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End-of-life costs of medical care for advanced stage cancer patients

Medicinski troškovi palijativne nege bolesnika sa karcinomom

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Abstract

Background/Aim. Cancer, one of the leading causes of mortality in the world, imposes a substantial economic burden on each society, including Serbia. The aim of this study was to evaluate the major cancer cost drivers in Serbia. **Methods.** A retrospective, in-depth, bottom-up analysis of two combined databases was performed in order to quantify relevant costs. End-of-life data were obtained from patients with cancer, who deceased within the first year of the established diagnose, including basic demographics, diagnosis, tumour histology, medical resource use and related costs, time and cause of death. All costs were allocated to one of the three categories of cancer health care services: primary care (included home care), hospital outpatient and hospital inpatient care. **Results.** Exactly 114 patients were analyzed, out of whom a high percent (48.25%) had distant metastases at the moment of establishing the diagnosis. Malignant neoplasms of respiratory and intrathoracic organs were leading causes of morbidity. The average costs *per* patient were significantly different according to the diagnosis, with the highest (13,114.10 EUR) and the lowest (4.00 EUR) ones observed in the breast cancer and melanoma, respectively. The greatest impact on total costs was observed concerning pharmaceuticals, with 42% of share (monoclonal antibodies amounted to 34% of all medicines and 14% of total costs), followed by oncology medical care (21%), radiation therapy and interventional radiology (11%), surgery (9%), imaging diagnostics (9%) and laboratory costs (8%). **Conclusion.** Cancer treatment incurs high costs, especially for end-of-life pharmaceutical expenses, ensued from medical personnel tendency to improve such patients' quality of life in spite of nearing the end of life. Reimbursement policy on monoclonal antibodies, in particular at end-stage disease, should rely on cost-effectiveness evidence as well as documented clinical efficiency.

Key words:
health care costs; serbia; carcinoma; drug therapy; antibodies, monoclonal; terminal care.

Apstrakt

Uvod/Cilj. Maligna oboljenja jedan su od vodećih uzroka smrtnosti u svetu, čije lečenje ima veliki finansijski uticaj na budžete zdravstvenih sistema svakog društva, uključujući Srbiju. Cilj ovog rada bio je da se odredi strukutura najvećih troškova tokom lečenja obolelih od karcinoma u Srbiji. **Metode.** Retrospektivna analiza baze podataka tipa "odozdonagore" sprovedena je da bi se kvantifikovali relevantni troškovi. Analizirani su podaci bolesnika koji su preminuli tokom prve godine nakon postavljanja dijagnoze: demografski podaci, dijagnoza, histologija tumora, troškovi upotrebe svih medicinskih usluga, vreme i uzrok smrti. Svi troškovi su pridodati jednoj od tri kategorije lečenja: primarna, vanbolnička i bolnička nega. **Rezultati.** Analizirana su 114 bolesnika, pri čemu su najveći deo činili bolesnici sa prisutnim udaljenim metastazama u trenutku postavljanja dijagnoze (48,25%). Vodeći uzrok smrtnosti bili su maligniteti respiratornih organa. Prosečni troškovi po bolesniku bili su značajno različiti u odnosu na vrstu karcinoma, pri čemu su najveći troškovi zabeleženi kod bolesnica sa tumorom dojke (13 114,10 EUR), a najniži kod bolesnika sa melanomom (4,00 EUR). Najveći finansijski uticaj na ukupne troškove odnosio se na lekove, 42% (među njima, troškovi za monoklonska antitela iznosili su 34% sredstava, ili 14% u odnosu na ukupne troškove), zatim troškovi za medicinsku negu u onkologiji (21%), terapiju zračenjem i intervencijsku radiologiju (11%), hirurgiju (9%), dijagnostiku snimanjem (9%) i laboratorijske troškove (8%).

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Zaključak. Lečenje obolelih od karcinoma uključuje velike troškove, posebno za lekove za bolesnike u terminalnom stadijumu bolesti, uz nepredvidiv ishod lečenja. Unapređivanjem i finansiranjem programa za ranu detekciju bolesti i odgovarajućom politikom refundiranja na nacionalnom nivou (npr. troškova lečenja monoklonskim antitelima) moglo bi se očekivati više koristi i manje ekonomskog opterećenja društva troškovima za lečenje malignih oboljenja.

Ključne reči:
zdravstvena zaštita, troškovi; srbija; karcinomi; lečenje lekovima; antitela, monoklonska; nega, terminalna.

Introduction

Cancer is one of the most important world public health concerns and the leading cause of mortality in the developed world [1]. It is estimated that the number of global cancer deaths will increase from 7.4 million in 2004 to 11.8 million in 2030 [2]. In the European region, mortality of cancer amounted for 166 *per* 100,000 inhabitants, in the year 2008, and the number of cancer cases will probably increase for 40% in most of these countries, in 2015 [3, 4]. High mortality rates were also observed in the rest of the world, with the exceptions of South-East Asia and South-Mediterranean Region, where mortality rates of cancer in the year 2008 amounted for 125 and 127 *per* 100,000 inhabitants, respectively [3].

Recent Serbian history and its geographical location determine its, to some extent, peculiar situation at the Continent. In the last three decades, several ecological accidents occurred in the region, starting with Chernobyl disaster. Military conflicts, involving problems of depleted uranium during NATO bombing campaign, post-war syndrome and problems of post-communist society, which led to elevated levels of anxiety and mood disorders in general population [5], probably significantly contributed to rising cancer incidence rates in some malignant neoplasms [6, 7]. In the nation-wide population-based cancer data for Serbia, a significant increase in overall cancer incidence and mortality within the observed 10-year period (1999–2009) was found, as well as the alarmingly high mortality rates in Serbia compared to the rest of Europe [7]. In the 2009, cancer mortality rate amounted 181.1 for men and 113.8 for women, *per* 100,000 inhabitants. In the same period, lung cancer showed the highest incidence rate among men, achieving 70.8/100,000 among male population, and the most common cancer among women was breast cancer, with the same incidence rate among female population [7]. Furthermore, lung cancer is the fourth of ten most common causes of death by disease, gender and age among the Serbian population in 2012 [8].

Malignant diseases impose a substantial economic burden on each society. According to the US National Institute of Health, Americans spent 77.4 billion dollars for direct medical costs for cancer care, in the year 2008 [9]. There are published estimates that one third of all aforementioned costs of cancer treatment incur in the final year of disease and almost 80% of that amount is spent in the last month [10]. In the European Union (EU), health cancer costs reached 51 billion euro, with health care accounting for 40% in 2009 [11].

Serbian health system practice and its financing are predominantly hospital-oriented [12]. Therefore, there is necessity to evaluate major cancer cost drivers in order to achieve more efficient health policy strategies.

The aim of this study was to assess major cancer cost drivers in Serbia. Two major research questions were discussed, namely whether there is a cost difference among the patients at primary care, hospital inpatient and hospital outpatient care, as well as on the major cost drivers.

Methods

Study design and patients selection

A retrospective data base analysis was utilized in order to answer to the relevant research questions [13]. An in-depth bottom-up analysis of consumption patterns and service provision expenses related to cancer diagnosis, treatment and related issues was conducted from the third party payer's perspective, i.e. from the national Republic Fund of Health Insurance (RFHI). The wide proportions of costs in Serbia also comprise out-of-pocket patients' expenditure [14], but these and indirect, loss productivity related costs, remain out of the scope of this study.

Two national cancer databases were reviewed, concerning newly diagnosed patients from the Central Serbia region, which can be regarded representative of national cancer incidence and prevalence rates [15]. They were treated in the university tertiary health care hospital, in a 2-year period (January 1, 2010–Decembar 31, 2011). Those were RFHI database and Oncology registry of morbidity and mortality, provided by the Institute of Public Health of Serbia "Dr Milan Jovanović - Batut", Belgrade. Out of the 1st database were collected information on medical costs and consumption, and the 2nd database supplemented the clinical and epidemiological evidence for the same patients. In total, for 1,222 patients completed data emerged from combining both databases. Out of them, patients were selected, who were newly diagnosed and deceased within the observed period (i.e. all of them deceased within the first year since the diagnosis was established). For some of them, discrepancy of two databases occurred, i.e. cancer incidence date was closely approaching the date of death, which was clarified by the clerks in charge by data handling procedure. Due to these reasons and other minor lacking data, 37 cases out of 151 deceased were eliminated. In total, 114 complete patient files remained to be analysed [15].

Structure and pricing of the used recourses

Each patient received initial chemotherapy, surgical and/or radiation treatment, according to the attending oncolo-

gist's recommendations following confirmed diagnosis, malignancy stage and grade determination [16]. Basic demographics, diagnosis, tumour histology and clinical stage at diagnosis, medical recourse use, related costs, time and cause of death were obtained for each patient. The structure of calculated costs is shown in Figure 1.

The official RFHI pricelist was applied at the time of the service provision. Exchange rates were calculated according to average official exchange rates of the National Bank of Serbia during the observed period (1 EUR = 100.60 RSD).

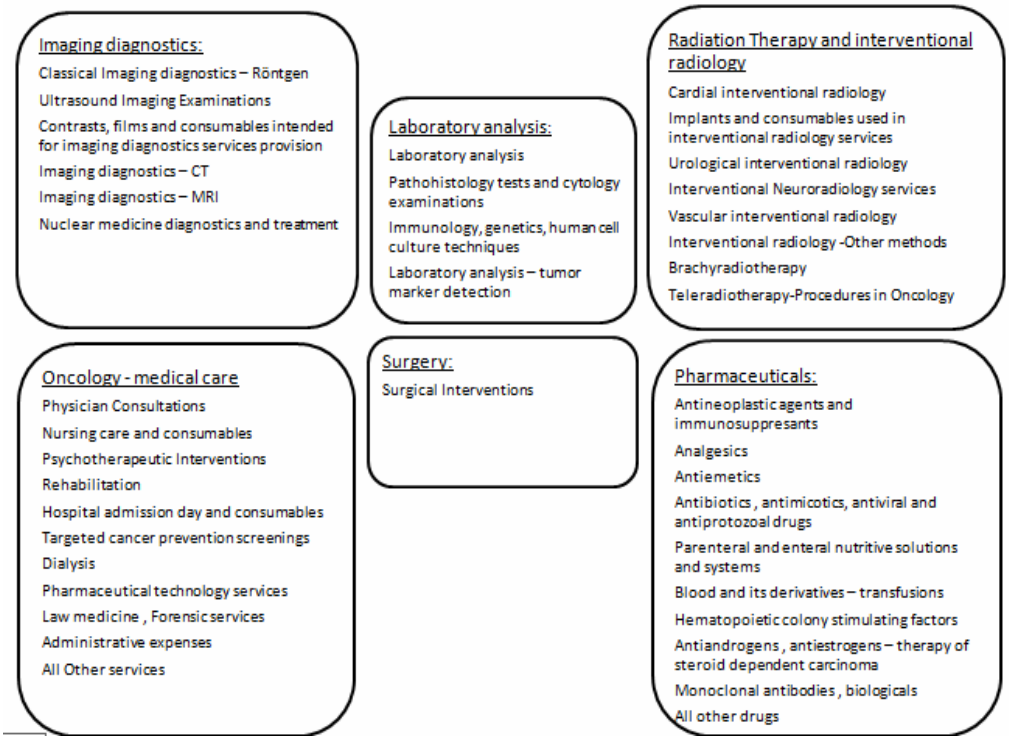


Fig. 1 – Structure of calculated costs for the study subjects

The total health care cost of end of life care was calculated and analysed for the one of the three categories of cancer health care services: primary care (outside the hospital), hospital outpatient and hospital inpatient costs for the observed patients.

Statistical analysis

Categorical variables were presented as frequencies of certain categories, while continuous variables were summarized as mean, standard deviation and 95% confidence interval (CI). The significance of the difference between continual variables was tested by Kruskal-Wallis analysis. The relationship between survival days, total costs and the International Classification of Diseases (ICD-10) diagnosis was tested by Spearman's coefficient of correlation; thereafter, impact of ICD-10 diagnosis and costs on survival was analysed by multiple regression analysis. Statistical analyses were performed using Microsoft Office Excel 2007 and Statistical Software PASW Statistics 18.

The study was conducted in line with The Declaration of Helsinki and has been approved by the regional Ethics Committee of the University Clinical Center Kragujevac, Serbia. Decision number 01-5978 issued on May 28, 2013.

Results

A total number of observed patients, who deceased within the first year from the moment of establishing the diagnosis, were 114 (77 male and 37 female), with the mean age of 67 ± 9 years (mean ± standard deviation). The greatest proportions of them were patients with present distant metastasis at the moment of establishing the diagnosis and the unstaged malignancies (48.25% and 38.60%, respectively) (Table 1).

Table 1

Patients' distribution according to the stage of the disease at the time of establishing the diagnosis of cancer

Cancer stage at the diagnosis	Patients, n (%)
Carcinoma *in situ*	–
Cancer localized within primary tissue/organ of origin	2 (1.75)
Locally advanced malignancy	6 (5.26)
Locally advanced malignancy spreading to the nearby lymph nodes	7 (6.14)
Presence of distant metastasis	55 (48.25)
Unstaged malignancies	44 (38.60)

Most frequent morbidity causes classified according to ICD-10 are shown in Table 2. Malignant neoplasms of respiratory and intrathoracic organs were leading causes of morbidity, followed by malignant neoplasms of digestive organs and breast, accounting for 73% of all the cancer cases.

Table 2
Most frequent types of malignant neoplasms (MNs) causing morbidity in patients

Diagnosis (Diagnosis codes of ICD-10)	Patients, n (%)
MNs of respiratory and intrathoracic organs (C30-C39)	45 (39.47)
MNs of digestive organs (C15-C26)	31 (27.19)
MNs of breast (C50-C50)	7 (6.14)
MNs of female genital organs (C51-C58)	7 (6.14)
MNs of urinary tract (C64-C68)	7 (6.14)
MNs of ill-defined, other secondary and unspecified sites (C76-C80)	6 (5.26)
MNs of male genital organs (C60-C63)	5 (4.39)
MNs, stated or presumed to be primary, of lymphoid, hematopoietic and related tissue (C81-C96)	3 (2.63)
MNs of lip, oral cavity and pharynx (C00-C14)	1 (0.88)
Melanoma and other MNs of skin (C43-C44)	1 (0.88)
MNs of eye, brain and other parts of central nervous system (C69-C72)	1 (0.88)

ICD – International Classfication of Diseases.

Average medical costs *per* patient according to the ICD-10 diagnosis, including CI 95% limits, are shown in Figure 2. They are significantly different among the diagnosis groups (C^2 = 19.307, p = 0.037). The highest cost *per* patient (13,114.10 EUR) was observed in breast cancer (C50-C50), and the lowest cost in melanoma and other malignant neoplasms of the skin (C43-C44) (4.00 EUR).

Average medical costs *per* patient with regards to service groups and according to ICD-10 diagnosis groups were presented in Figure 3. These costs are significantly different according to different kind of services (for primary care C^2 = 33.533, $p < 0.001$; hospital outpatient care C^2 = 51.231, $p < 0.001$; hospital inpatient care C^2 = 23.006, p = 0.011).

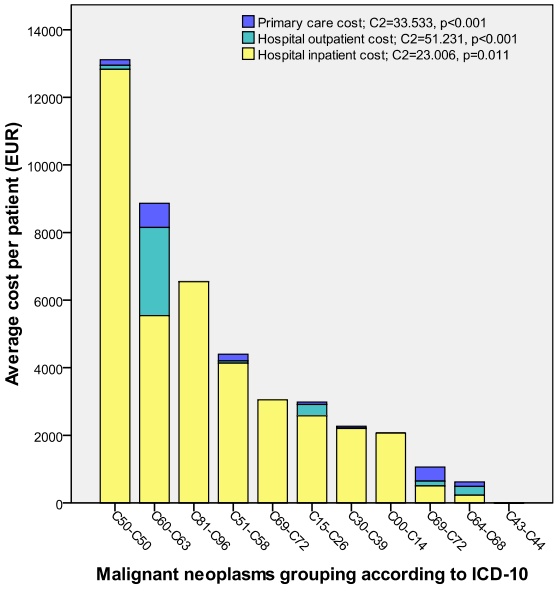
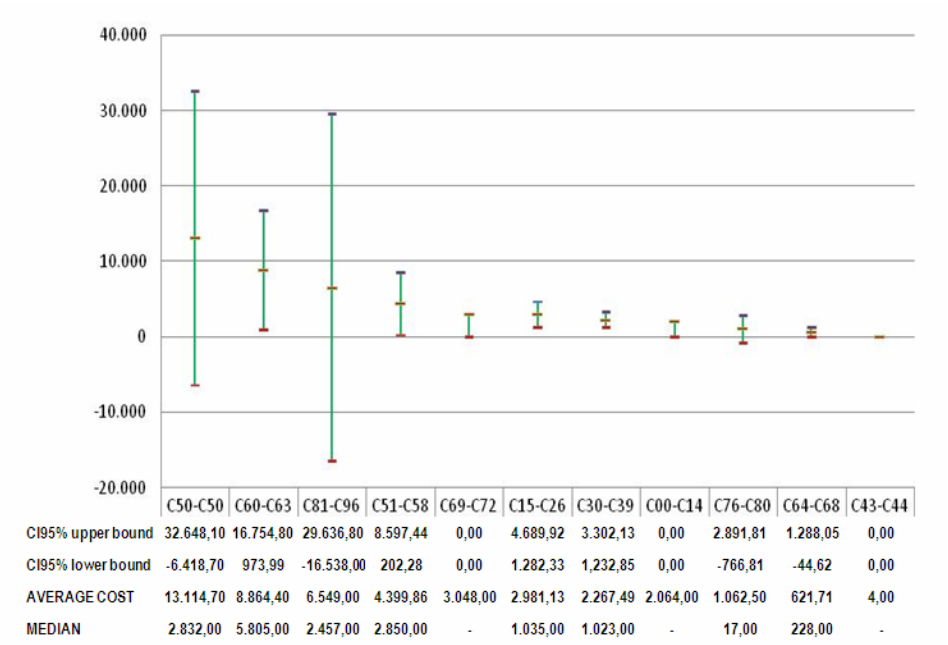


Fig. 3 – Average medical cost (EUR) *per* patient according to International Classification of Diseases (ICD)-10 and the groups of services (primary care, hospital outpatient and hospital inpatient care).
The ICD-10 code groups are explained in Table 2.

The greatest impact on total medical costs was observed concerning pharmacotherapy cost. Share of pharmaceuticals cost was 42.37% [monoclonal antibodies (MABs) amounted



	C50-C50	C60-C63	C81-C96	C51-C58	C69-C72	C15-C26	C30-C39	C00-C14	C76-C80	C64-C68	C43-C44
CI95% upper bound	32.648,10	16.754,80	29.636,80	8.597,44	0,00	4.689,92	3.302,13	0,00	2.891,81	1.288,05	0,00
CI95% lower bound	-6.418,70	973,99	-16.538,00	202,28	0,00	1.282,33	1,232,85	0,00	-766,81	-44,62	0,00
AVERAGE COST	13.114,70	8.864,40	6.549,00	4.399,86	3.048,00	2.981,13	2.267,49	2.064,00	1.062,50	621,71	4,00
MEDIAN	2.832,00	5.805,00	2.457,00	2.850,00	-	1.035,00	1.023,00	-	17,00	228,00	-

Fig. 2 – Average medical costs *per* patient (Eur) according to the International Classification of Diseases (ICD)-10 malignancy group. The ICD-10 code groups are explained in Table 2.

14,52% of total costs (and 34% of all medicines cost], as shown in Table 3.

Oncology–medical care cost amounted to 21%, followed by radiation therapy cost and interventional radiology, surgery, imaging diagnostics and laboratory tests costs (Figure 4).

Average survival *per* diagnosis group expressed in months is presented in Figure 5. The longest survival was observed among the patients with malignant neoplasm of male genital organs (C60-C63) with observed average survival of 8.31 months. The shortest survival, which amounted 0.13 months, was recorded in patients with melanoma and

Table 3

Average drug acquisition cost *per* patient

Cost domain (EUR *per* patient)	Average (CI 95% lower – upper limit) (EUR)	Proportion of total costs – %
Total cost	3,481.77 (2,220.45–4,743.09)	100.00
Costs of all medicines (MABs included)	1,475.08 (628.45–2,321.70)	42.37
Costs of MABs	505.47 (-223.44–1,234.39)	14.52

MABs – monoclonal antibodies; CI – confidence interval.

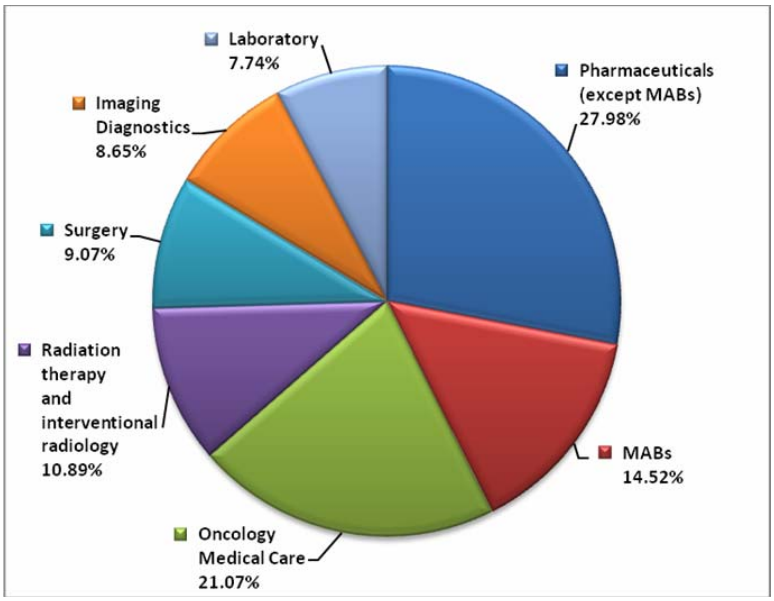


Fig. 4 – Structure and percentage ratio of average medical costs *per* patient with advanced stage of carcinoma.
MABs – monoclonal antibodies.

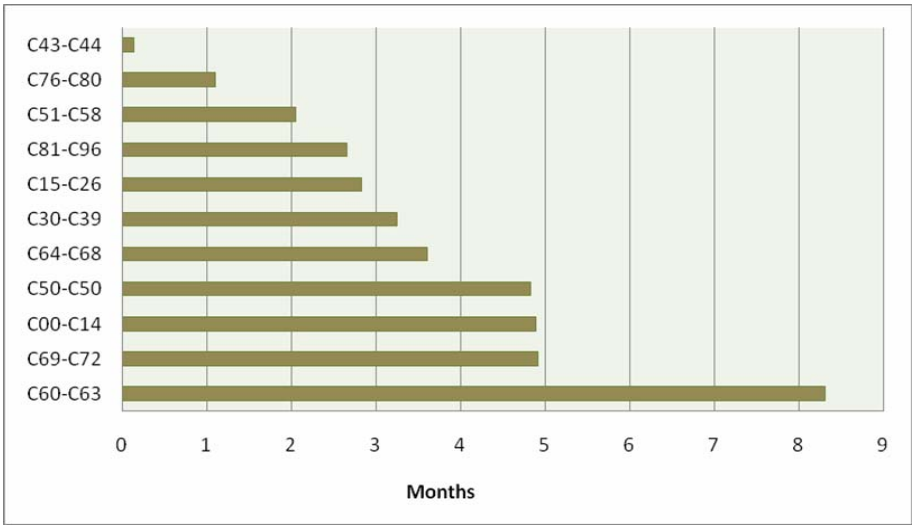


Fig. 5 – Average survival of deceased patients according to the International Classification of Diseases (ICD)-10 malignancy group (expressed in months)
The ICD-10 code groups are explained in Table 2.

other malignant neoplasms of the skin (C43-C44). Correlation between survival and ICD 10 diagnosis and costs showed low degree of correlation (r = 0.087, r = 0.134, respectively). Thereafter, multiple regression analysis was performed and no significant influence of costs and ICD 10 diagnosis, as constants, on survival (F = 2.066, p = 0.132) was observed.

From our patients' database, average end-of-life costs of medicines for each patient were calculated (approximately 1,475.08 EUR). The results showed that about 4.4 % of the total costs for medicines was needed for cancer related end-of-life pharmaceutical costs during the observed period.

Discussion

Our results are in accordance with official ones, i.e. cancer mortality in Serbia among patients with malignant disease was highest at the age of 60 to 69 among ones with lung cancer [17].

Total costs for medicines in Serbia in 2010 and 2011 amounted approximately 710 million Euro *per* year [18, 19]. In these two years, 21,139 and 21,007 people died due to all kinds of malignant diseases in Serbia [20, 21].

There is an upward trend of more aggressive end-of-life cancer treatment in the world, according to the study performed among US patients older than 65 years [22], which is consistent with our study results. One of the observed occurrences is a more frequent administration of chemotherapy within the two final weeks of life, as well. Our results correspond to these data, i.e. the most of the expenses of patients in terminal stages of malignancies resulted from hospital inpatient care, where received chemotherapy contributed to the highest costs [10]. Besides expensive treatment options, some of the diagnostic imaging procedures as well as invasive radiology procedures have been clearly described as major cost drivers in the recent findings from the region [12, 23].

Pharmacotherapy cost included in our analysis accounted for 42.37% of all cancer related health costs *per* patient. Overall, health care spending for cancer care in EU reaches 4% of total health care expenditure, with the highest inpatient care costs accounting for 56% of cancer related costs. Medicines expenditure varies substantially between countries, from 15% in Lithuania to 61% in Cyprus [11]. With regards to chemotherapy cost within the final weeks of life, our data is in accordance with the observed worldwide trend, resulting in a medicines share of 42% of total direct medical costs. MABS influenced total expenditure for pharmacotherapy with one third of value (14.52%; or 34% of all medicines costs).

Limitations of the study

There is an apparent lack of education and awareness contributed to underreporting of all newly cancer cases in Serbia [15]. In spite of all efforts to improve such practice, such as decentralization, active data collection promotion, informatics support, etc., there is still a large probability of time delay for registering these patients, which might lead to shorter survival periods of official records compared to the actual survival periods.

Cost data were related only to the direct medical costs which have accrued since the diagnosis date. Although Payer's perspective has been adopted, substantial improvement in future would present inclusion of lost productivity related indirect costs of cancer. In case of late diagnosed terminal stage population, calculation of premature death cost to the society, based on Grossman's human capital approach [24] would be particularly helpful. Nevertheless such analysis remains out of scope or the budget for this study.

Policy interventions needed in future

In spite of currently cutting edge medical technologies, cancer treatment incurs high costs and its outcomes remain unpredictable [25]. The growing need of today is implementation of efficient measures in order to cut down such costs, but to preserve an appropriate and satisfactory health care system, in order to handle malignant diseases successfully. One of the appropriate options is to promote and finance cancer-screening programs. Costs of cancer treatment rise with the disease progression and therefore allocation of certain financial recourses to cancer screening programs would result in lower costs and more affordable health care.

At the European Cancer Congress 2013, data from a large European survey was presented suggesting that colorectal cancer mortality fell by 73% in men and 82% in women in 11 European countries [26]. The reduction was greater considering the population where screening rate was higher. The same promising results were obtained from cervical cancer screening. Unfortunately, breast and prostate cancer screening has not shown such promising results. A possible reason for those findings could be the fact that when colorectal and cervical cancers are considered, the screening precursor lesion is the target; therefore its removal will not allow them to turn into cancer. This is not the case for breast and prostate cancers, where screening programs simply result in early detection of such diseases and their higher incidence. The results of our study show that among the most frequent morbidity causes are malignant neoplasms of digestive organs (27.19%) and female genital organs (6.14%). Therefore, more aggressive implementation of screening programs for those diseases would bring benefits.

On the other hand, most frequent morbidity causes were malignant neoplasms of respiratory and intrathoracic organs and there is an urge to find another approach to reduce mortality and cancer costs. One of the proposals come from the Florida Society of Clinical Oncology [27]. They suggest some measures, in order to attempt to reduce health care costs without restricting access and reducing payments for such care. Proposed measures consisted of implementing patient management through overall good clinical practice, including organized and established path of disease management, as well as enlargement of palliative hospi-

ce care for patients in the final stage of the disease. As Marsland et al. [27] further suggested, significant savings could be achieved through evidence based therapy options, but adjusted for individual patient needs, trained personnel to evaluate patients for treatment related toxicities and prevent symptoms escalation. Therefore, it could be possible to avoid some unnecessary hospital admissions. Discussion between physicians and terminally ill patients concerning less aggressive medical care would bring some more benefits in terms of better quality of life outcomes and fewer costs [28].

Each particular malignant entity should be reconsidered in order to bring adequate measures for its prevention, treatment and cutting costs. Serbia belongs to eastern European middle income countries with limited public budget and recourses for conducting its own health technology assessments. Therefore policy makers have a greater need to rely on predominantly foreign health technology assessments recommendations such as National Institute for Health Excellence, while making their own decisions. However, transferability of a health technology assessment has limitations, especially in oncology. Local adjustment of such data is necessary, particularly due to services pricing, labour wages and budget differences compared to mature economies [29].

Conclusion

In a series of 114 patients who deceased within the first year from the moment of established cancer diagnosis, the greatest impact on total treatment costs was achieved by medicines, with largest share of monoclonal antibodies. It emerged mostly from medical personnel tendency to improve such patients` quality of life, in spite of nearing the end of life. It is expected that more benefit would be brought from regulatory rationalized reimbursement policy, especially for monoclonal antibodies therapy at the end-stage disease.

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CORRIGENDUM

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The fifth author Florian Gutzwiller should be listed as: Florian S. Gutzwiller

The correction has been made to the online version of that issue of the Journal which is available at: http://www.vma.mod.gov.rs/eng/vojnosanitetski-pregled/archive/2015#.VYPCZlKdfKE