical Procedures (Outpatient)	0,32±2,38 (0,00-50,00)
Dialysis	0,56±2,84 (0,00-38,00)
Classical Imaging diagnostics – Röntgen	1,56±5,26 (0,00-83,00)
Ultrasound Imaging Examinations	0,56±1,72 (0,00-25,00)
CT Imaging diagnostics	3,11±7,87 (0,00-89,00)
Magnet Resonance Imaging	0,09±0,37 (0,00-4,00)
Interventional Neuroradiology services	0,00±0,03 (0,00-1,00)
Cardial interventional radiology	0,12±0,52 (0,00-6,00)
Urological interventional radiology	0,30±1,32 (0,00-22,00)
Vascular interventional radiology	0,01±0,16 (0,00-4,00)
Interventional Radiology -Other methods (biopsies, cyst punctuations, nonvascular int. etc)	0,07±1,16 (0,00-27,00)
Brachyradiotherapy (intracavitary) Procedures in Oncology	0,02±0,19 (0,00-4,00)
Monoclonal Antibodies (standard doses used)	1,26±7,69 (0,00-124,00)
Rehabilitation Services	0,11±1,34 (0,00-30,00)

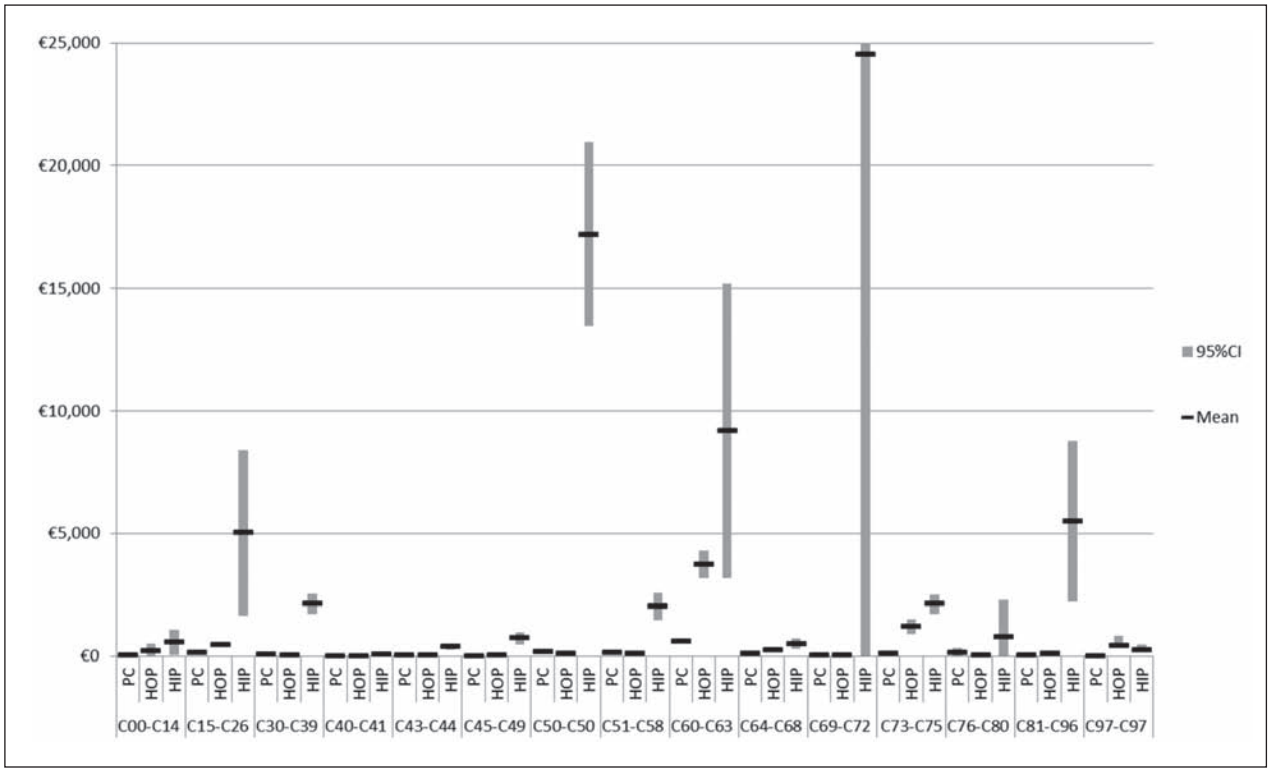

Figure 5. Box Plot presenting values of Primary Care – PC; Hospital Outpatient – HOP; Hospital Inpatient – HIP costs per patient /major ICD-10 malignancy group.
* (C69-C72 - Brain tumors as extreme outliers were presented by mean and lower confidence interval limit only, due to the extremely large CI95% span)

for money (37). Thanks to medical technology from humanitarian aid programmes, the pressure to provide access to radiation therapy in Serbia has been relieved during the past decade (38). The substantial drug utilization volume relates to the problems of chemotherapy toxicity and coping with its adverse effects (39). The serious and unfortunately very common occurrence of febrile neutropenia demands the administration of costly colony-stimulating factors (40). The most far-reaching budget impact among pharmaceuticals is attributed to monoclonal antibody administration (41). Serbia's current restrictive Insurance Fund reimbursement policy limits the availability of these agents. Nevertheless ongoing positive macroeconomic developments in the market are likely to foster further growth of consumer demand in the region.

The reported resource use and expenditure attributed to certain ICD-10 malignancy codes is rather modest compared to the published estimates in mature markets. This is mostly due to substantially higher labor wages in the West (42). Nevertheless there is some, limited evidence on the cost of illness coming from the broader region, particularly on testicular cancer in Ukraine (43), oral carcinoma in Greece (44) and lung cancer in Turkey (45). One commonly noticed pattern is that values from the Commonwealth of Independent Nations are lagging behind Balkan values, while Mediterranean assessments belong to a similar scale, taking into account the chronological distance among data.

The indirect costs due to lost productivity, which in most high income economies heavily outweigh the direct cost of care, were not considered, in view of the Payer's perspective adopted in this study (46). So far one major Polish study has provided assessment of cancer-related productivity losses in the region (10). This contributes to the widespread perception of cancer morbidity being an outstanding consumer of na-

tional health budgets worldwide (47). The combined budget impact of this patient cohort and our mean costs over the first six months of medical care far outstrip the values (€ 7600-€ 8100 in Serbia, 5-year projection) reported for ovarian cancer in the Central and Eastern Europe region by Kim K *et al.* (48). The reason for such inconsistency probably lies in the fact that these assessments were based on the Delphi panel method while our study provides in-depth microcosting in the real world setting.

Study limitations

Out of the initial prevalence pool of approximately 8.500 patients in the region only 1.222 incidence cases were ultimately analyzed. The reason for this was the fact that the most intensive laboratory and imaging diagnostics (49), as well as pharmacological, surgical and radiation treatment protocols are being applied from a few weeks up to several months after initial diagnosis. Another chronological concentration of medical resource consumption belongs to the terminal months of life and palliative care (50). In order to avoid handling patient files in their clinically quiet, reemission stage of disease, the authors decided to focus on newly diagnosed patients.

Some 2.035 patients were eliminated due to the fact they have received tertiary care in one of the remaining 6 tertiary care facilities in the country, most of them in the capital, Belgrade. Lacking insight into their Insurance claims, the authors were forced to abandon these cases due to incomplete data. Only those 1.222 cases with complete records in terms of clinical, epidemiology data and resource use were selected for final analysis.

The Central Serbian region may be regarded as a source of disputable external validity due to the limitation of geographic heterogeneity of sampling throughout the country (51). Nevertheless official Public Health Institute of Serbia data provide evidence of similar incidence rates for major malignant disorders among the country's various regions.

Indirect costs of lost productivity were not measured or assessed in this study. This means that any complete real world assessment of the cost of cancer care would very likely provide at least twice as high values as the ones reported (52). Such estimates could be obtained from published data in similar middle income Eastern European settings (53). The core reason for not making this effort lies in the fact that the authors adopted the Payer's perspective. This approach does neatly reflect the rising issue of out-of-pocket expenses and cancer affordability for the lower income European citizens.

Extensive prospective research on the impact of policy measures to contain the cost of oncology treatment protocols will be essential in the future of the Balkans region.

Conclusion

Our findings imply points of obvious assymetry and considerable differences in the initial costs of oncology care between the main ICD-10 malignancy groups. Some of the most expensive to treat diagnoses in terms of cost per patient, were in decreasing order of appearance: C69-C72 Malignant neoplasms of the eye, brain and other parts of the central nervous system; C50 - Malignant neoplasm of the breast; C60-C63 Malignant neoplasms of male genital organs; C81-C96 Malignant neoplasms, stated or presumed to be primary, of lymphoid, hematopoietic and related tissue and C15-C26 Malignant neoplasms of the digestive organs. Such a landscape of resource use for individual cancers, previously unknown in Southeastern Europe, would allow for more targeted, evidence-based allocation of resources in line with contemporary epidemiology and the predicted demand for services. The second most important finding is the high proportion of pharmaceutical costs, 57 % , an unprecedented value compared to high income neighbors. A large part of these are actually the cost of monoclonal antibody administration (30 % of total cost of care). Thus drug pricing, reimbursement policy and the dissemination of cost-effectiveness evidence on major treatment protocols may be essential in this European region (54). These policy measures would be potentially far more important in improving outcomes and decreasing the cost of care than in a western European clinical setting (55). The fact revealed by previous research that advanced stage cancer patients have more complex needs

and more costly care is confirmed by our mean and total values.

Although the population targeted by the study comprised newly diagnosed cases and their initial diagnosis and treatment costs, some 12 % patients (151 cases) died in their first year from diagnosis. Due to metastasis and advanced tumor stage these patients ended their lives rather soon, most of them within the first 2.5 months from diagnosis.

Knowledge on the diversity of resource use patterns and the costs attributed to particular cancer forms in Serbia may be partially generalizable to the other national health systems of the Western Balkans region. This may be expected, since Serbia serves as a model for the exposed weaknesses of the post-socialist health system transformation and its downside effects, which are typical of a wider Eastern European context (17). The essential question of transferring cost-effectiveness estimates coming from developed markets into middle and low income economies will remain high on the agenda in the future (42). Eastern European policy makers are slowly becoming aware of the need to fund and conduct field assessments in these countries, taking into account the unique local cost drivers, patterns of practice and stakeholders interests. More ambitious research on service utilization patterns and the cost of cancer care will become a growing need throughout low and middle income countries worldwide in the near future (56, 57). Evidence based resource allocation in line with market demand for medical services and cost-effectiveness estimates would provide improved value for money in the Balkans oncology.

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