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Outcomes of Initial Therapy in Patients with Ovarian, Fallopian Tube, or Peritoneal Cancer: Insights from a German Clinical Cancer Registry Analysis

N. Abdel-Rahman[1*], M. El-Sayed[1], T. Fawzy[1]

[1]Department of Surgical Oncology, Faculty of Medicine, Cairo University, Cairo, Egypt.

***E-mail** ✉ surgical.oncology.6@emailprovider.net

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ABSTRACT

Current ovarian cancer (OC) treatment follows the "Three-Pillar-Model," which includes surgery, chemotherapy, and maintenance therapy. This study presents the first comprehensive analysis of a federal cancer registry for OC patients from Berlin and Brandenburg in Germany. The main aim was to assess established quality indicators, including surgical outcomes, use of adjuvant chemotherapy, and completeness of surgical staging in early-stage disease. Data from the Clinical Cancer Registry of Brandenburg and Berlin covering 2009–2019 were examined. Study objectives were defined by a panel of specialized physicians. Analyses included descriptive statistics and survival evaluations. A total of 2,771 primary OC cases were evaluated. Histological subtypes largely aligned with expectations, with high-grade serous OC predominating in advanced stages. Complete surgical staging was achieved in 57% of FIGO I–IIA cases, while macroscopic complete resection was accomplished in 53% of patients with FIGO stage >III. Five-year survival rates ranged from 79% for FIGO I to 40% for FIGO III. The proportion of patients receiving adjuvant chemotherapy exceeded 50%. These findings provide insight into quality metrics and treatment outcomes, demonstrating generally favorable results for patients with primary OC. Nevertheless, observed gaps highlight areas for improvement and can inform the development of new quality indicators to enhance patient care.

Keywords: Lymphadenectomy, Ovarian cancer, Adjuvant chemotherapy, Primary surgery

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Introduction

In recent years, both the diagnosis and treatment approaches for primary and recurrent ovarian cancer (OC) have undergone substantial advancements. Among these, the development and incorporation of maintenance therapy have significantly reshaped therapeutic strategies for OC patients [1, 2]. Nevertheless, the emergence of innovative treatment models introduces new complexities in patient management, influencing both medical professionals and their patients. In Germany, approximately 7,500 new cases of ovarian, fallopian tube, or peritoneal cancer are diagnosed annually. These malignancies represent the fifth most common cancers among German women, with an incidence rate of 4.8%, following breast, colorectal, lung, and endometrial cancers. Despite their relatively lower incidence, OC continues to have the highest mortality rate among all gynecological cancers [3, 4]. Nearly two-thirds of patients present with advanced disease (FIGO stages IIIB–IV) at initial diagnosis [5]. This late detection is largely attributed to the disease's vague and non-specific symptoms—such as abdominal discomfort—and the absence of effective early diagnostic tools or screening programs aimed at improving survival outcomes like overall survival (OS) and progression-free survival (PFS). While such outcomes are frequently reported through clinical trials and national cancer registries, "real-world data" from population-based cancer registries are equally crucial. These data not only highlight diagnostic and therapeutic gaps in clinical practice but also provide valuable insights that can inspire future clinical trial hypotheses.

This study represents the first comprehensive analysis based on cancer registry data from the two major German federal states—Berlin and Brandenburg. The project stems from a collaborative initiative between the "Project Group Ovarian Cancer Berlin/Brandenburg" and the regional cancer registry. The registry collects extensive clinical and demographic data for patients diagnosed with ovarian, fallopian tube, and peritoneal cancers. This initial analysis focuses on several key aspects of OC management: the accuracy of surgical staging in early-stage disease (up to FIGO IIA), the significance of systematic pelvic and paraaortic lymphadenectomy and omentectomy, the frequency of achieving complete macroscopic resection in advanced cases, and the use of neoadjuvant and adjuvant chemotherapy. Additionally, it examines pathological findings, particularly tumor grading (high vs. low grade). These parameters were selected due to their well-documented influence on survival outcomes, such as the prognostic value of complete tumor resection and proper staging in early OC.

Materials and Methods

Data and methods

Data source and study design

This evaluation utilized data from the Clinical Cancer Registry for Brandenburg and Berlin, which officially began collaborative operations on July 1, 2016. While Berlin initiated its comprehensive registration system at that time, Brandenburg had already established a long-standing tradition of cancer registration exceeding two decades, previously based on voluntary collaboration with statutory health insurers.

The study examined two main endpoints: first, a descriptive overview of ovarian cancer cases (including histopathological subtypes and FIGO stages) and their management (surgical interventions and systemic therapies) in Brandenburg and Berlin between 2016 and 2018; second, a five-year overall survival analysis stratified by FIGO stage and histopathological subtype. Due to the requirement for longer follow-up periods, survival analyses were restricted to data from Brandenburg, covering diagnoses made from 2009 to 2015.

To ensure comprehensive mortality tracking, the registry cross-referenced its data with the death records of the joint cancer registry serving Berlin, Brandenburg, Mecklenburg-Western Pomerania, Saxony-Anhalt, and the Free States of Saxony and Thuringia (GKR). The GKR integrates information from civil registration offices and public health authorities, guaranteeing full capture of death data. Through this collaboration, the Clinical Cancer Registry of Brandenburg and Berlin also receives supplementary mortality data not directly reported to it, ensuring completeness. At the time of analysis, the GKR had processed death certificates up to the end of 2015, and this information was subsequently incorporated into the registry's database.

The analyses presented in this study were conducted using data available as of August 12, 2020, for diagnosis, chemotherapy, and mortality information, and as of October 3, 2020, for surgical data from the Clinical Cancer Registry of Brandenburg and Berlin.

Inclusion and exclusion criteria

Patients diagnosed with ovarian, peritoneal, or fallopian tube cancer were identified using the following diagnostic classifications: ICD-10 codes C56, C57.0, C48.1–C48.2, and ICD-O code C57.9. Cases diagnosed as sarcomas or germ cell stromal tumors were excluded. Additionally, in situ carcinomas and borderline malignant variants of ovarian, peritoneal, and fallopian tube cancers were not included in this analysis.

For therapy-related assessments, the patient's state of treatment was considered, whereas analyses concerning FIGO stage distribution and overall survival were based on the state of residence at the time of diagnosis. Unless indicated otherwise, the treatment location was defined as the state in which the initial tumor-resecting surgery was performed for ovarian, fallopian tube, or peritoneal cancer. Surgical tumor removal was identified using OPS codes 5-652, 5-653, 5-661, 5-682, 5-683.1/.2/.6/.7, 5-687, 5-651.8/.9/.a, 5-665.4, and 5-543.0/.1/.2/.4.

It should be noted that the total number of cases analyzed varied depending on the inclusion criteria specific to each research question. Overall, 1272 patients were included in the analysis, with smaller subgroups identified for parameters such as "macroscopic complete resection," "comprehensive surgical staging in early-stage disease," "neoadjuvant treatment," and "adjuvant chemotherapy."

Criteria for histopathological grading classification

Tumors classified as grade G1 were grouped under "low-grade," while those graded G3 or G4 were categorized as "high-grade." For intermediate-grade (G2) tumors, classification was based on histologic subtype: serous and

clear cell carcinomas were assigned to the high-grade group, while mucinous and endometrioid types were categorized as low-grade. Cases with non-specific or indeterminate histologies (e.g., adenocarcinoma NOS, carcinoma NOS) were excluded from analyses where histopathological grading was a factor. However, these cases were included in analyses that did not differentiate between low- and high-grade tumors.

Identification of therapies and macroscopic complete resection

Surgical procedures were identified via OPS codes. Systematic lymphadenectomy was determined using OPS codes 5-402, 5-404, 5-406, 5-407, 5-685.1/.2/.3, 5-685.41/.42/.43, and 5-686.1/.2/.3. Furthermore, cases reporting the examination of more than two lymph nodes were also classified as having undergone systematic lymphadenectomy, even in the absence of a specific OPS code. Omentectomy procedures were identified with OPS code 5-543.2. The frequency of each therapeutic procedure was reported as the number or percentage of tumor cases in which the respective intervention was performed.

A macroscopically complete resection was defined as achieving a global R0 or R1 resection status. In situations where a global R classification was missing but a local R0 category (without metastasis) or documentation of complete remission was present, the case was likewise regarded as macroscopically complete resection. Information on complete remission was obtained from tumor progression data.

For chemotherapy analysis, any patient with a documented initiation of systemic therapy was categorized as having received chemotherapy. The sequencing of chemotherapy in relation to surgery (i.e., neoadjuvant vs. adjuvant) was determined by comparing the start date of systemic therapy with the date of the initial tumor-resecting surgery.

Statistical analysis

All analyses were stratified according to FIGO stage and histopathological grading. Both absolute and relative frequencies were computed. Overall survival (OS) was defined as the time from diagnosis to death from any cause, or to the censoring date of December 31, 2015. Survival data were analyzed using Kaplan–Meier methodology, with 60-month survival probabilities reported by FIGO stage and histopathological grading. Comparisons between survival curves were conducted using the log-rank test, with statistical significance set at $p < 0.05$. Analyses were performed using IBM SPSS Statistics version 24.0. Additionally, survival plots with 95% confidence intervals and numbers at risk were created using RStudio version 4.1.0 with the survminer package.

Results and Discussion

Between 2016 and 2018, a total of 1500 primary cases of ovarian, fallopian tube, or peritoneal cancer were documented among residents of Brandenburg and Berlin. For the period 2009–2015, 1303 cases were recorded, excluding sarcomas, germ cell stromal tumors, as well as in situ and borderline malignant carcinomas. Additional details regarding patient selection and inclusion criteria are illustrated in **Figure 1**.

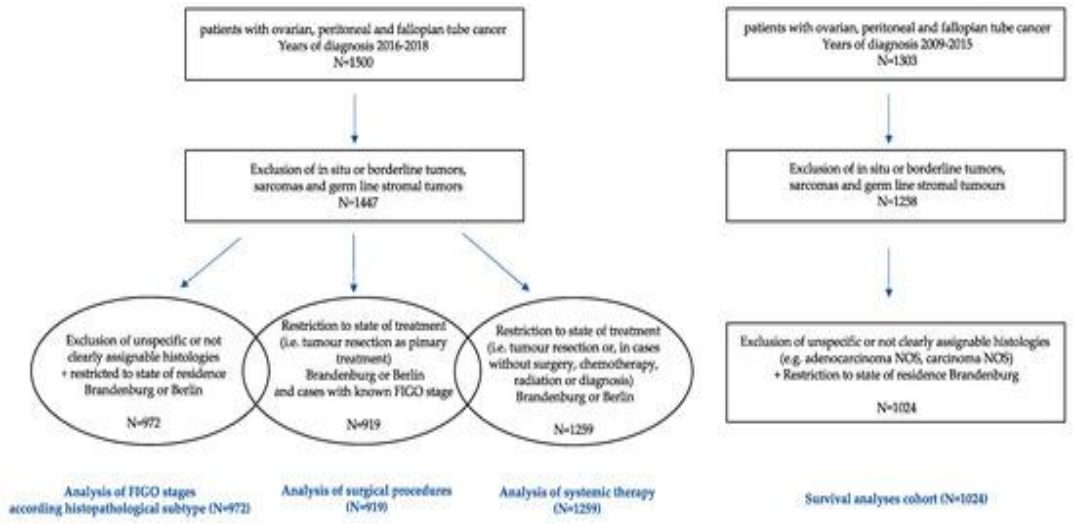


Figure 1. Flow chart illustrating the selection criteria and process.

Results for FIGO stage, histology, and grading

After narrowing the dataset to include only serous, non-serous, and clear cell carcinoma cases, the total number of eligible patients decreased to 972. Among these, high-grade carcinomas were most frequently diagnosed at FIGO stage III (47%), whereas low-grade carcinomas were predominantly detected at FIGO stage I (55%) **(Figure 2 and Table 1)**. Serous carcinoma represented the most prevalent histological subtype.

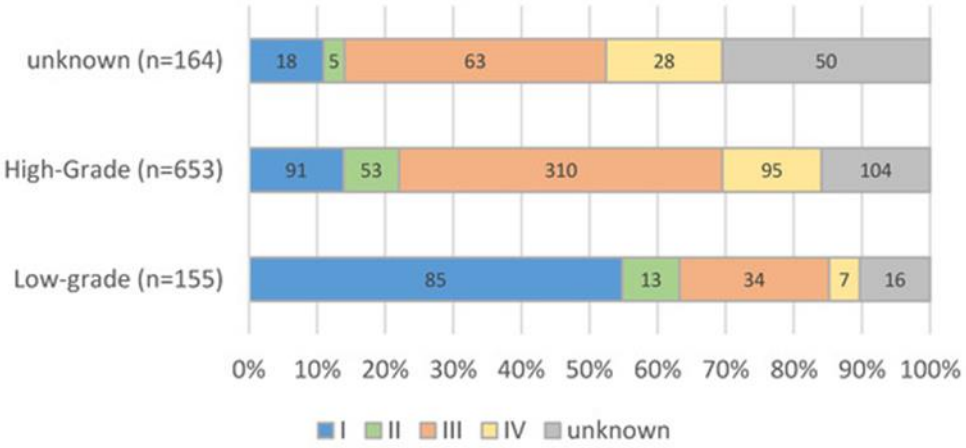


Figure 2. Distribution of FIGO stages by histopathological subtype for cases diagnosed between 2016 and 2018 (n = 972).

Table 1. General cohort characteristics.

	Years of Diagnosis 2016–2018, Patients from Brandenburg and Berlin (n = 972)		**Year of Diagnosis 2009–2015, Patients from Brandenburg (n = 1024)** [1]	
Median age (years)	66.3		67.7	
State of residence	n	%	n	%
Brandenburg	478	49.2	1024	100.0
Berlin	494	50.8	NA	
FIGO stage				
I	194	20.0	207	20.2
II	71	7.3	77	7.5
III	407	41.9	408	39.8
IV	130	13.4	180	17.6
not specified	170	17.5	152	14.8
Grading				
low	155	15.9	138	13.5
high	653	67.2	730	71.3
unknown/not specified	164	16.9	156	15.2
Histology group[2]				
Serous	798	82.1	809	79
Non-serous (endometrioid, mucinous)	140	14.4	179	17.5
Clear cell	34	3.5	36	3.5

[1] This subset of patients was utilized exclusively for survival assessment and is presented solely for comparative reference. 2 All germ cell tumors and sarcomas were omitted from the analyses. Additionally, tumor types that could not be definitively categorized as serous, non-serous, or clear cell were excluded from evaluations in which histopathological grading played a role—such as analyses of survival outcomes or FIGO stage distribution by subtype.

Surgical evaluation and macroscopic tumor resection outcomes

The surgical component of the study included 919 individuals, reflecting a refined cohort selected based on criteria related to "tumor staging" and "macroscopically complete resection." These patients, diagnosed between 2016 and 2018 across FIGO stages I–IV, received treatment within Berlin or Brandenburg.

In early-stage disease (FIGO I–IIA), systematic lymphadenectomy was conducted in 57% of patients in Brandenburg and 60% in Berlin. Overall, the data revealed no significant disparities between early and advanced disease stages or between the two states **(Figure 3)**. The performance of omentectomy in early-stage cases was reported in 68% of patients in Brandenburg and 75% in Berlin **(Figure 4)**.

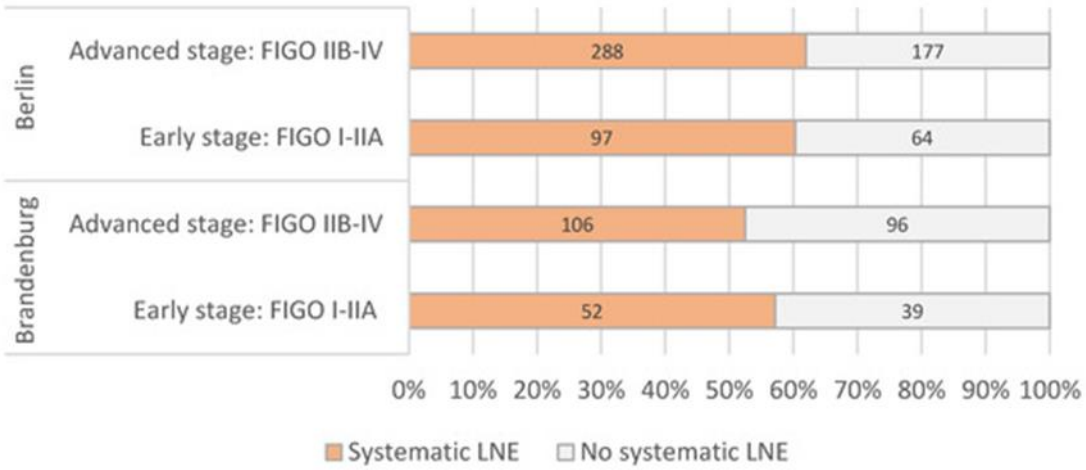


Figure 3. Percentage of primary ovarian cancer patients who underwent or did not undergo systematic pelvic and paraaortic lymphadenectomy, categorized by FIGO stage (n = 919; diagnosis years 2016–2018).

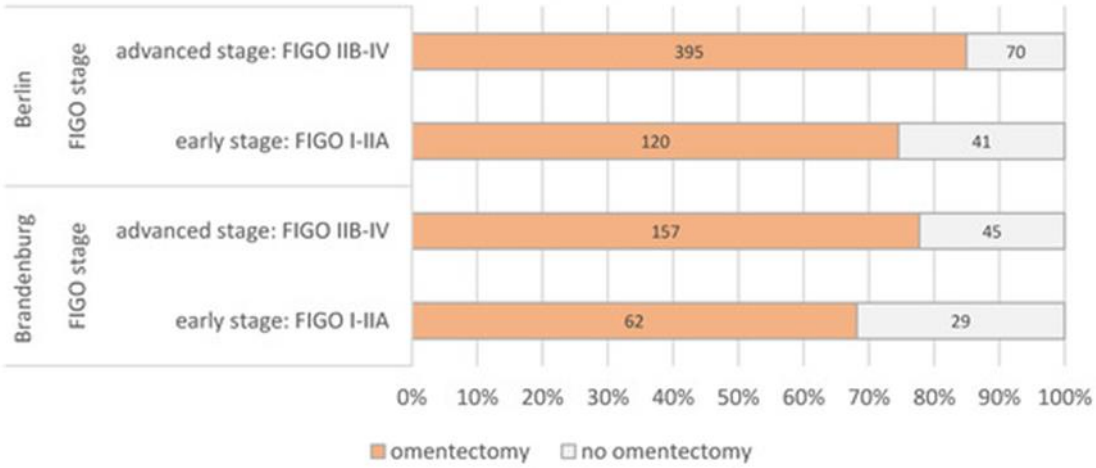
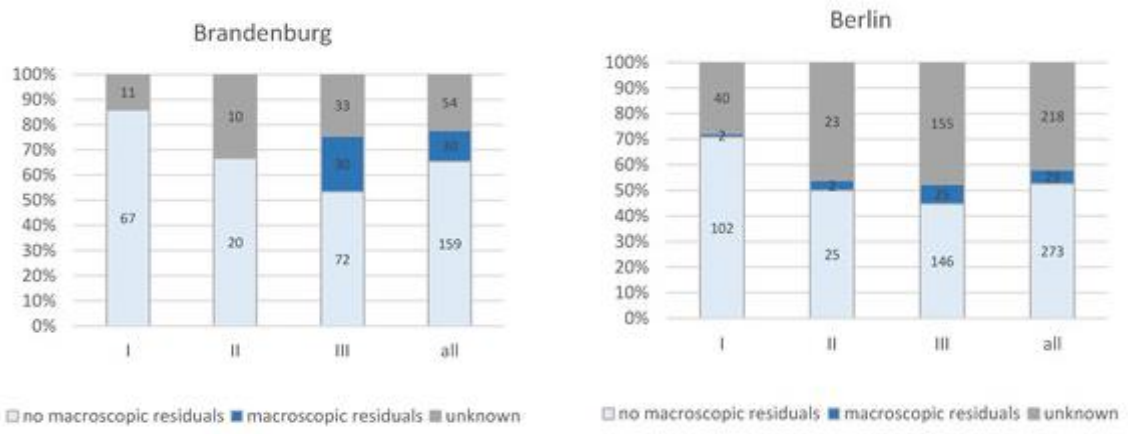


Figure 4. Percentage of primary ovarian cancer patients who underwent or did not undergo omentectomy, presented by FIGO stage (n = 919; diagnosis years 2016–2018).

Figure 5 illustrates the proportion of patients achieving macroscopically complete resection across FIGO stages I to III, comparing treatment outcomes between the federal states of Berlin and Brandenburg. As anticipated, earlier stages demonstrated noticeably higher rates of complete macroscopic tumor removal. For the most prevalent stage, FIGO III, complete resection was achieved in 53% of patients in Brandenburg and 45% in Berlin. It is important to emphasize, however, that a substantial number of cases lacked recorded data on resection status.



a) b)

Figure 5. Percentage of patients achieving macroscopically complete resection by FIGO stage and by treatment region (Berlin vs. Brandenburg) (n = 763; FIGO I: n = 222, FIGO II: n = 80, FIGO III: n = 461).

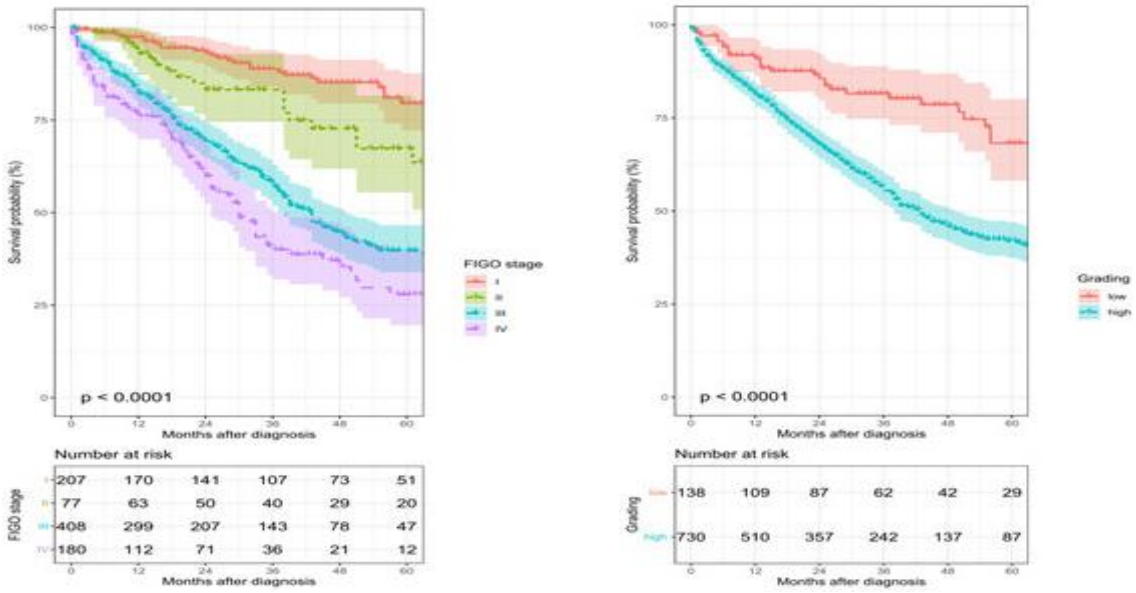
Systemic therapy

To examine the utilization of systemic therapy by FIGO stage, data from both federal states encompassing 1,259 patients diagnosed between 2016 and 2018 were analyzed. In contrast to the surgical analyses described in Section 3.2, the treatment location in this context referred to the federal state where the initial tumor resection occurred, or—if no surgery was performed—the state where chemotherapy, radiotherapy, or diagnosis took place.

Overall, chemotherapy was recorded in 54% of all patients treated in Brandenburg or Berlin across all FIGO stages. Among all cases, neoadjuvant chemotherapy accounted for 6%, while adjuvant chemotherapy was documented in 41%. Of those receiving adjuvant chemotherapy, 81% began treatment within eight weeks following their first tumor resection. Notably, patients in advanced disease stages were more likely to initiate chemotherapy within this eight-week period compared with those in early stages.

Survival analysis results

Both FIGO stage and histopathological grading emerged as significant predictors of overall survival (Figure 6). Patients with FIGO stage III disease exhibited an absolute 5-year survival rate of 40%, while those with stage IV disease had a rate of 28%. In contrast, early-stage patients (FIGO I and II) demonstrated considerably better outcomes, with 5-year survival rates of 79% and 67%, respectively. A pronounced survival difference was also evident between tumor grades—high-grade carcinomas showed a 42% 5-year survival rate compared to 68% for low-grade tumors. Survival data used in this analysis were exclusively derived from the Brandenburg Cancer Registry for cases diagnosed between 2009 and 2015.



a) b)

Figure 6. Five-year survival stratified by FIGO stage ((a), n = 872) or tumor grading ((b), n = 868) for patients diagnosed between 2009 and 2015.

This study represents the first comprehensive evaluation of data from the federal cancer registry of Berlin and Brandenburg, focusing on several clinical aspects of primary ovarian cancer (OC) management. While there are some analyses from other German states or through quality certification assessments, the current work results from a collaborative effort of clinical and scientific experts. A comparable assessment involving over 600 OC patients has been conducted in Bavaria, although the findings have only been presented in a poster at a national congress and are not yet available as a full-text publication [6].

Despite advances in systemic therapies for OC, primary upfront debulking surgery remains a cornerstone in the treatment of both primary and recurrent disease. Surgery constitutes a critical component of the so-called "three-pillar strategy," which includes surgical intervention, systemic chemotherapy, and maintenance therapy. Notably, achieving macroscopic complete resection of all visible intra-abdominal tumors is a key factor influencing both progression-free survival (PFS) and overall survival (OS) in primary and recurrent settings.

Nevertheless, several clinical questions remain unanswered. These include the optimal timing for debulking surgery, the best preoperative evaluation methods to identify patients eligible for complete macroscopic resection, and strategies to minimize surgery-related morbidity and mortality. Careful consideration of these factors is essential, as they directly impact survival outcomes such as PFS and OS. The present analysis highlights the high standard of care for OC patients in Berlin and Brandenburg, in line with nationally and internationally established quality metrics [7, 8]. Additionally, recent evidence suggests a general decline in cancer mortality across Europe [8]. The stage-specific five-year survival rate for FIGO stage III patients is 40%, consistent with previously published data [9]. Moreover, the rate of macroscopic complete resection during primary upfront debulking in advanced disease remains high [10].

However, limitations exist, particularly regarding accurate documentation of macroscopic tumor residuals. International guidelines recommend that surgeons explicitly report postoperative residuals as either macroscopic complete resection, residuals <10 mm, or residuals >10 mm. In the Berlin/Brandenburg cancer registry, this is currently recorded using the TNM classification with R status (R0, R1, R2), which is outdated for OC. This represents a major limitation of the current database, which will be addressed prospectively based on these findings.

Regarding surgical staging in early-stage OC and the administration of adjuvant therapy, the data show variability. The rate of systematic para-aortic and pelvic lymphadenectomy ranged between 52% and 61%, falling below expected levels. This is noteworthy given the importance of comprehensive lymphadenectomy for proper staging, as incomplete staging has been associated with significantly worse PFS and OS (5-year PFS 79% vs. 61%, 5-year OS 89% vs. 71%) [11–16]. However, it is unclear whether these findings reflect actual clinical practice or inconsistencies in reporting. The considerable variation observed suggests that reporting inaccuracies may play a

role. Similarly, the documented rates of adjuvant systemic therapy in advanced-stage disease were suboptimal, but this may largely reflect underreporting, as adjuvant therapy in Germany is frequently administered outside the surgical center, often in outpatient settings. The data also indicate that neoadjuvant therapy is relatively infrequent in primary OC within Berlin and Brandenburg.

Conclusion

These "real-world" data provide valuable insights into the quality of care and treatment outcomes for OC patients. While survival outcomes and treatment characteristics appear favorable, the analysis also highlights significant gaps in reporting and database consistency. Updating the cancer registry is crucial, particularly to incorporate new therapeutic approaches such as maintenance therapy, as well as long-term survivorship issues. Continuous revision is further justified by the rapid evolution of treatment guidelines. For instance, the ESGO updated quality indicators for advanced OC surgery in 2020, and integration of such indicators into registry data could enhance the assessment of care quality for OC patients [7].

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Conflict of Interest: None

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Ethics Statement: None

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