https://doi.org/10.31925/farmacia.2022.1.24 **ORIGINAL ARTICLE**

THE DIRECT COSTS BURDEN OF BEVACIZUMAB IN SOUTH-WEST ROMANIA

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Abstract

As costs for cancer treatment increase with the reimbursement of new treatments and increasing of patients' number, prevention and prior detection efforts become even more cost-effective and potentially cost saving. The global economic burden of cancer is mostly unknown. Even though bevacizumab is one of the most prescribed and used angiogenesis inhibitors, it is among the most expensive drugs. This study aimed to generate statistical analyses of the total amounts reimbursed by the Romanian National Health Insurance Fund for treating cancer with Avastin® in Dolj County, Romania, from January 1st, 2020 to March 31st, 2021. We aimed to estimate the real-world incremental costs associated with the use of bevacizumab for metastatic breast cancer, advanced non-small cell lung cancer, metastatic cancer of the colon or rectum, ovarian cancer, advanced renal cell cancer, and cervical cancer. From the total of 351 patients treated with bevacizumab, 114 (31.67%) had colon cancer and 69 (19.17%) had rectum cancer. After we investigated the economic burden of bevacizumab, we observed the highest percentage for the malignant tumour of the colon from all the direct costs. We compared the costs of bevacizumab treatment on diseases and months, observing the highest burden for colon cancer in almost all the months. Molecules such as bevacizumab are adding an appreciable cost burden to the public funded Health Care System and more studies that evaluate their cost-effectiveness are needed.

Rezumat

Pe măsură ce costurile tratamentelor pentru cancer cresc, eforturile de prevenție și depistare precoce devin cost-eficiente și pot reduce costurile. Povara economică globală a cancerului este în mare parte necunoscută. Cu toate că bevacizumab este unul dintre cei mai prescriși și utilizați inhibitori ai angiogenezei, el este și printre cele mai scumpe medicamente. Scopul studiului a fost generarea de analize statistice ale sumelor rambursate de Fondul Național de Asigurări de Sănătate pentru tratarea cancerului cu Avastin® în județul Dolj, România, de la 1 martie 2020 până la 31 martie 2021. Am realizat o analiză economică pentru a estima costurile incrementale asociate administrării de bevacizumab pentru cancer de sân metastatic, de colon sau rect, cancer pulmonar avansat fără celule mici, cancer avansat renal, ovarian și de col uterin. Dintre cei 351 de pacienți tratați cu bevacizumab, 114 (31,67%) au prezentat cancer de colon și 69 (19,17%) cancer de rect. Investigând povara economică prezentată de bevacizumab, am observat că procentul cel mai mare al costurilor directe a fost pentru cancerul de colon. Am comparat costurile tratamentului cu bevacizumab în funcție de categoria de boală și de luna prescrierii, observând că povara economică cea mai ridicată a fost în aproape toate lunile în cazul neoplasmului de colon. Molecule precum bevacizumab adaugă o povară economică însemnată asupra costurilor suportate de către Sistemului Național de Sănătate finanțat din fonduri publice și sunt necesare mai multe studii pentru evaluarea rentabilității.

Keywords: costs, economic burden, bevacizumab, colon cancer

Introduction

The economic burden of cancer is considerable in all countries of the world [6] and it reflects not only the healthcare spending, but also the lost productivity because of morbidity and premature death from this disease [5]. As cancer treatment costs increase through

reimbursement of new treatments and with the increasing of patients' number, prevention and prior detection efforts become even more cost-effective, and potentially cost-saving [6].

There is no "one size fits all" cancer treatment because there are over 200 forms of cancer [56, 58], and the worldwide economic burden of cancer is generally unknown, but data is accessible in many countries [7, 13, 30, 37]. The available statistics show that in 2020, global oncology spending totalled 167 billion US dollars [60]. Six years earlier, it was only a fraction of this: 74 billion dollars [60]. In 2017, cancer healthcare expenditures in the European Union totalled €57.3 billion, and the additional expenses were €10.6 billion and €47.9 billion, respectively, for productivity losses related to sickness and early death [57].

With these facts in mind, it is projected that cancer treatment expenses would continue to climb rapidly over the next few decades [32].

Bevacizumab (Avastin®; Roche Pharma AG, Germania) is a humanized anti-VEGF monoclonal IgG1 antibody (molecular weight, 149 kDa) that reduces angiogenesis by neutralizing all VEGF isoforms and preventing their interaction to VEGF receptors [59].

Bevacizumab was authorized in the European Union (EU) for the first time on January 12, 2005, being approved as the first-line treatment of patients having metastatic cancer of the colon or rectum (mCRC), along with 5- fluorouracil/folinic acid (intravenous) or 5-fluorouracil/folinic acid/oxaliplatin (intravenous) or irinotecan [21]. Nowadays, it is approved world-wide, including in Romania, for various solid tumour indications comprising the treatment of metastatic breast cancer (MBC), advanced non-small cell lung cancer (NSCLC), advanced renal cell carcinoma, ovarian and cervical cancer [12, 15, 17, 27, 33, 34, 40, 42, 43].

Additional research is being undertaken at the present to determine the possible therapeutic value of bevacizumab in combination with other anticancer agents [2, 54].

Even though bevacizumab is one of the most prescribed and used angiogenesis inhibitors [20], like any biological therapy, it is among the most expensive drugs [11].

Assessing the economic burden of bevacizumab used as treatment in different types of cancer, it is a constant issue of perpetual concern for researchers and policy-makers to measure the cost of illness (COI) and to conduct ongoing assessments of the treatment's prospective costs and benefits. COI helps measure the magnitude of the problem by incorporating direct expenditures (medical costs and non-medical costs), productivity losses and intangible costs of cancer [26].

The aim of this study was to generate statistical analyses of the amounts reimbursed by the National Health Insurance Fund for treating cancer with Avastin® in Dolj County, Romania, from January 1st, 2020 to March 31st, 2021, conducting a retrospective cost analysis based on the data reported by the hospitals from the county.

Materials and Methods

We performed an economic analysis to explore the incremental costs associated with the use of bevacizumab for seven types of cancer: metastatic cancer of the colon or rectum, metastatic breast cancer, advanced non-small cell lung cancer, advanced renal cell cancer, ovarian cancer and cervical cancer in Dolj County, Romania.

The study was undertaken based on the approval of the Ethics Committees of the University of Medicine and Pharmacy Craiova, Romania. All patients gave their consent in accordance with the Declaration of Helsinki.

Following global data protection standards, we used anonymised individual patient data submitted by hospitals in Dolj County, Romania, at the Health Insurance House of Dolj. The patients' dataset extracted from the Health Insurance House of Dolj from January 1st, 2020 to March 31st, 2021 included the following demographic and clinical information: patient gender, disease, hospital and treatment.

We investigated service burden and costs in association with bevacizumab treatments.

Statistical analysis

The statistical analysis was effectuated using the software GraphPad Prism 9.1.2 (GraphPad Software, San Diego, CA, USA). Descriptive statistics were presented as number/values with percentages from the total. Mann-Whitney U test was used for assessing the differences between continuous variables for two groups. The results were considered statistically significant for P-value less than 0.05.

Results and Discussion

From the 351 patients treated with bevacizumab in Dolj County, Romania, 114 (31.67%) had colon cancer and 69 (19.17%) had rectum cancer, as presented in Figure 1.

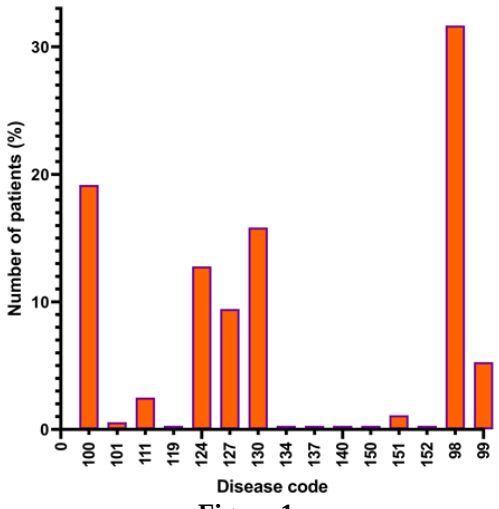

Figure 1.
Number of patients for every disease

On the third and fourth place, as number of patients treated with bevacizumab the patients with ovary cancer: 57 (15.83%) and breast cancer: 46 (12.78%) were placed. More than half were males (209, 59.54%).

After we investigated the economic burden of bevacizumab in Dolj County, Romania, we observed the highest percentage for malignant tumour of the colon (38.29%) from all the direct costs, followed by breast cancer (22.21%) and rectum cancer (16.91%), as in Table I.

Table I

Direct costs by disease

Disease (code)	EUR
Malignant tumour of the colon (098)	83,972,081.03 (38.29%)
Malignant tumour of the recto-sigmoid junction (099)	8,950,995.70 (4.08%)
Malignant tumour of the rectum (100)	37,089,812.73 (16.91%)
Malignant tumour of the anus and anal canal (101)	317,685.73 (0.14%)
Malignant tumour of the bronchi and lungs (111)	3,927,994.05 (1.79%)
Mesothelioma (119)	55,983.37 (0.03%)
Malignant tumour of the breast (124)	48,706,447.57 (22.21%)
Cervical cancer (127)	22,841,877.81 (10.42%)
Malignant tumour of the ovary (130)	12,566,710.55 (5.73%)
Malignant tumour of the prostate (134)	76,428.02 (0.03%)
Malignant tumour of the kidney, except the renal pelvis (137)	411,609.72 (0.19%)
Malignant bladder tumour (140)	14,961.10 (0.01%)
Malignant tumour of the lymph nodes, secondary and unspecified (150)	33,622.23 (0.02%)
Secondary malignant tumour of the respiratory and digestive organs (151)	188,522.49 (0.09%)
Secondary malignant tumour with other locations (152)	125,347.37 (0.06%)
Total	219,280,079.47

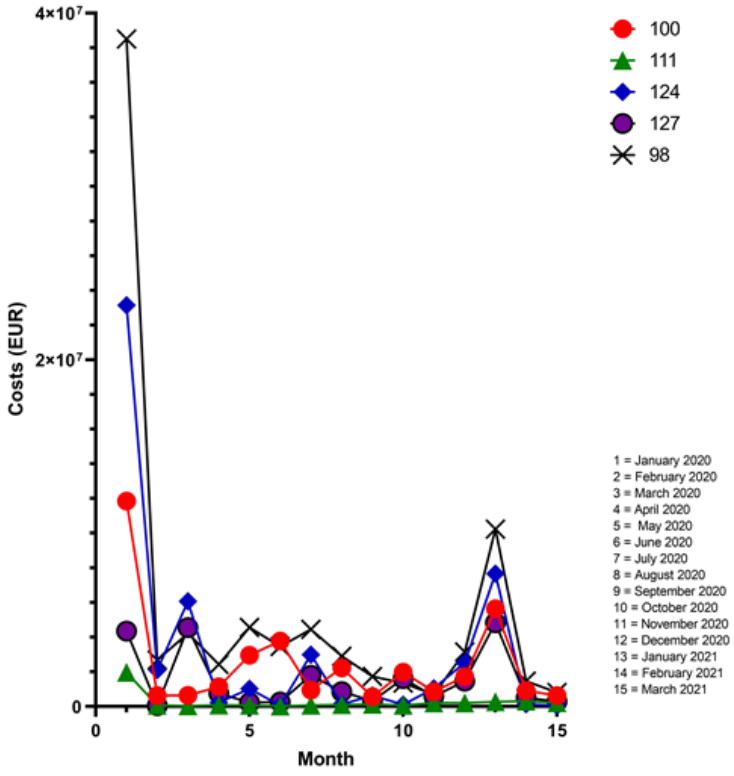

Figure 2.

The direct costs by month and disease

We compared the costs of bevacizumab treatment on diseases and months, observing the highest burden for colon cancer in almost all the months, followed by breast cancer. The results are depicted in Figure 2. The total number of patients decreased in 2021 compared to 2020, with significantly smaller costs for January and March (for both months, P-value was less than 0.0001). In February, the burden of bevacizumab costs was also smaller in 2021 compared to 2020, but not statistically significant (P = 0.1171) (Figure 3).

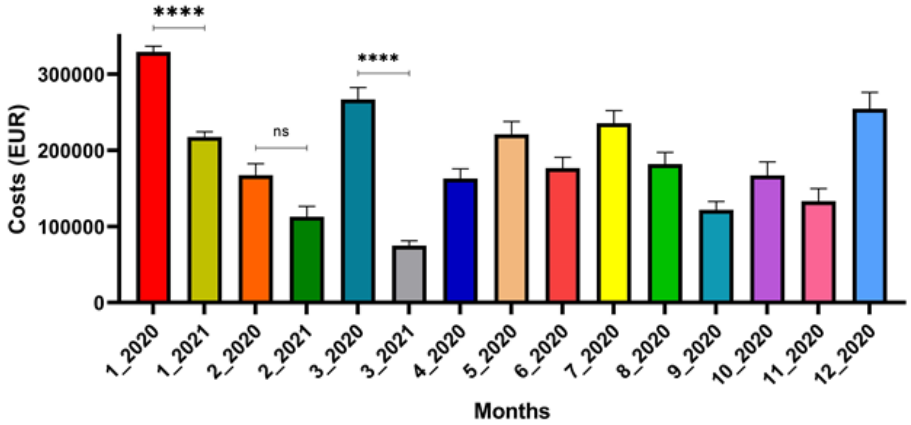

Figure 3.
Direct costs on months

Cancer places a financial strain on patients, health-care systems and governments as a result of increased healthcare costs and lost potential owing to morbidity and early mortality [52]. The primary goal of health policies worldwide is to ensure that medications are available and accessible [48]. All these considering that modern medicine is in perpetual development, from different types of new treatments [49] to advanced diagnostic methods [39, 45].

The national epidemiological profiles of cancer burden in the Global Burden of Disease (GBD) study are heterogeneous because of the exposure to different risk factors, economic context, lifestyle and health-care systems [14].

There are three primary approaches to treating cancer, according to the guides: surgery, radiation, and pharmacological therapy (including chemotherapy, hormone therapy, targeted therapy and immunotherapy) [50]. There are cases when patients receive all three modalities of treatment, while, for other patients, only one or two types are enough [1]. Treatment costs vary by the type and extent of the therapeutic methods needed by the patient.

Additionally, there is an annual increase in the number of people diagnosed with cancer, as well as the number of people receiving treatment for cancer [8]. There is no National Cancer Register set in Romania, so there are no updated statistics regarding colorectal cancer available for our country [23]. Data can only be theorized comparing with the neighbouring countries.

Moreover, with this trend continuing, cancer treatment expenses are likely to continue to climb tremendously over the next few decades.

The opportunity of introduction and reimbursement of new therapies such as targeted therapeutic agents as monoclonal antibodies for solid tumours have reformed cancer care and is promptly changing treatment approaches across common cancer disease sites [53].

Bevacizumab improves progression-free survival or overall survival in breast, colorectal, cervical, ovarian and lung cancer [21, 38, 41, 43, 47]. Romania's provincial health budgets might face considerable financial pressures due to the high cost of bevacizumab's procurement. Vascular endothelial growth factor A (VEGF) is a powerful proangiogenic growth factor that promotes the growth, migration, and survival of endothelial cells [10]. VEGF is considered a highly important target of anticancer therapy, being one of the main proteins expressed by tumour cells [31]. Oncology drugs that inhibit the growth of VEGF are increasingly being employed in the clinic [4, 16, 21, 22, 24, 25, 36, 51].

Previous economic reviews of bevacizumab in patients with mCRC in the United States of America, the United Kingdom, Canada, Australia and Israel indicated a lack of cost-effectiveness [9, 18, 19], rGBM in Canada [28], mCC in the USA [46], and ovarian cancer in Canada and Belgium [3, 35] and a systematic evaluation including ten countries reported that the cost-effectiveness of bevacizumab in NSCLC was inconclusive [29]. High proportion of costs with targeted therapies as bevacizumab in the first line in Wild type Kirsten ras oncogene (WT KRAS) patients with mCRC could make the national health system unsustainable in some countries [44].

We found that most patients treated with bevacizumab were suffering of colorectal cancer (50.84%) and more than half were males (209, 59.54%). This correlates with the fact that according to 2020 statistics for Romania, 14.1% males and 11.8% women were newly diagnosed with CRC [55]. This data is also consistent with the fact that our study established that the highest percentage of direct costs allots to malignant tumour of the colon (38.29%), followed by breast cancer (22.21%) and in the third place, rectum cancer (16.91%).

The most plausible reason for the fact that the total number of patients went significantly down in the first trimester of 2021 comparing to 2020 is the influence of SARS-CoV-2 pandemic. The first months of 2020 were pandemic-free or at least at the very first beginning of the SARS-CoV-2 pandemic, so this explains the

higher number of patients that were treated in that period of time.

This is the first study in our country that analyses data regarding economic burden aspects of cancer treatment involving bevacizumab, using clear data provided by National Health System.

The low number of patients and the fact that we assessed data for only one region of Romania can be considered as limitations, but this is the first step in generating furthermore extensive prospective analyses that can estimate the economic burden of cancer.

Conclusions

Colon cancer was the most frequently treated malignancy with bevacizumab in Dolj County, Romania, and hence the largest direct cost of this type of targeted therapy was observed in patients with colon tumours. More screening programs should be implemented especially in low-middle income countries in order to lower mortality rates and, implicitly, financial burden as monoclonal antibody-based therapies, bevacizumab including, represent a modern approach in the Medical Oncology field and are more than ever present in daily practice.

Nevertheless, these types of therapies are a fairly appreciable cost burden for the Romanian involved stakeholders (health care system/payers/insurers), so more studies that evaluate their cost-effectiveness are needed.

Conflict of interest

The authors declare no conflict of interest.

References

1. Arruebo M, Vilaboa N, Sáez-Gutierrez B, Lambea J, Tres A, Valladares M, González-Fernández A, Assessment of the evolution of cancer treatment therapies. *Cancers (Basel)*, 2011; 3(3): 3279-3330.
2. Artene SA, Turcu-Stiolica A, Hartley R, Ciurea ME, Daianu O, Brindusa C, Alexandru O, Tataranu LG, Purcaru SO, Dricu A, Dendritic cell immunotherapy *versus* bevacizumab plus irinotecan in recurrent malignant glioma patients: a survival gain analysis. *Onco Targets Ther.*, 2016; 9: 6669-6677.
3. Ball G, Xie F, Tarride JE, Economic evaluation of bevacizumab for treatment of platinum-resistant recurrent ovarian cancer in Canada. *Pharmacoecon Open*, 2018; 2(1): 19-29.
4. Bergers G, Song S, Meyer-Morse N, Bergsland E, Hanahan D, Benefits of targeting both pericytes and endothelial cells in the tumor vasculature with kinase inhibitors. *J Clin Invest.*, 2003; 111(9): 1287-1295.
5. Bradley CJ, Neumark D, Luo Z, Schenk M, Employment and cancer: findings from a longitudinal study of breast and prostate cancer survivors. *Cancer Invest.*, 2007; 25(1): 47-54.
6. Bradley CJ, Yabroff KR, Dahman B, Feuer EJ, Mariotto A, Brown ML, Productivity costs of cancer mortality in the United States: 2000-2020. *J Natl Cancer Inst.*, 2008; 100(24): 1763-1770.
7. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.*, 2018; 68(6): 394-424.
8. Canadian Cancer Society and the National Cancer Institute of Canada: Canadian Cancer Statistics 2005. Toronto: Canadian Cancer Society; 2005. 2. Cancer Surveillance and Epidemiology Unit, Cancer Care Nova Scotia. Cancer Drug Cost Data for Nova Scotia. Cancer Care Nova Scotia; 2006; Halifax, NS.
9. Carter HE, Zannino D, Simes RJ, Schofield DJ, Howard K, Zalcberg JR, Price TJ, Tebbutt NC, The cost effectiveness of bevacizumab when added to capecitabine, with or without mitomycin-C, in first line treatment of metastatic colorectal cancer: results from the Australasian phase III MAX study. *Eur J Cancer*, 2014; 50(3): 535-543.
10. Duffy AM, Bouchier-Hayes DJ, Harmey JH, Vascular Endothelial Growth Factor (VEGF) and Its Role in Non-Endothelial Cells: Autocrine Signalling by VEGF. In: Madame Curie Bioscience Database, 2000-2013; Austin (TX): Landes Bioscience.
11. Duong M, Wright E, Yin L, Martin-Nunez I, Ghatage P, Fung-Kee-Fung M, The cost-effectiveness of bevacizumab for the treatment of advanced ovarian cancer in Canada. *Curr Oncol.*, 2016; 23(5): e461-e467.
12. Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, Chevreau C, Filipek M, Melichar B, Bajetta E, Gorbunova V, Bay JO, Bodrogi I, Jagiello-Gruszfeld A, Moore N, AVOREN Trial investigators, Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet*, 2007; 370(9605): 2103-2111.
13. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, Znaor A, Bray F, Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*, 2019; 144(8): 1941-1953.
14. Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O, Abdelalim A, Abdoli A, Abdollahpour I, Abdulle ASM, Global Burden of Disease Cancer Collaboration, Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol.*, 2019; 5(12): 1749-1768.
15. Garcia AA, Hirte H, Fleming G, Yang D, Tsao-Wei DD, Roman L, Groshen S, Swenson S, Markland F, Gandara D, Scudder S, Morgan R, Chen H, Lenz HJ, Oza AM, Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the California, Chicago, and Princess Margaret Hospital phase II consortia. *J Clin Oncol.*, 2008; 26(1): 76-82.
16. Gherman A, Cainap C, Vesa SC, Havasi AD, Trifon A, Cainap SS, Crisan O, Irimie A, Efficacy of cetuximab/panitumumab after previous bevacizumab

in metastatic colorectal cancer. *Farmacia*, 2020; 68(4): 656-664.
17. Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, Schwartz MA, Benson AB 3rd, Eastern Cooperative Oncology Group Study E3200, Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol.*, 2007; 25(12): 1539-1544.
18. Goldstein DA, Chen Q, Ayer T, Chan KKW, Virik K, Hammerman A, Brenner B, Flowers CR, Hall PS, Bevacizumab for Metastatic Colorectal Cancer: A Global Cost-Effectiveness Analysis. *Oncologist*, 2017; 22(6): 694-699.
19. Goldstein DA, Chen Q, Ayer T, Howard DH, Lipscomb J, El-Rayes BF, Flowers CR, First- and second-line bevacizumab in addition to chemotherapy for metastatic colorectal cancer: a United States-based cost-effectiveness analysis. *J Clin Oncol*., 2015; 33(10): 1112-1118.
20. Harris AL: Chapter 9 - Clinical strategies to inhibit tumor vascularization, Editor(s): Domenico Ribatti, Francesco Pezzella, Tumor Vascularization, Academic Press, 2020; 147-176, ISBN 9780128194942.
21. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe Gwen, Rogers B, Ross R, Kabbinavar F, Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med.*, 2004; 350(23): 2335-2342.
22. Inai T, Mancuso M, Hashizume H, Baffert F, Haskell A, Baluk P, Hu-Lowe DD, Shalinsky DR, Thurston G, Yancopoulos GD, McDonald DM, Inhibition of vascular endothelial growth factor (VEGF) signaling in cancer causes loss of endothelial fenestrations, regression of tumor vessels, and appearance of basement membrane ghosts. *Am J Pathol.*, 2004; 165(1): 35-52.
23. Ionescu EM, Tieranu CG, Maftei D, Grivei A, Olteanu AO, Arbanas T, Calu V, Musat S, Mihaescu-Pintia C, Cucu IC, Colorectal Cancer Trends of 2018 in Romania - an Important Geographical Variation Between Northern and Southern Lands and High Mortality *Versus* European Averages. *J Gastrointest Cancer*, 2021; 52(1): 222-228.
24. Jain RK, Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science*, 2005; 307(5706): 58-62.
25. Jain RK, Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. *Nat Med.*, 2001; 7(9): 987-989.
26. Jo C, Cost-of-illness studies: Concepts, scopes, and methods. *Clin Mol Hepatol.*, 2014; 20(4): 327-337.
27. Kabbinavar F, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, Griffing S, Bergsland E, Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol.*, 2003; 21(1): 60-65.
28. Kovic B, Xie F, Economic evaluation of bevacizumab for the first-line treatment of newly diagnosed glioblastoma multiforme. *J Clin Oncol.*, 2015; 33(20): 2296-2302.
29. Lange A, Prenzler A, Frank M, Golpon H, Welte T, von der Schulenburg JM, A systematic review of the cost-effectiveness of targeted therapies for metastatic non-small cell lung cancer (NSCLC). *BMC Pubm Med.*, 2014; 14: 192: 1-11.
30. Luengo-Fernandez R, Leal J, Gray A, Sullivan R, Economic burden of cancer across the European Union: A population-based cost analysis. *Lancet Oncol.*, 2013; 14(12): 1165-1174.
31. Mancuso MR, Davis R, Norberg SM, O'Brien S, Sennino B, Nakahara T, Yao VJ, Inai T, Brooks P, Freimark B, Shalinsky DR, Hu-Lowe DD, McDonald DM, Rapid vascular regrowth in tumors after reversal of VEGF inhibition. *J Clin Invest.*, 2006; 116(10): 2610-2621.
32. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML, Projections of the cost of cancer care in the United States: 2010-2020. *J Natl Cancer Inst.*, 2011; 103(2): 117-128.
33. Miles DW, Chan A, Dirix LY, Cortés J, Pivot X, Tomczak P, Delozier T, Sohn JH, Provencher L, Puglisi F, Harbeck N, Steger GG, Schneeweiss A, Wardley A, Chlistalla A, Romieu G, Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol.*, 2010; 28(20): 3239-3247.
34. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D, Davidson NE, Paclitaxel plus bevacizumab *versus* paclitaxel alone for metastatic breast cancer. *N Engl J Med.*, 2007; 357(26): 2666-2676.
35. Neyt M, Vlayen J, Devriese S, Camberlin C, First- and second-line bevacizumab in ovarian cancer: A Belgian cost-utility analysis. *PLoS One*, 2018; 13(4): e0195134: 1-16.
36. Nieder C, Wiedenmann N, Andratschke N, Molls M, Current status of angiogenesis inhibitors combined with radiation therapy. *Cancer Treat Rev.*, 2006; 32(5): 348-364.
37. Pearce A, Sharp L, Hanly P, Barchuk A, Bray F, de Camargo Cancela M, Gupta P, Meheus F, Qiao YL, Sitas F, Wang SM, Soerjomataram I, Productivity losses due to premature mortality from cancer in Brazil, Russia, India, China, and South Africa (BRICS): A population-based comparison. *Cancer Epidemiol.*, 2018; 53: 27-34.
38. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Láng I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Rüschoff J, Suto T, Greatorex V, Ward C, Straehle C, McFadden E, Dolci MS, Gelber RD, Herceptin Adjuvant (HERA) Trial Study Team, Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med.*, 2005; 353(16): 1659-1672.
39. Popa P, Streba CT, Caliţă M, Iovănescu VF, Florescu DN, Ungureanu BS, Stănculescu AD, Ciurea RN, Oancea CN, Georgescu D, Gheonea DI, Value of endoscopy with narrow-band imaging and probe-based confocal laser endomicroscopy in the diagnosis of preneoplastic lesions of gastrointestinal tract. *Rom J Morphol Embryol.*, 2020; 61(3): 759-767.

40. Reck M, von Pawel J, Zatloukal P, Ramlau R, Hirsh V, Leighl N, Mezger J, Archer V, Moore N, Manegold C, Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. *J Clin Oncol.*, 2009; 27(8): 1227-1234.
41. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Injle JN, Wolmark N, Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med.*, 2005; 353(16): 1673-1684.
42. Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F, Cassidy J, Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. *J Clin Oncol.*, 2008; 26(12): 2013-2019.
43. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH, Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med.*, 2006; 355(24): 2542-2550.
44. Sehnalova I, Rihova B, Nemecek R, Kintrova K, Demlova R, The real-world cost and effectiveness study of treating mCRC with bevacizumab followed by cetuximab or panitumumab in WT KRAS patients. *Farmacia*, 2020; 68(3): 572-578.
45. Serbanescu MS, Oancea CN, Streba CT, Plesea IE, Pirici D, Streba L, Plesea RM, Agreement of two pre-trained deep-learning neural networks built with transfer learning with six pathologists on 6000 patches of prostate cancer from Gleason2019 Challenge. *Rom J Morphol Embryol.*, 2020; 61(2): 513-519.
46. Shao C, Siddiqui MK, Takyar J, Zhou W, Sen S, Economic burden of advanced cervical cancer: A systematic literature review. *Value in Health*, 2018; 21(Suppl.1): S27.
47. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L, Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med.*, 2001; 344(1): 783-792.
48. Taerel AE, Turcu-Stiolica A, Study on the range of drugs authorized in Romania – a determinant element for the accessibility and availability of drugs. *Farmacia*, 2009; 57(2): 254-259.
49. Turcu-Stiolica A, Popescu M, Bubulica M, Oancea C, Nicolicescu C, Manda C, Neamtu J, Croitoru O, Optimization of Gold Nanoparticles Synthesis using Design of Experiments Technique. *Rev Chim (Bucharest)*, 2017; 68(7): 1518-1523.
50. Ungureanu BS, Sandulescu L, Şurlin V, Sparchez Z, Saftoiu A, Surgical hepatic resection *vs.* ultrasonographic guided radiofrequency ablation in colorectal liver metastases: what should we choose?. *Med Ultrason.*, 2014; 16(2): 145-151.
51. Wedam SB, Low JA, Yang SX, Chow CK, Choyke P, Danforth D, Hewitt SM, Berman A, Steinberg SM, Liewehr DJ, Plehn J, Doshi A, Thomasson D, McCarthy N, Koeppen H, Sherman M, Zujewjski J, Camphausen K, Chen H, Swain SM, Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer. *J Clin Oncol.*, 2006; 24(5): 769-777.
52. Yabroff KR, Lund J, Kepka D, Mariotto A, Economic burden of cancer in the United States: estimates, projections, and future research. *Cancer Epidemiol Biomarkers Prev.*, 2011; 20(10): 2006-2014.
53. Zahavi D, Weiner L, Monoclonal Antibodies in Cancer Therapy. *Antibodies (Basel)*, 2020; 9(3): 34: 1-20.
54. https://clinicaltrials.gov.
55. https://gco.iarc.fr.
56. www.cancer.gov.
57. www.canceratlas.cancer.org.
58. www.cancerresearchuk.org.
59. www.ema.europa.eu, The European Medicines Agency. European Public Assessment Report. Avastin Product Information. Avastin-H-C-582-II-23, August 2008.
60. www.statista.com.