**„CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST**
**DOCTORAL SCHOOL**
**FIELD OF MEDICINE**

# *The complications of treating neoplastic diseases with Bevacizumab*

## *SUMMARY OF THE DOCTORAL THESIS*

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# Table of Content

By far the best-known and first discovered anti-angiogenic therapeutic agent is Bevacizumab, a recombinant humanized monoclonal anti-VEGF antibody used in the treatment of numerous neoplastic diseases (such as breast cancer, cervical cancer, tubal cancer, ovarian cancer, primary peritoneal cancer, colorectal cancer, clear cell renal carcinoma, non-small cell lung cancer, and brain tumors), in advanced (unresectable), recurrent, or metastatic stages of disease, both as monotherapy and in combination with other therapeutic agents (chemotherapy and/or immunomodulators), as first-line treatment as well as in subsequent lines or in maintenance therapy [1].

Bevacizumab provides overall survival benefits demonstrated by multiple clinical studies; however, these vary in magnitude depending on the type of tumor being treated, and in certain cases the survival benefit is limited to only a few months or even weeks [2].

Undoubtedly, considering that the therapeutic indication often involves an advanced loco-regional unresectable, recurrent, or metastatic neoplasm, even a minimal survival benefit is desirable for the patient when associated with an acceptable quality of life.

Nevertheless, Bevacizumab is associated with a series of complications—some severe, life-threatening, and frequent—that can significantly impact patients' quality of life. In addition to common medical complications (arterial hypertension, congestive heart failure, venous thromboembolism, proteinuria, posterior reversible encephalopathy syndrome, ischemic and hemorrhagic strokes, hematological disorders, septic complications, allergic reactions or infusion-related reactions), Bevacizumab therapy may cause a broad range of surgical complications (some potentially fatal), such as fistulous and perforative complications, delayed wound healing, tumor-associated hemorrhage, various types of bleeding, arterial aneurysms and dissections, necrotizing fasciitis, or osteonecrosis of the jaw [1].

**The motivation for choosing the topic** "Complications of Bevacizumab treatment in neoplastic diseases" becomes evident in light of the above. The theoretical benefits that Bevacizumab therapy might bring with respect to progression-free survival may be counteracted by complications, and overall survival may be reduced due to the impossibility of continuing systemic therapy in the context of surgical interventions/medical treatments/hospitalizations that become necessary.

Moreover, certain interventions that become necessary give rise to technical dilemmas that can place the oncologic surgeon in challenging situations [3]. At the same time, patients' quality of life may be diminished both physically (through the appearance of difficult-to-tolerate complications—e.g., recto/entero-vaginal fistulas) and psychologically

(e.g., the need for a definitive colostomy, which is difficult to accept, especially for young patients) [3].

**The hypothesis of the doctoral research** is that certain risk factors for developing Bevacizumab-related complications can be identified, either patient-related (such as specific comorbidities or pre-existing/concomitant therapies, particular biological, paraclinical, or imaging findings) or tumor-related (location, histopathology, immunohistochemistry, genetics, etc.).

The secondary hypothesis is that Bevacizumab may impair quality of life to such an extent in patients who develop therapy-associated complications that the resulting physical and psychological discomfort (including that caused by the need for additional medical care) may render an increase in overall survival of only a few weeks undesirable.

**Research methodology** – To achieve the objectives of the doctoral research, an extensive review of the available international literature was initially conducted, not limited solely to data regarding Bevacizumab, but also including the topic of tumor angiogenesis and the therapeutic pathways for its inhibition. In addition, evolutionary, pathogenic, diagnostic, and therapeutic aspects of all solid tumors that may constitute a therapeutic target for Bevacizumab (Avastin® or its biosimilars/generics) were studied.

The review of the international literature aimed to define the current state of knowledge and to clarify the anticipated impact that the doctoral research could have on the advancement of the field. All bibliographic references were managed using the specialized software Mendeley Reference Manager, version 2.94.0, together with the browser add-ins (Mendeley Web Importer) and the Microsoft Word add-in (Mendeley Cite) — all freely available online [4].

Following the review of the international literature, the research plan was finalized by defining the objectives, establishing the final study design and research instruments, and defining the patient cohorts and inclusion/exclusion criteria.

Data collection was conducted by extracting information from the electronic database and by reviewing the physical medical records archived by the healthcare institution. Some of the data were obtained through direct or telephone interviews with patients, who were informed about the purpose of the interview and/or signed a consent form to participate in the doctoral research.

After the database was assembled, the information was anonymized by removing any elements that could lead to the identification of the enrolled patients.

The review of the international literature was complemented by a retrospective analysis of patients treated with Bevacizumab (Avastin® or biosimilars/generics) at the "Prof. Dr. Alexandru Trestioreanu" Oncological Institute, Bucharest (IOB) between 2017 and 2021. The aim was to describe the clinical experience of Bevacizumab use in a large real-world cohort of patients with malignant tumors, assessing the effectiveness, safety, and cost of therapy, and identifying prognostic factors for the occurrence of Bevacizumab-related surgical/medical complications.

During this period, over 9,000 cycles of Bevacizumab (Avastin® or biosimilars/generics) were administered to 625 unique oncologic patients.

The third component of the study consisted of a prospective observational analysis involving two cohorts — the global sample included all patients treated at IOB with Bevacizumab (or biosimilars/generics) for various neoplastic conditions between January 2023 and June 2024.

Patients were grouped into two cohorts as follows:

Study cohort – patients treated with Bevacizumab (Avastin® or biosimilars/generics) for solid tumors who developed therapy-associated surgical/medical complications;

Control cohort – patients treated with Bevacizumab who did not develop complications.

All treated patients were included consecutively regardless of age, sex, or other criteria.

Exclusion criteria included a follow-up period shorter than 6 months or the existence of other clear causes for the reported complications, unrelated to Bevacizumab therapy.

Within the prospective study, efforts were made to confirm the findings of the earlier retrospective analysis. The research focused on a descriptive statistical evaluation of Bevacizumab-associated complications and the characteristics of the population in which these complications occur, a statistical correlation analysis between the occurrence of complications and patient- or tumor-specific factors, and finally an assessment of the impact these complications have on patients' quality of life and oncologic outcomes.

The study monitored oncologic evolution, the emergence of Bevacizumab-associated medical/surgical complications, and the need for additional treatments/surgical interventions/additional hospitalization/intensive care support.

The processing and statistical interpretation of the collected data included a descriptive analysis of the complications occurring under the applied therapy and of the populations in which these complications appear. A global analysis was performed — Study group vs. Control group — and a secondary analysis between the different elements identified as risk factors for the occurrence of complications. Data were presented as means (standard deviations) for quantitative variables and as frequencies for qualitative variables.

To compare results between groups, t-tests or Mann–Whitney tests were used. To compare results between different subgroups of identified risk factors, Chi-square tests and logistic regression were applied. Validation of the various characteristics assessed as prognostic factors for the occurrence of complications was performed using linear regression and logistic regression techniques. The threshold for statistical significance was set at $p < 0.05$.

The doctoral research was further complemented by the development of a clinical guide aimed at improving the clinical selection of patients who may benefit from Bevacizumab therapy by maximizing the benefit–risk ratio, as well as by the elaboration of a clinical scoring system for stratifying patients into risk categories (high, intermediate, and low). Prospective multicenter external validation will be the subject of more advanced postdoctoral research.

The doctoral thesis aimed to analyze the complications associated with Bevacizumab therapy in oncological practice, with emphasis on identifying the typologies of adverse reactions, the factors influencing them, their impact on oncologic outcomes and patient quality of life, and the development of clinical tools for risk stratification. The established objectives guided the research and were achieved through a series of successive and complementary studies.

**Objective 1:** Identification of the types of complications associated with Bevacizumab therapy and development of a descriptive statistical analysis — This objective was achieved through the retrospective analysis of patients treated at the Bucharest Oncological Institute (Chapter 5). The study highlighted the frequency of major complications (hemorrhagic, thrombotic, gastrointestinal, renal) and their distribution according to demographic and clinical characteristics.

The results confirmed that Bevacizumab is associated with a particular toxicity profile distinct from that of other oncologic therapies, and their statistical quantification constituted the premise for subsequent objectives.

The initial results (fully consistent with the existing literature) showed that these events are not rare and that, although most can be managed with supportive treatment, some may become life-threatening. Therefore, identifying their typology and distribution formed the foundation for analyzing risk factors and developing subsequent predictive models.

**Objective 2:** Identification of factors influencing the occurrence of complications — By correlating clinical and biological variables with the occurrence of complications (Chapter 7), significant factors were identified such as advanced age, presence of cardiovascular comorbidities, history of abdominal surgery, and specific tumor characteristics (local extension, pelvic location).

These findings showed that the occurrence of complications is not a random event but can be anticipated by integrating clinically accessible risk factors.

The practical relevance of these results is considerable, as they allow the identification of vulnerable patients before initiating treatment. Thus, oncologists may implement preventive measures, adjust doses, or reconsider the appropriateness of therapy, optimizing the risk–benefit balance.

**Objective 3:** Assessment of the impact of complications on oncologic outcomes and on quality of life — The studies included in Chapter 8 demonstrated that the occurrence of complications negatively influences overall survival and progression-free survival through treatment delays or interruptions. Furthermore, the quality-of-life analysis showed a significant impact on functional status, body image, and social integration, with lasting effects, especially in cases of severe complications. The importance of this evaluation lies in the fact that, in oncology, success can no longer be measured exclusively through survival indicators but must also consider maintaining a dignified and functional life. This perspective confirmed the need for a multidimensional approach that goes beyond oncologic survival to include psychosocial and economic parameters.

**Objective 4:** Development of a risk score and a method for patient stratification — In Chapter 9, an original predictive model was developed, based on the integration of clinical, histological, and biological data into machine learning algorithms. The model allowed the stratification of patients into high-, intermediate-, and low-risk categories with high accuracy in predicting complications.

This risk score represents a first in local practice and serves as a practical tool that can later be adapted into clinical guidelines and decision-support platforms. Its practical utility lies in the fact that, when applied prospectively, it can guide therapeutic decisions: low-risk patients may be treated with maximal benefit, while high-risk patients may be redirected to alternative therapeutic options or monitored more closely.

**Objective 5:** Identification of the risk profile of Bevacizumab administration in specific patient categories — Based on the analyzed data, several patient subgroups with increased risk profiles were identified — for example, elderly patients, those with cardiovascular or renal comorbidities, patients with pelvic tumors, and those with a history of recent major surgery.

Conversely, patients without comorbidities and with tumors in more limited stages exhibited a low risk of severe complications.This risk profile enables individualized therapeutic indication and increases the likelihood of safe and effective Bevacizumab administration.

**Future Directions of Research -** Further research should focus on expanding prospective analyses, testing and refining the proposed risk score, as well as integrating it into clinical decision-support information systems. The multicenter study should aim at the prospective validation of the model, the integration of the risk score into clinical software applications, and a more detailed exploration of the economic and psychosocial dimensions.

**Personal Contributions –** The author's original contributions are found in the special section of the thesis and may be summarized as follows:

- Creation of a clinical database (Chapter 5) through the retrospective analysis of patients treated with Bevacizumab at the Bucharest Oncological Institute, representing the first systematic national-level study on this topic.
- Documentation of illustrative clinical cases (Chapter 6), which provided educational and practical value by presenting severe complications and their management approaches.
- Statistical analysis of risk factors (Chapter 7), through which significant correlations were identified between clinical and biological variables and the occurrence of complications, offering objective evidence on the mechanisms involved.
- Integration of the quality-of-life perspective and economic impact (Chapter 8), achieving a comprehensive approach that highlighted the psychosocial dimensions

and the costs associated with treatment — aspects rarely investigated in the Romanian literature.

- Development and initial validation of an original predictive model (Chapter 9), based on modern artificial intelligence methods, which enabled patient stratification according to complication risk and provided a foundation for personalized therapeutic decision-making.
- Proposal of a clinical framework for patient selection (Chapter 9), through the definition of a risk profile and eligibility criteria designed to optimize the benefit–risk ratio of Bevacizumab therapy.

Alignment of Romanian research with international trends, through the application of analytical methods comparable to those used in reference centers, and paving the way for the integration of predictive tools into current practice.

These contributions are measurable and explicitly reflected in the chapters and sections indicated, representing the author's original input to scientific knowledge in the field. By fully achieving the proposed objectives, the thesis demonstrates that it is possible to comprehensively characterize the complications associated with Bevacizumab therapy and that concrete solutions exist for anticipating and reducing them. The integrated analysis of Bevacizumab-associated complications can offer both a better understanding of risk factors and clinical consequences, as well as practical solutions for therapy personalization.

By fulfilling the proposed objectives, the work contributes to the development of safer, more effective, and patient-centered oncology, opening perspectives for future research and for the integration of predictive tools into current medical practice. The results obtained hold both scientific value — by expanding knowledge in the field — and practical value, by providing an instrument directly applicable in clinical settings. This work is part of the effort to modernize Romanian oncology and marks a transition toward personalized medicine based on real clinical data, safer and more effective.

## The studies conducted and their main results

### Study 1 – Retrospective study of patients treated with Bevacizumab at IOB (2017–2021)

The method used was an open, observational, retrospective study conducted under real-world conditions on patients treated for malignant solid tumors at the Bucharest Oncological Institute "Prof. Dr. Al. Trestioreanu." All patients who received systemic therapy based on Bevacizumab between January 1, 2017 and December 31, 2021 were

included. No exclusion criteria were specified. Specific case data were obtained from patient files, electronic records, and the review of paraclinical, imaging, histopathological, and genetic results. The effectiveness of Bevacizumab treatment was assessed through the analysis of progression-free survival (PFS) and overall survival (OS).

The study included 657 treatment episodes with Bevacizumab, corresponding to 625 unique patients. Inclusion in the study was not limited by indication or tumor origin, thus providing a heterogeneous, uncontrolled "real-world" population. Naturally, this also represents one of the study's limitations, as the composition of the study cohort is strongly influenced by the accessibility of our hospital and differs from that of other centers, potentially making the sample not fully representative of "real-world" oncologic practice as a whole.

Our cohort included primarily patients with colorectal cancer (nearly 60% of treatment episodes), but also advanced ovarian cancer (20.09%), breast cancer (8.07%), lung cancer (7.15%), cervical cancer (4.72%), and other primary sites (vagina, vulva, peritoneum, central nervous system) — although this last category included a very small number of patients (8 treatment episodes). First-line treatment was administered to 229 patients (185 colorectal, 18 breast, 26 NSCLC), while subsequent lines of treatment were administered to 428 patients.

**Table 1. Sociodemographic characteristics of the patients and treatment indication**

| Variable | N (%) |
|---|---|
| **Sex** | |
| Male | 238 (38.08%) |
| Female | 387 (61.92%) |
| **Age** | 57.6 years (range 21-85) |
| <65 years | 234 (37.44%) |
| ≥65 years | 391 (62.56%) |
| **Comorbidities** | |
| Hypertension | 227 (36.32%) |
| Diabetes | 90 (14.40%) |
| Chronic pulmonary disease | 43 (6.88%) |
| Other cancers | 7 (1.12%) |
| **Treatment episodes according to the primary tumor origin*** | |
| CRC | 386 (58.75%) |
| NSCLC | 47 (7.15%) |
| CS | 53 (8.07%) |
| OC | 132 (20.09%) |
| CC | 31 (4.72%) |
| Other | 8 (1.22%) |
| **Metastatic site(s)**** | |
| Liver | 391 (62.56%) |

| | |
|---|---|
| Lung | 344 (55.04%) |
| Peritoneum | 156 (24.96%) |
| Bone | 43 (6.88%) |
| Central nervous system | 32 (5.12%) |
| Other | 64 (10.24%) |

N – number of cases; % - procentage from total number of cases; CRC-colorectal cancer; NSCLC-pulmonary cancer non-small cell; CS-breast cancer; OC- ovarian cancer; CC- cervical cancer; * patients may receive multiple treatment episodes with Bevacizumab for different indications, which are counted separately;** patients may have multiple metastatic sites, and these are counted separately.

**Table 2. Effectiveness of Bevacizumab-based therapies by tumor type**

| | ORR (RP and RC) | | Clinical benefits | PFS | | OS | |
|---|---|---|---|---|---|---|---|
| | N (%) | CI 95% | N (%) | Median (months) | CI 95% | Median (months) | CI 95% |
| **Colorectal (n=379)** | | | | | | | |
| 1L (n=294) | 179 (60.9) | 42.9-68.9 | 185 (62.9) | 13.5 | 8.6-18.6 | 26.3 | 9.1-43.5 |
| Lines 2+ (n=85) | 23 (27.1) | 16.5-41.6 | 68 (80.0) | 6.2 | 4.7-7.7 | 9.3 | 7.7-10.9 |
| **Ovarian (n=127)** | | | | | | | |
| Lines 2+ | 42 (31.5%) | 14.4-46.1 | 76 (59.8) | 7.0 | 1.3-12.7 | 11.5 | 6.0-17.0 |
| **Sân (n=51)** | | | | | | | |
| 1L (n=23) | 15 (65.2) | 51.1-79.3 | 19 (82.6) | 10.2 | 6.1-14.3 | 19.7 | 16.0–23.4 |
| Lines 2+ (n=28) | 17 (60.7) | 46.2-73.8 | 23 (82.1) | 8.1 | 5.6-10.6 | 15.6 | 12.5-18.7 |
| **NSCLC (n=32)** | | | | | | | |
| 1L (n=27) | 18 (66.7) | 48.1-80.9 | 20 (74.1) | 7.4 | 6.0-8.9 | 12.6 | 8.8-16.4 |
| Lines 2+ (n=5) | 3 (60) | 23.0-88.0 | 4 (80.0) | 8.4 | 3.7-13.1 | 13.1 | 0.1-26.2 |
| **Altele (n=21)** | | | | | | | |
| Lines 2+ | 13 (61.9) | 32.5– 91.3 | 21 (100) | 11.2 | 2.3-20.1 | 19.7 | 4.0-35.3 |

Abbreviations: 1L – first line of therapy; Lines 2+ – second or subsequent lines of treatment; NSCLC – pulmonary cancer non-small cell; ORR – overall response rate; RP – partial response; RC – complete response; PFS – progression-free survival; OS – overall survival; N – number of cases; % - percentage; CI – confidence interval

Toxicity of any grade related to Bevacizumab was reported in 434 patients and included: bleeding (the most common form being mild nasal or gingival bleeding), arterial hypertension, proteinuria, impaired wound healing, gastrointestinal perforation, other types of perforative/fistulous complications, septic complications, thromboembolic events, abdominal pain, diarrhea, nausea/vomiting, and fatigue.

Treatment was discontinued due to adverse events in 81 patients (12.33%). Mortality within this cohort consisted of 3 patients (thromboembolic or septic complications).

In our study population, patients received an average of 13 (range 1–76) doses of Bevacizumab per treatment episode, with an average quantity of 657 mg/dose. The total acquisition cost of the necessary Bevacizumab between 2017–2021 was approximately 25.5 million euros, with a median treatment episode cost of 38,812 euros. The addition of Bevacizumab to standard chemotherapy increases the total cost of treatment by 213%.

A total of 126 patients required hospitalization or extended hospital stays due to Bevacizumab-induced toxicity for a period of 2–24 days — there was a statistically significant association between grade 3–5 adverse events and hospitalization ($p = 0.002$).

Beyond the added acquisition cost of the drug itself, Bevacizumab increases hospitalization-related costs when severe adverse events occur. Hospitalization costs were the direct costs allocated to each patient by the Internal Analytical Accounting System and included fixed costs (accommodation, utilities) and variable expenses, such as laboratory analysis costs and other diagnostic procedures, the cost of antineoplastic medication and comedication, instruments, medical devices, and consumables. The increase in generated costs is a major concern for healthcare management worldwide.

Among the observed complications, some required surgical procedures (17 cases) — such cases were associated with hospital stays of 10–32 days and an increase in hospitalization-related costs of 150–495% compared to the standard treatment cost for patients who did not develop severe adverse events.

Bevacizumab remains a high-cost therapy, but it can add clinical benefits (such as overall survival, progression-free survival, and response rate) when used in combination with standard chemotherapy. Results similar to those observed in controlled studies can be seen even in unselected patient cohorts, under the uncontrolled conditions of "real-world" oncologic practice.

**Study 2 – Illustration of the management challenges in patients who develop complications associated with Bevacizumab therapy**

The study was based on the presentation of a special case encountered by the author of the thesis during routine practice in the First Department of General and Oncologic Surgery at the "Prof. Dr. Alexandru Trestioreanu" Oncological Institute in Bucharest, meant to illustrate the specific therapy-related complications that may occur during treatment with Bevacizumab and the multitude of medical/oncologic/surgical challenges they bring.

**Case presentation:** A 43-year-old female patient presented with transit disturbances (constipation) and rectal bleeding that had begun approximately six months earlier and was

diagnosed by colonoscopy with a lower rectal tumor. Biopsy samples revealed a moderately differentiated G2 adenocarcinoma. The case was staged as cT3N1M1PUL – stage IV.

Given the metastatic status and the absence of a tight stenosis, treatment was initiated with 28 sessions of external radiotherapy combined with XELOX chemotherapy. After three months, dimensional progression of the secondary pulmonary lesions was noted, with a stationary appearance of the rectal lesion. It was therefore decided to continue chemotherapy (Capecitabine and Oxaliplatin), but Bevacizumab was added, leading to complete regression of the pulmonary metastases.

Under these circumstances, an anterior rectosigmoid resection was performed, followed by a low colorectal mechanical anastomosis and a "protective" ileostomy. On postoperative day 5, an anastomotic fistula occurred, manifested by the drainage of feculent material through the drainage tubes (approximately 80 ml/24 hours). Considering the patient's clinical condition (absence of fever or signs of acute abdomen), biological parameters (absence of leukocytosis), imaging findings (absence of pelvic collections), and the fact that the drains collected the entire fistulous output, a conservative treatment approach was chosen. The evolution was favorable, with closure of the fistulous tract in 20 weeks (confirmed by CT-irrigography).

Unfortunately, after these 20 weeks — five months after surgery — a new PET-CT showed recurrence of the pulmonary lesions, and a follow-up CT one month later showed numerical and dimensional progression. Chemotherapy was initiated again, initially XELOX and later FOLFIRI in association with Bevacizumab, achieving control of disease progression.

Given the stable appearance of the pulmonary lesions after 10 months of this therapy, the absence of rectal recurrence documented by colonoscopy, and the patient's strong preference (she insisted on restoring bowel continuity despite the risks explained by the medical team — risks related to both the surgical intervention and the interruption of systemic therapy), the decision was made to reverse the ileostomy. The intervention took place 18 months after the initial rectal resection. Postoperative evolution was favorable, with resumption of intestinal transit.

However, six months after the intervention, in the context of resuming Bevacizumab therapy, the patient developed a supranastomotic colo-vaginal fistula, clinically manifested by the passage of fecal material through the vagina and confirmed by imaging. To treat this fistula, the patient underwent a procedure consisting of takedown of the low anastomosis, evacuation of the pelvic collection, and creation of a diverting colostomy.

After surgical repair of the colo-vaginal fistula, the patient could no longer resume a complete systemic therapy protocol and was treated only with capecitabine. As expected, evolution was unfavorable, with numerical and dimensional progression of the pulmonary metastases (M1PUL) and the appearance of hepatic and peritoneal metastases.

The patient died seven months after the colostomy (26 months from diagnosis). Although a 26-month survival is within the expected range for metastatic colorectal cancer, it is reasonable to assume that in the absence of fistulous complications, oncologic evolution would have been significantly better, potentially allowing consideration of other therapeutic options (such as resection of resectable pulmonary lesions or more intensive systemic therapies).

**Surgical difficulties raised by the case -** In this patient, there were not one but two fistulous complications associated with Bevacizumab therapy. The first — the anastomotic fistula — most likely resulted from impaired tissue healing and scarring induced by anti-angiogenic therapy. A surgical technical error is unlikely, since the fistula did not appear in the first 2–3 postoperative days. Normally, once such a complication occurs, the optimal therapeutic approach is reoperation with takedown of the low colorectal mechanical anastomosis and creation of a terminal colostomy. Since the patient categorically refused a colostomy — most likely definitive (because the chances of later restoration of bowel continuity were minimal) — we were forced to adopt a conservative treatment strategy. Although ultimately successful, this approach required a prolonged period (approximately 20 weeks) during which the patient needed constant medical care.

After resuming Bevacizumab therapy and the appearance of a complex supranastomotic colo-vaginal fistula, we again faced the need to rest the fistulous area to reduce inflammation, requiring colostomy creation. The necessary surgical technique inevitably results in devascularization of the distal colonic segment previously used in the anastomosis (its blood supply now coming only from the colic arcade, which must be divided during the intervention). Resection of the ischemic distal colon therefore becomes necessary. By shortening the remaining colon, future restoration of bowel continuity becomes unrealistic, especially given the prior mobilization of the splenic flexure during the original rectal resection to achieve a low-tension anastomosis. Another difficulty was the presence of significant postoperative adhesions, compounded by inflammatory processes (secondary to the fistula) and post-radiation changes (a heavily irradiated pelvis with fibrotic, sclerotic, and fragile tissues). In addition, the patient would require a second surgical intervention later to treat the fistulous tract, performed electively after local inflammation subsided. Thus,

correction of the colo-vaginal fistula required two sequential surgical procedures, limiting subsequent oncologic therapy options and delaying treatment at a time when it was critically needed due to pulmonary lesions.

**Quality-of-life consequences and psychological distress -** Regarding the patient's quality of life, the burden of this case was substantial. To manage the fistulous complications associated with Bevacizumab therapy, the patient required constant medical care (three weekly medical visits for repeated lavage and drainage care for 20 weeks during conservative treatment of the anastomotic fistula) and multiple hospitalizations, leading to massive disruption of social and professional life. A secondary consequence of this disruption was significant financial strain.

Moreover, she required a surgical intervention that resulted in a definitive colostomy, which the patient perceived as mutilating.It is important to note that she had firmly opposed any definitive stoma from the beginning of multimodal therapy and reluctantly accepted a temporary protective ileostomy. In this context, the patient developed a clinically manifest depressive syndrome, accompanied by severe disturbances in self-image and social functioning, leading to deterioration of family relationships and sexual dynamics.

**Impact on oncologic outcomes -** Delayed postoperative healing and targeted treatments dedicated to managing the fistulous complications prevented the resumption of maintenance cytostatic therapy, leading to numerical and dimensional progression of the pulmonary lesions.

The systemic therapy resumed later could not compensate for the therapeutic delay, and disease progression occurred. The prognosis was unfavorable, and expected survival was reduced.

**Study 3 – Complications of Bevacizumab therapy encountered in practice**

**Materials and Methods –** an open, observational, prospective study conducted under real-world conditions of current oncologic practice on patients treated with Bevacizumab or biosimilars for malignant solid tumors at the Bucharest Oncological Institute "Prof. Dr. Al. Trestioreanu" (IOB) during the period 1 January 2022 – 30 June 2024, in a consecutive manner. The follow-up period for patients was extended until 31 December 2024, when patients were censored prior to analysis. This ensured a minimum follow-up period of 6 months.

Specific case data were obtained from patient files, electronic records, and by reviewing paraclinical, imaging, histopathological, and genetic results. The collected data included: demographic variables (age, sex), comorbidities and relevant medical history,

history of the neoplastic disease (tumor origin, histology, immunohistochemistry, genetic characteristics, metastatic sites, date of diagnosis, start of treatment, progression, death), treatment-related aspects (line of therapy, combined therapies, dosage, duration of treatment, adverse events, treatment response).

To more accurately assess survival periods, patients were checked monthly through the CNAS platform, which allows verification of a patient's insurance status. The platform returns not only the insurance status but also whether a patient's death has been recorded, which, combined with monthly checking, allowed exact identification of the patient's survival time.

All patients who started treatment were asked to subjectively assess their quality of life before initiation of the first cycle with the anti-angiogenic agent, and those who developed complications were asked to reassess their quality of life after the onset of the complication. This reassessment was performed during regular visits or during hospitalizations related to the consequences of the complications.

Data were analyzed using combined methods with the statistical software SPSS 23.0, the advanced statistics modules of Microsoft Excel, and the interactive web platform Google Colab (also used to generate figures and graphs based on clinical data).

**Descriptive statistics of the study population**

In total, the database contained 395 records (367 unique patients, plus 28 records corresponding to patients who received Bevacizumab/biosimilars in multiple therapeutic lines for the same neoplasm, or as treatment for two distinct cancers). Patients were divided into two cohorts based on a binary variable (ComplBev), coded as 1 for patients who developed any Bevacizumab/biosimilar-associated complication, regardless of severity or type, and 0 for those who did not develop complications. Thus, we obtained a study group (patients with complications) containing 177 records and a control group (patients without complications) containing 218 records.

A descriptive statistical analysis of Bevacizumab-associated complications occurring in our sample was performed. We recorded 177 patients who developed at least one therapy-associated complication (44.81%) and 218 patients who tolerated the medication without any adverse reaction (55.19%). The mean number of complications per patient was 2.27 (± 1.17), with extremes between 1 and 5 complications. The mean time to development of the first complication was 9.03 months, with extremes between 0.5 and 74 months. In conclusion, time to the first Bevacizumab-associated complication is generally short, with

most complications occurring within the first year, and with a tendency toward lower values (around 5 months).

We attempted to determine whether there was a correlation between the number of complications and the time to the first complication. The Pearson correlation coefficient between the two variables (NrComplBev – coding the number of complications, and TimpComplBev – coding the time to onset of complications) was r = 0.0002, a value indicating no linear relationship between the variables. In other words, early onset of complications is not associated with a higher number of complications; the development of complications likely depends on other factors such as individual predisposition, associated pathology, cumulative exposure, etc.

The Pearson correlation analysis for pre-therapeutic variables (clinical, paraclinical, and tumoral) did not reveal strong correlations between the pre-therapeutic profiles of patients and the number of complications developed or the time to onset of the first complication.

Most patients who developed therapy-associated complications (143 patients) had mild or moderate complications. However, the study group also included 31 patients who developed severe complications (classifiable as CTCAE Grades 3–5 – Common Terminology Criteria for Adverse Events [6]). These 31 patients represent 7.85% of the overall cohort.

**Table 3. Distribution of developed complications**

| Type of complication | N (%) | Severity | | |
|---|---|---|---|---|
| | | Low | Moderate | Severe |
| **Cardiovascular** | **64 (16.20%)** | **15** | **29** | **20** |
| Arterial hypertension | 34 (8.61%) | 7 | 24 | 3 |
| Arrhythmias | 1 (0.25%) | 0 | 1 | 0 |
| Deep vein thrombosis | 18 (4.56%) | 3 | 2 | 13 |
| Pulmonary thromboembolism | 6 (1.52%) | 0 | 2 | 4 |
| Hemorrhage (intratumoral) | 5 (1.26%) | 1 | 4 | 0 |
| **Infectious** | **49 (12.41%)** | **10** | **25** | **14** |
| Sepsis | 7 (1.77%) | 0 | 2 | 5 |
| Abscess | 10 (2.53%) | 2 | 5 | 3 |
| Urinary tract infections | 13 (3.29%) | 6 | 5 | 2 |
| Infecții plagă | 4 (1.01%) | 1 | 3 | 0 |
| Pneumonia | 3 (0.76%) | 0 | 1 | 2 |
| Other | 12 (3.04%) | 1 | 9 | 2 |
| **Thoraco-pulmonary or ENT** | **12 (3.04%)** | **3** | **8** | **1** |
| Dispneea | 5 (1.26%) | 0 | 4 | 1 |
| Pulmonary hemorrhage | 1 (0.25%) | 0 | 1 | 0 |
| Rinitis | 1 (0.25%) | 0 | 1 | 0 |
| Hemorrhage (epistaxis) | 5 (1.26%) | 3 | 2 | 0 |
| **Gastro-intestinal** | **49 (12.41%)** | **9** | **26** | **14** |
| Diarrhea | 7 (1.77%) | 2 | 3 | 2 |
| Nausea/Vomiting | 10 (2.53%) | 4 | 6 | 0 |
| Stomatitis | 3 (0.76%) | 2 | 1 | 0 |
| Gastritis/Ulcer | 1 (0.25%) | 0 | 1 | 0 |

| | | | | |
|---|---|---|---|---|
| Abdominal pain | 7 (1.77%) | 1 | 5 | 1 |
| Digestive fistula/perforation | 13 (3.29%) | 0 | 4 | 9 |
| Ileus/Oclusion | 2 (0.51%) | 0 | 2 | 0 |
| Digestive hemorrhage | 6 (1.52%) | 0 | 4 | 2 |
| **Genito-urinary** | **42 (10.63%)** | **8** | **23** | **11** |
| Proteinuria | 33 (8.35%) | 8 | 21 | 4 |
| Genito-urinary fistula | 2 (0.51%) | 0 | 0 | 2 |
| Renal impairment | 6 (1.52%) | 0 | 1 | 5 |
| Others | 1 (0.25%) | 0 | 1 | 0 |
| **Hematological** | **81 (20.51%)** | **38** | **35** | **8** |
| Anemia | 34 (8.61%) | 21 | 13 | 0 |
| Leucopenia | 24 (6.08%) | 10 | 8 | 6 |
| Thrombocytopenia | 20 (5.06%) | 6 | 12 | 2 |
| Neutropenia | 2 (0.51%) | 1 | 1 | 0 |
| Pancytopenia | 1 (0.25%) | 0 | 1 | 0 |
| **Neurologic** | **18 (4.56%)** | **7** | **9** | **2** |
| Neuropaties | 6 (1.52%) | 4 | 2 | 0 |
| Headache/migraine | 6 (1.52%) | 2 | 3 | 1 |
| Stroke | 6 (1.52%) | 1 | 4 | 1 |
| **Metabolic/nutritional** | **4 (1.01%)** | **3** | **1** | **0** |
| Dehydratation | 3 (0.76%) | 3 | 0 | 0 |
| Anorexia | 1 (0.25%) | 0 | 1 | 0 |
| **Cutaneous** | **5 (1.26%)** | **0** | **5** | **0** |
| **General complications** | **65 (16.46%)** | **17** | **45** | **3** |

N – number of patients; % - percentage from total.

### Identification of risk factors for the occurrence of complications

We performed a univariate logistic regression in an attempt to identify potential predictive factors for the occurrence of complications, and we included the results in Table 4.

**Table 4. Univariate logistic regression of risk factors for the occurrence of complications**

| Variable | OR | CI 95% | p-value* |
|---|---|---|---|
| Ischemic heart disease | 2.50 | [1.13, 5.53] | 0.0235 |
| Congestive heart failure | 2.31 | [1.10, 4.84] | 0.0263 |
| Chronic anticoagulant therapy | 2.96 | [1.31, 6.67] | 0.0090 |
| Coagulation abnormalities | 1.84 | [1.09, 3.12] | 0.0235 |
| Valvulopathies | 1.89 | [1.09, 3.27] | 0.0236 |
| Thromboembolic history | 3.03 | [1.14, 8.07] | 0.0261 |
| Colorectal cancer | 1.60 | [1.07, 2.39] | 0.0218 |
| Cervical cancer | 1.98 | [1.02, 3.86] | 0.0445 |
| Breast cancer | 0.31 | [0.12, 0.79] | 0.0138 |
| Serous carcinoma | 0.50 | [0.31, 0.82] | 0.0058 |
| Invasive ductal/lobular carcinoma | 0.29 | [0.11, 0.78] | 0.0147 |
| G3 | 1.91 | [1.38, 2.49] | 0.0123 |

However, in the multivariate analysis, all these factors no longer reached the threshold of statistical significance.

The loss of significance does not necessarily indicate that these factors are not clinically relevant, but rather that there are complex interactions between them that influence the statistical outcome.

## Study 4 – Quality of life, medical care–related costs, and oncologic outcomes in patients who develop complications specific to Bevacizumab therapy

### Oncologic outcomes of Bevacizumab therapy

The oncologic outcomes of Bevacizumab therapy were evaluated through survival parameters: overall survival (OS) and progression-free survival (PFS). In our sample, the median OS (estimated from the Kaplan–Meier curve) was 23 months.

When comparing the study group (patients with complications) and the control group (patients without complications), we found that OS was similar between the two groups, the differences not reaching statistical significance (log-rank test: $\chi^2 = 0.017$, $p = 0.896$).

Given the result of the unadjusted univariate log-rank test (which showed that, in isolation, the occurrence of complications does not appear to influence overall survival), we performed a multivariable Cox regression to evaluate the effect of each variable on the risk of death, adjusted for the influence of the others. In the multivariable analysis, in addition to the occurrence of complications, we included response to therapy (partial/quasi-complete response, stable disease, or disease progression), disease type (advanced/unresectable, metastatic, recurrent), neoplastic disease stage, and tumor differentiation grade — all factors consistently considered significant for the subsequent course of disease.

The presence of complications was not associated with an increased risk of death in this model. Although the hazard ratio was >1 (HR = 1.06), the wide confidence interval and nonsignificant p-value (0.7024) indicate a lack of a clear effect. Similarly, disease stage did not appear to be associated with an increased risk of death (HR = 1.05, 95% CI 0.4946–2.2257, $p = 0.9004$). Patients with poorer therapeutic response (progression < stable disease < partial response < quasi-complete response) had a significantly higher risk of death. The HR = 3.00 (95% CI 2.40–3.77, $p < 0.001$) indicates that with each step toward a weaker response, the patient's risk of death triples. Patients with metastatic disease or poorly differentiated tumors had a 3–4 times higher risk of death (HR: 4.31, 95% CI 2.18–8.52, $p < 0.001$, and HR: 1.72, 95% CI 1.26–2.36, $p < 0.001$, respectively).

If we analyze the overall survival of patients treated with Bevacizumab based on the primary tumor location, we observe significant differences among neoplasms. Thus, the median OS values estimated from Kaplan–Meier curves were: Colorectal: 26 months, Cervical: 21 months, Other origins: 19 months, Breast: 18 months, Pulmonary: 15 months, Ovarian/Tubal/Primary Peritoneal: 14 months.

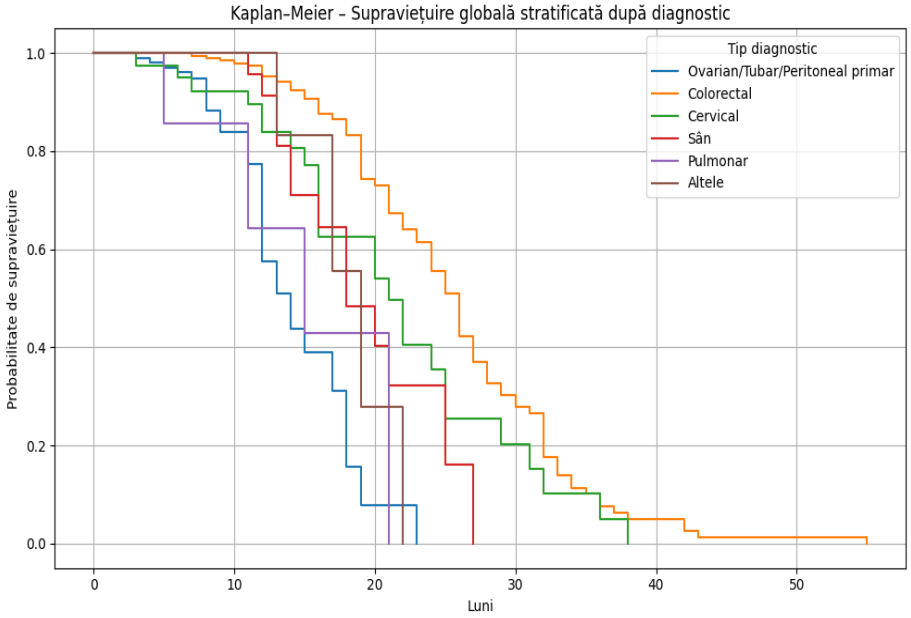


**Figure 1. Kaplan–Meier curves for OS by primary tumor location.**

Overall survival appears to be strongly influenced by the location of the primary tumor, with the best outcomes observed in colorectal cancers and the poorest outcomes in ovarian or primary peritoneal cancers. The result of the nonparametric Kruskal–Wallis test for comparing overall survival durations across the six cancer types confirms this (H statistic: 63.53, p-value < 0.00001). The multivariate log-rank test provides a similar result (Statistic: 99.18, p-value < 0.005).

When comparing progression-free survival based on the occurrence of Bevacizumab-associated complications, we did not observe statistically significant differences between the groups (log-rank test: $\chi^2 = 2.27$, $p = 0.13$), although patients with complications appeared to have a mean PFS approximately 4 months longer than those without complications (19 vs. 15 months), an apparently paradoxical effect but without statistical significance.

Because the unadjusted univariate log-rank test indicated that the occurrence of complications does not significantly influence overall survival, we applied a multivariable Cox regression model to estimate the effect of each factor on the risk of progression, adjusting for the influence of the other variables.

In the multivariate analysis, in addition to the occurrence of complications, we included response to therapy (partial/quasi-complete response, stable disease, or progression under treatment), disease type (advanced/unresectable, metastatic, recurrent), neoplastic stage, and tumor differentiation grade — factors known to influence disease evolution.

The proportional hazards Cox model was used to evaluate the relationship between PFS and several clinicopathological factors: the presence of Bevacizumab-associated complications, tumor response, disease stage, tumor differentiation grade, and disease type.

The analysis showed that the initial response to treatment with Bevacizumab is a strong and significant predictor of progression risk (HR = 1.67, $p < 0.001$).

Tumor differentiation grade also influenced progression risk, with more aggressive tumors being associated with a higher hazard ratio than well-differentiated ones (HR = 1.42, $p = 0.0014$). Recurrent disease was associated with a higher risk of progression than locally advanced or metastatic disease (HR = 3.67, $p < 0.0001$). Conversely, the occurrence of complications did not independently influence the risk of progression (HR = 0.92, $p = 0.43$), and the influence of initial disease stage became less relevant when other tumor characteristics and treatment response were considered (HR = 1.03, $p = 0.89$).

Subsequently, we analyzed progression-free survival in patients treated with Bevacizumab based on the location of the primary tumor and observed significant differences across neoplasms. Again, colorectal cancer ranked highest in terms of PFS (16 months).The poorest outcomes were recorded in lung cancer (8 months) and ovarian/primary peritoneal cancer (7 months). The nonparametric Kruskal–Wallis test confirmed that tumor location significantly influences PFS (H statistic: 114.25, p-value < 0.00001). The multivariate log-rank test — a more conservative test that accounts for censoring — also suggested that the differences in PFS by primary tumor location are likely real, as the results were statistically significant (Statistic: 156.79, p-value < 0.005).

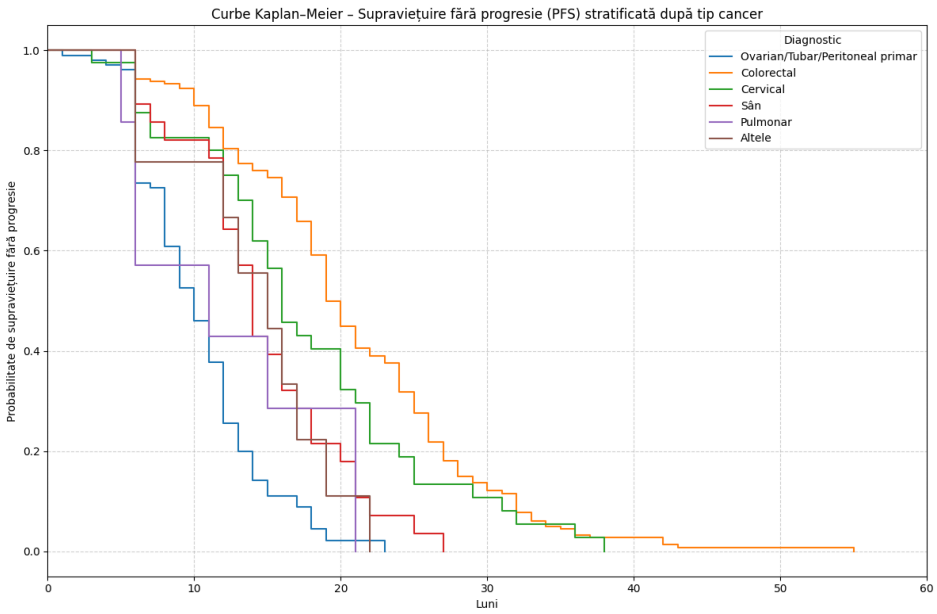


**Figure 2. Kaplan–Meier curves for PFS by primary tumor location**

**Discontinuation/cessation of Bevacizumab treatment**

Complications frequently led to temporary interruption or even permanent discontinuation of Bevacizumab treatment, due to deterioration of the patients' general condition and biological parameters, exacerbation of chronic comorbidities, or the occurrence of specific types of complications (which, according to the drug label, mandate treatment cessation — e.g., fistulo-perforative complications or severe hemorrhagic events). The result of the log-rank test for OS was $\chi^2 = 6.85$, df = 2, p = 0.032.

While short interruptions did not appear to significantly affect OS (p = 0.39), permanent discontinuation of therapy was associated with a significant reduction in survival time. This reflects either the severity of the complications or the lack of other effective therapeutic options. In contrast, the effect of treatment interruption or cessation on PFS was clear and statistically significant (log-rank test for PFS $\chi^2 = 10.93$, df = 2, p = 0.0042). Patients with temporary interruptions of Bevacizumab had a significantly shorter PFS than those who did not require interruptions (p = 0.044), although the magnitude of the difference was relatively small. However, permanent treatment discontinuation resulted in a significantly shorter PFS compared to patients without treatment interruption (p = 0.0016).

**Consequences of complications**

Complications associated with Bevacizumab often require additional medical care that generates extra costs, increases strain on the healthcare system, and—importantly—causes discomfort to patients, who must undergo medical procedures that are sometimes invasive. Of the 177 patients who developed at least one complication associated with Bevacizumab/biosimilars, 152 (85.88%) required medical care ranging from simple outpatient recommendations/interventions to multidisciplinary medical procedures and even surgical interventions. A total of 507 outpatient visits were recorded for complication management. Day-case or inpatient hospitalization was required for 125 patients (70.62%), while admission to the Intensive Care Unit (ICU) was necessary for 39 cases (22.03%). Most ICU admissions were for preoperative preparation and postoperative monitoring (30 patients – 16.75%). Among the 30 patients requiring surgery, indications included hemorrhagic complications, septic complications, bowel obstruction, or fistulo-perforative events. For three patients admitted to the ICU, early mortality (≤ 30 days from onset of the complication) was recorded: two due to septic complications leading to multiorgan failure, and one due to massive pulmonary thromboembolism followed by respiratory arrest.

Given that at IOB the fixed daily hospitalization cost is currently estimated at 689 RON, the total cost generated by complications over 36 months (enrollment + follow-up

period: 1 January 2022 – 31 December 2024) was 572,285 RON, equivalent to approximately 38,000 EUR per year. To this, we must add the costs of medical investigations, treatments, and staff salaries, which are typically 2–10 times higher than the fixed costs depending on case complexity. Using an average multiplier of 5, these costs amount to approximately 190,000 EUR/year. Thus, the total annual cost generated by managing complications associated with Bevacizumab therapy is 228,000 EUR/year, a significant burden for any institution.

Moreover, complications generate considerable numbers of outpatient consultations, medical visits, day-case and continuous hospitalizations, and ICU admissions. This overloads medical staff and leads to delays in scheduling other patients who present to our institution, regardless of pathology or treatment/monitoring needs.

**Quality of life and functional dependency in patients who develop complications**

The onset of complications generally results in a decline in quality of life. If before starting therapy patients self-rated their quality of life as good or very good—reflecting an optimal biological condition that allowed tolerance of systemic therapy—after the appearance of complications and the experience of required medical procedures, patients perceived a reduction in their quality of life.

On average, patients reported a decline in quality of life by one category from the pre-treatment assessment (mean = 0.97, SD = 1.02). Patients who developed severe complications reported 2–4 category decreases, with larger declines associated with longer hospitalization durations, ICU admission, the need for surgical intervention, and the extreme severity of complications (life-threatening situations).

We assessed the change in patient dependency level by analyzing shifts in ECOG performance status compared with pre-treatment values. The occurrence of complications translated into an average increase of approximately 0.5 points in performance score, reflecting a moderate functional impact on patients' overall condition.

**Study 5 – Development of clinical tools for selecting patients predisposed to developing complications associated with Bevacizumab therapy**

We used several predictive models developed through machine learning to estimate the risk of developing complications associated with Bevacizumab, based on pre-therapeutic variables:

- simple logistic regression – a model based on linear relationships between predictors and log-odds, relatively sensitive to outliers and noisy variables, but offering the advantage of easily interpretable coefficients in a clinical context;

- penalized logistic regression with Elastic Net – a method combining the advantages of L1 regularization (sparsity, variable selection) and L2 regularization (stability);
- Random Forest – a robust nonlinear model based on decision trees, with high capacity to capture complex relationships;
- XGBoost – a boosting-type model (incrementally improves errors), providing the highest accuracy, superior performance on complex data, and good handling of imbalance, but at the cost of reduced interpretability.

The statistical analysis and development of the predictive models were carried out using an interactive cloud-based Jupyter notebook platform (Google Colab).

All models were tested, and following evaluation we identified the model with the best performance (optimized 80/20 Random Forest), which was subsequently used to generate clinically applicable tools — a risk score and an interactive HTML-based form providing access to an automated risk calculator.

**Table 5. Variables and point values of the logistic-derived score**

| Variable | Category and score |
|---|---|
| Age | < 65 years – 0 points<br>≥ 65 years – 1 point |
| Urea | < 40 mg/dl – 0 points<br>≥ 40 mg/dl – 1 point |
| Leucocytes | < 10.000/mmc – 0 points<br>≥ 10.000/mmc – 1 point |
| Hemoglobin | ≥ 10 g/dl – 0 points<br>< 10 g/dl – 1 point |
| Transaminases (TGO/TGP) | < 40 U/l – 0 points<br>≥ 40 U/l – 1 point |
| Creatinine | < 1.5 mg/dl – 0 points<br>≥ 1.5 mg/dl – 1 point |
| Stage | Stadiul I-II – 0 points<br>Stadiul III-IV – 1 point |
| Diferentiation | G1-G2 – 0 points<br>G3 – 1 point |
| Lymphovascular invasion | Absentă – 0 points<br>Prezentă – 1 point |
| Type of cancer | Breast, Ovarian, Cervical – 0 points<br>Colo-rectal, Pulmonary, Other – 1 point |

**Table 5. Risk thresholds of the clinical score**

| Punctaj | Risk category | Probability of complications |
|---|---|---|
| 0-3 points | Low risk | < 25% |
| 4-6 points | Intermediate risk | 25–60% |
| 7-10 points | High risk | > 60% |

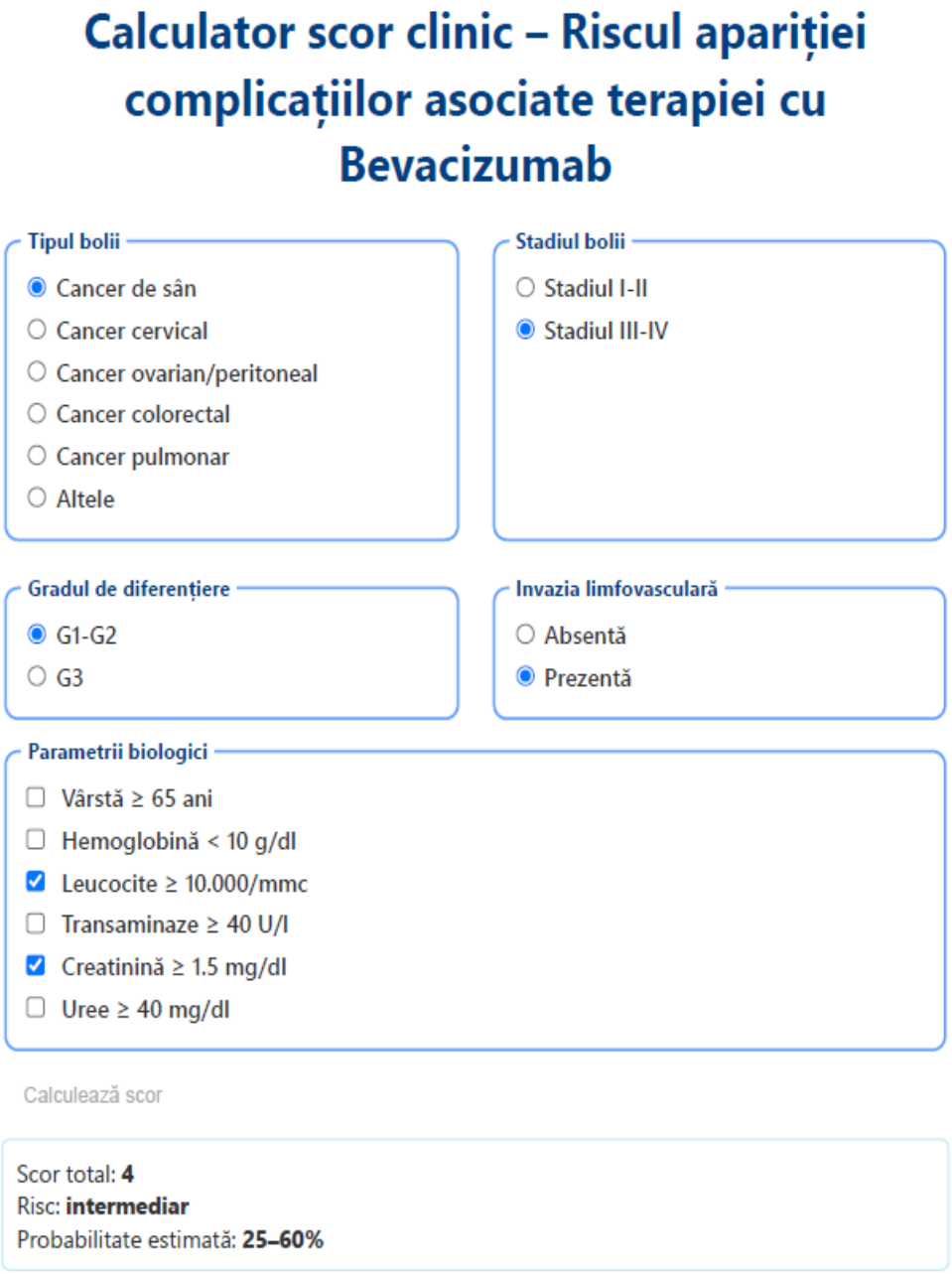


**Figure 3. Demonstration of the functionality of the interactive HTML form**

## References

[1] European Medicine Agency. Avastin - Annex I Summary of Product Characteristics. 2023.

[2] Simion L, Rotaru V, Cirimbei C, Stefan DC, Gherghe M, Ionescu S, et al. Analysis of Efficacy-To-Safety Ratio of Angiogenesis-Inhibitors Based Therapies in Ovarian Cancer: A Systematic Review and Meta-Analysis. Diagnostics 2023;13. https://doi.org/10.3390/diagnostics13061040.

[3] Chitoran E, Cirimbei C, Simion L, Tănase B, Ştefan D-C, Luca DC, et al. Fistula complications of bevacizumab therapy in metastatic colorectal cancer – oncology

surgeon's point of view: a case presentation. Oncolog-HematologRo 2022;4:29. https://doi.org/10.26416/ONHE.61.4.2022.7414.

[4] Download Mendeley Reference Manager For Desktop Windows | Mendeley n.d. https://www.mendeley.com/download-reference-manager/windows (accessed March 9, 2024).

[5] Savlovschi C, Serban D, Andreescu C, Dascalu A, Pantu H. Economic analysis of medical management applied for left colostomy. Chirurgia (Bucur) 2013;108:666–9.

[6] National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf (accessed March 6, 2024).

## List of published scientific papers

**A. Papers published in international journals indexed in ISI / PubMed:**

**1. Chitoran, E.;** Rotaru, V.; Ionescu, S.-O.; Gelal, A.; Capsa, C.-M.; Bohiltea, R.-E.; Mitroiu, M.-N.; Serban, D.; Gullo, G.; Stefan, D.-C.; et al. **Bevacizumab-Based Therapies in Malignant Tumors—Real-World Data on Effectiveness, Safety, and Cost**. *Cancers* 2024, 16, 2590. (https://www.mdpi.com/2072-6694/16/14/2590)

DOI: 10.3390/cancers16142590 (https://doi.org/10.3390/cancers16142590)

Impact factor 4,5 (SCIE)/ Quartile Q1 (Oncology) - First author – Type of article: Original Research (Chapter 5)

**2. Chitoran, E.;** Rotaru, V.; Stefan, D.-C.; Gullo, G.; Simion, L. **Blocking Tumoral Angiogenesis VEGF/VEGFR Pathway: Bevacizumab—20 Years of Therapeutic Success and Controversy.** *Cancers* 2025, *17*, 1126. (https://www.mdpi.com/2072-6694/17/7/1126)

DOI: 10.3390/cancers17071126 (https://doi.org/10.3390/cancers17071126)

Impact factor 4,5 (SCIE)/ Quartile Q1 (Oncology) - First author – Type of article: Systematic review (Chapter 1 and și Chapter 2)

**3. Chitoran E,** Rotaru V, Gelal A, Ionescu S-O, Gullo G, Stefan D-C, Simion L. **Using Artificial Intelligence to Develop Clinical Decision Support Systems—The Evolving Road of Personalized Oncologic Therapy.** *Diagnostics* 2025, 15, 2391. (https://www.mdpi.com/2075-4418/15/18/2391)

DOI: 10.3390/diagnostics15182391 (https://doi.org/10.3390/diagnostics15182391)

Impact factor 3,3 (SCIE)/ Quartile Q1 Medicine, General and Internal) First author – Type of article: Original Research (Chapter 7 și Chapter 9)

**B. Papers published in BDI-indexed journals:**

**1. Chitoran, E.;** Cirimbei, C.; Simion, L.; Tănase, B.; Ştefan, D.C.; Luca, D.C.; Rotaru, V. Fistula complications of bevacizumab therapy in metastatic colorectal cancer – oncology surgeon's point of view: a case presentation. First published: 13 decembrie 2022. Editorial Group: MEDICHUB MEDIA. DOI: 10.26416/OnHe.61.4.2022.7414. Din anul 2013 indexata in EBSCO Academic Search & One Belt, One Road Reference Source. https://www.medichub.ro/reviste-de-specialitate/oncolog-hematolog-ro/fistula-complications-of-bevacizumab-therapy-in-metastatic-colorectal-cancer-oncology-surgeon-s-point-of-view-a-case-presentation-id-7414-cmsid-68

**First author – Type of article: Case presentation (Chapter 6)**