Research Square

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Ovarian Cancer - Poor Prognosis in Association with Neoadjuvant Therapy

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Research Article

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Abstract

More than 70% of ovarian cancers are diagnosed in advanced stages. Prognosis, in particular for stages FIGO III and FIGO IV unfavorable. In recent years enhancements in drug therapy improved survival rates. Beside clear benefits of novel agents potential merits due neoadjuvant therapeutic settings are currently subject of controversial debate. Comprehensive data from cancer registries hold the potential to shed light on the ongoing controversy. Analyses on tumor conferences and course of therapy were based Data from the Cancer Registry of Rhineland-Palatinate at the Institute for Digital Health Data, Germany. Patients diagnosed with ovarian cancer between 2016 and 2023 and available reports on surgery and medical treatment were included. At first the influence of tumor conferences on treatment decisions was evaluated. Next, event-free and overall survival were investigated in relation to neoadjuvant therapies. Analyses were performed using R. A total of 1,704 ovarian cancer patients who underwent surgery and systemic therapy were included. Neoadjuvant therapies were reported more frequently in association with tumor conferences than adjuvant therapies. Statistical analyses revealed that event-free and overall survival were significantly more favorable for tumors without neoadjuvant therapy ($p < 0.0001$). Comprehensive cancer registry data provide insight into all administered therapies and thus enable unbiased evaluation of treatment outcome. Analyses of cancer registry data are independent of clinical studies and include overarching information from inpatient and outpatient oncological institutions.

Introduction

Approximately one in every 74 women in Germany will be diagnosed with ovarian cancer during her lifetime [1]. Survival is highly related to stage of the disease at diagnosis. Unfortunately, more than 70% ovarian tumors are only detected at advanced stages FIGO (Fédération Internationale de Gynécologie et d'Obstétrique; English: International Federation of Gynecology and Obstetrics) III or FIGO IV [1]. Delays in tumor detection is mainly caused by limitations of current screening methods [2]. Unfortunately advanced ovarian cancers are associated with poor prognosis mainly reflected by relative 5-year survival rates indicating about 40% survival for patients diagnosed with for FIGO III and about 20% survival for patients with metastatic stage FIGO IV [1]. Fortunately, the number of new cases, as well as incidence and mortality rates, have been declining in Germany for more than 20 years [1]. Particularly improvements in medical care have crucial impact on this trend. Special milestones were the introduction of novel substances such as inhibitors of the enzyme poly-ADP-ribose polymerase (PARP) and the antibody bevacizumab [3]. Beside clear benefits of novel agents the optimal course of therapy, with particular focus on neoadjuvant treatment, is still under debate. Advantages of neoadjuvant therapy approaches have been successfully established for various types of cancer, including breast cancer [4]. However, despite merit for other tumors potential benefits of neoadjuvant chemotherapy for ovarian cancer is subject of controversy [3]. As of yet, neoadjuvant concepts were and are investigated in various clinical studies [5]. Their results are also subject of discussion in the current S3 guideline for ovarian cancer, resulting in a recommendation for surgical removal of the tumor as the first therapeutic procedure [6]. However, there are still ongoing clinical trials with the aim to evaluate potential benefits of chemotherapeutic agents administered prior to tumor resection [7, 5]. Beyond controversy about recommendations regarding neoadjuvant approaches it is

known that the likelihood that cancer patients receive guideline-concordant treatment varies according to cancer type, age, comorbidities and treating institution [8]. Even in the presents of carefully established S3 guidelines, the decision on optimal treatment for each individual patient remains a balancing act. Particular challenges came along with the advantages of an enormously increased number of therapeutic options creating a high degree of complexity with respect to oncological treatment. Therefore, interdisciplinary consultation and recommendations for treatment strategies are an essential part of qualified patient care [9]. Such consultations are usually subject of tumor boards. First multidisciplinary tumor conferences were held in the 1970s. Today, implementation of tumor boards is a requirement in the certification process of the German Cancer Society. Noteworthy, even non-certified institutions and networks discuss cancer cases in tumor conferences [10]. Although a positive impact of tumor boards on treatment and survival of cancer patients is known, this effect has not yet been routinely recorded [3]. Fortunately, documentation of cancer cases discussed in interdisciplinary tumor conferences is available within the framework of cancer registration [11]. In addition to these conferences, cancer registries in Germany collect information on diagnosis, treatment, progression and death of all cancer patients. This information is reported to the registries from the inpatient and outpatient sector [12]. Based on this unique collection of real-world data, cancer registries hold the potential to contribute essentially to issues such as addressed in the herein performed investigation. On contrast to clinical studies cancer registration provides unbiased insight into actual treatment of all cancer patients and its impact on the course of the disease. Accordingly, in addition to reports on tumor conferences, the study reported here compared different neoadjuvant and adjuvant approaches and analyzed their impact on event-free and overall survival.

Patients and Methods

This investigation was based on information available in the database of the Cancer Registry of Rhineland-Palatinate in the Institute of Digital Health Data, Germany. Cancer registration in the German federal state Rhineland-Palatinate originally started on the level of epidemiological data, covering a population of approximately 4 million inhabitants. For this aim an epidemiological cancer registry was founded in 1997 and in 1998 the collection of basic information on incidence, prevalence, mortality and survival of cancer patients started. In 2016 the well established epidemiological cancer registration was transferred to the newly founded clinical-epidemiological cancer registry. Main focus of the new institution was the collection of comprehensive data regarding diagnosis, histo-pathological characteristics of tumors, treatment and follow-up of cancer patients, resident and/or treated in Rhineland-Palatinate. Digitalization of external data transmission and internal processing started in 2016. Since 2018 cancer registration in Rhineland-Palatinate is fully digitized. As of yet, each day more than 900 new reports are included into the database [13]. Since datasets need to be comparable among cancer registries in Germany, survey of data was standardized by introducing the nationwide uniform oncological dataset [11]. The current study included patients with ovarian cancer (International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification [ICD-10-GM] C56) diagnosed between January 2016 and December 2023. In addition, at least one report on tumor-therapeutic surgery and systemic therapy needed to be available. FIGO stages were calculated according to the currently valid international criteria

for TNM classification of malignant tumors [14]. For the evaluation of tumor conferences, tumors with at least one reported conference were compared with those without any report on a tumor board. Percentage of tumor conferences was calculated for each FIGO stage and for each therapy group. The first therapy group comprised patients who received neoadjuvant therapy but no adjuvant therapy. The second group comprised patients who received neoadjuvant and adjuvant therapy, and the third group included patients who received adjuvant therapy but no neoadjuvant therapy. Event-free and overall survival for the first 7 years after diagnosis were analyzed for each treatment group by Kaplan-Meier curves. P-values were calculated using log-rank test. Survival analyses were performed independently of the FIGO stage as well as for the most frequent stages FIGO III and FIGO IV. For event-free survival, recurrences or occurrence of metachronous distant metastasis, progression, a new tumor in the same organ and death of the patient were considered as events. Status of the data was November 3, 2025. Analyses were performed using R in R Studio [15, 16].

Results

A total of 1,704 patients with ovarian cancer was included in the present analysis. Distribution of FIGO stages was as follows: FIGO I 24%, FIGO II 6%, FIGO III 31%, and FIGO 49%. Reports on tumor conferences differed among stages (data not shown). In detail, tumor boards were reported for 53% of FIGO I tumors, 65% of FIGO II tumors, 58% FIGO stage III tumors and 46% of FIGO IV tumors. Evaluation regarding treatment approaches showed that tumor conferences were reported for 62% of tumors treated with adjuvant chemotherapy but not with neoadjuvant therapy. In the group harboring cases with neoadjuvant chemotherapy but without adjuvant treatment the proportion of tumors with tumor conferences was 70%. In the treatment group with neoadjuvant and adjuvant chemotherapy tumor boards were reported for 80% of included cases (Fig. 1).

Survival analyses were done at first independently of the FIGO stage and in a next step for FIGO III and FIGO IV separately. Evaluation of treatment success independent of FIGO stage showed similar survival rates for patients receiving neoadjuvant therapy followed by adjuvant therapy and patients with neoadjuvant therapy without adjuvant therapy (Fig. 2). In comparison to these two treatment groups patients who received adjuvant therapy without neoadjuvant treatment showed most favorable survival rates. This effect was statistically significant for event-free and overall survival (Figs. 2a and 2b, $p < 0.0001$). The analyses of FIGO III and FIGO IV separately showed different results. Results for FIGO III revealed again poor event-free and overall survival in associated with neoadjuvant treatment with or without adjuvant therapy. Even for FIGO III adjuvant therapy without neoadjuvant treatment showed most favorable outcome. These results were significant (Figs. 3a and 3b, $p = 0.008$). However, for patients diagnosed with FIGO IV no statistically significant effects were observed by comparison of the three therapy groups (Figs. 3c $p = 0.37$ and 3d $p = 0.47$).

Discussion

Distribution of FIGO stages of the herein analyzed ovarian cancer patients corresponds to proportions observed in Rhineland-Palatinate over time [17]. Percentage of tumor conferences varied between different

FIGO stages, ranging from 46% to 65%. To the best of our knowledge this is the first study investigating percentage of tumor boards in association with ovarian cancer stages. For other cancers, e.g. gastric cancer only slight differences among stages have been observed in Rhineland-Palatinate (unpublished results). However, one has to keep in mind that reports on such consultations are probably lower than actual numbers, since tumor conferences have only been subject to reporting requirements in the context of cancer registration since 2021 [11]. Analyses of the proportion of tumor boards per treatment approach showed that the percentage of reported conferences for tumors treated with neoadjuvant chemotherapy without subsequent adjuvant treatment was approximately 10% higher than for cases with adjuvant treatment without neoadjuvant therapy (Fig. 1). For approaches involving neoadjuvant and adjuvant chemotherapy, the proportion of reported tumor conferences was approximately 20% higher than for purely adjuvant therapies (Fig. 1). Thus, at 80%, most tumor conferences on ovarian cancer were reported for tumors with therapy approaches including neoadjuvant and subsequent adjuvant treatment (Fig. 1). The observation that tumor boards are reported more frequently in association with neoadjuvant therapy corresponds to previously published results for gastric cancer [18]. Our results underline the assumption that tumor conferences influence the course of treatment of oncological diseases significantly.

Tumor conferences aim to identify best treatment strategies for each cancer patient, since optimal treatment is fundamental for best possible survival rates. As of yet, debulking surgery followed by platinum-based chemotherapy represents standard primary treatment in particular for advanced ovarian cancers [6]. It has been shown that optimal debulking surgery with residual disease less than 1 cm is associated with improved overall survival [19]. However, neoadjuvant therapy has been suggested as alternative option for patients who are unable to undergo primary surgery with complete resection [20]. For such cases neoadjuvant treatment has been associated with increased rates of optimal debulking resection [20]. In contrast to the argumentation and recommendations of the current S3-guidline for ovarian cancer some studies announce no differences in survival between cases treated with neoadjuvant or without neoadjuvant treatment [20, 6]. In this context the analyses of the real-world data of cancer registries can contribute substantially by finding consensus in such controversies. Accordingly, the present investigation used the data of the Cancer Registry of Rhineland-Palatinate to addressed the question of a potential benefits of neoadjuvant treatment for ovarian cancer patients. Results reveal favorable clinical outcome with respect to event-free and overall survival for patients receiving adjuvant therapy without neoadjuvant treatment. Approaches with neoadjuvant treatment, independent of a subsequent adjuvant treatment, were significantly associated with worse course of disease. This was seen in analyses independent of FIGO stages (Fig. 2) as well as for the subgroup of ovarian cancer patients staged FIGO III (Figs. 3a and 3b). For patients with FIGO IV no significant effect was observed (Figs. 3c and 3d). The latter might be based on the presence of synchronous distant metastases in FIGO stage IV [14]. Metastatic ovarian cancers are generally associated with unfavorable prognosis, with poor relative 5-year survival [1]. Thus, different neoadjuvant and adjuvant therapeutic approaches might have only minor impact on event-free or overall survival due to the generally worse prognosis of FIGO IV.

Currently, neoadjuvant systemic therapy is not recommended as standard treatment for ovarian cancer, due to missing evidence for improved survival rates [21, 22]. As of yet it is recommended to wait for results

of ongiong studies on this topic [5]. However, the results of the analyses of comprehensive cancer registry data from Rhineland-Palatinate carried out here underscore the recommendation currently postulated in the S3 guideline to perform surgery before starting systemic therapy [6].

The herein performed investigation highlights the special value of cancer registry data. These data are crucial real-world data, which are based on comprehensive oncological information from the inpatient and outpatient sector. Accordingly, cancer registries provide an unbiased insight into the reality of treatment and its impact on the survival of cancer patients [12]. As demonstrated in the current case, registry data hold the potential to contribute substantially to the discussion about recommendations regarding neoadjuvant chemotherapy in patients with ovarian cancer.

Declarations

Disclosure statements

This research received no external funding. The authors declare no conflict of interest.

Data availability statement

Data is available upon request.

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Ethics declarations & trial registry information

Neither Informed consent nor IRB statement is required for our investigation, because population-based reporting of cancer cases to state cancer registries is mandated by law in Germany. In addition, analyses were done in a retrospective design using anonymized data.

Author contributions

KS and CJ designed and supervised this study. CM performed quality control and statistical analyses. All authors discussed obtained results. KS and CJ drafted the manuscript. All authors reviewed, edited and approved the final manuscript.

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Figures

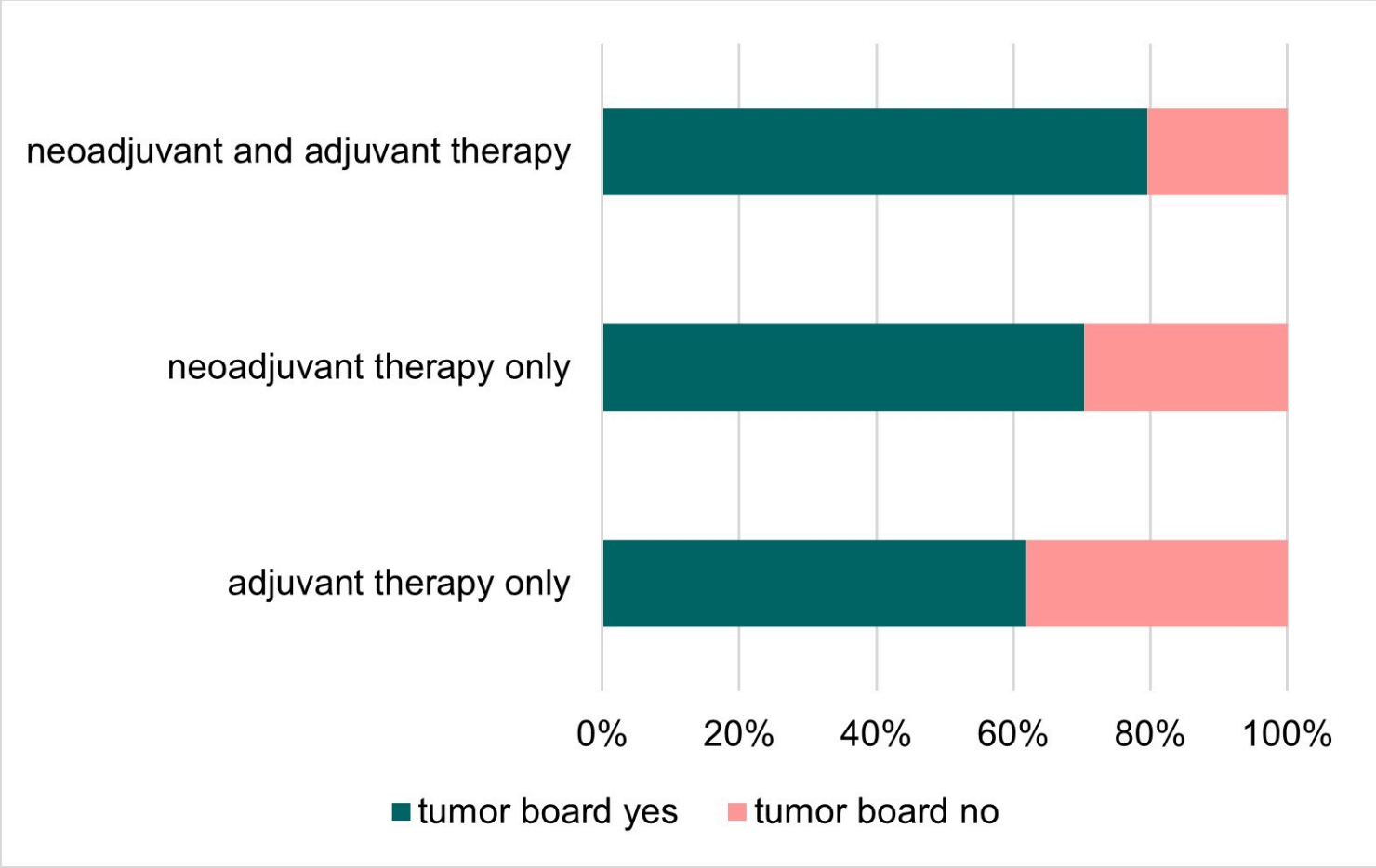


Figure 1

Proportion of reported tumor conferences per treatment approach for ovarian cancer

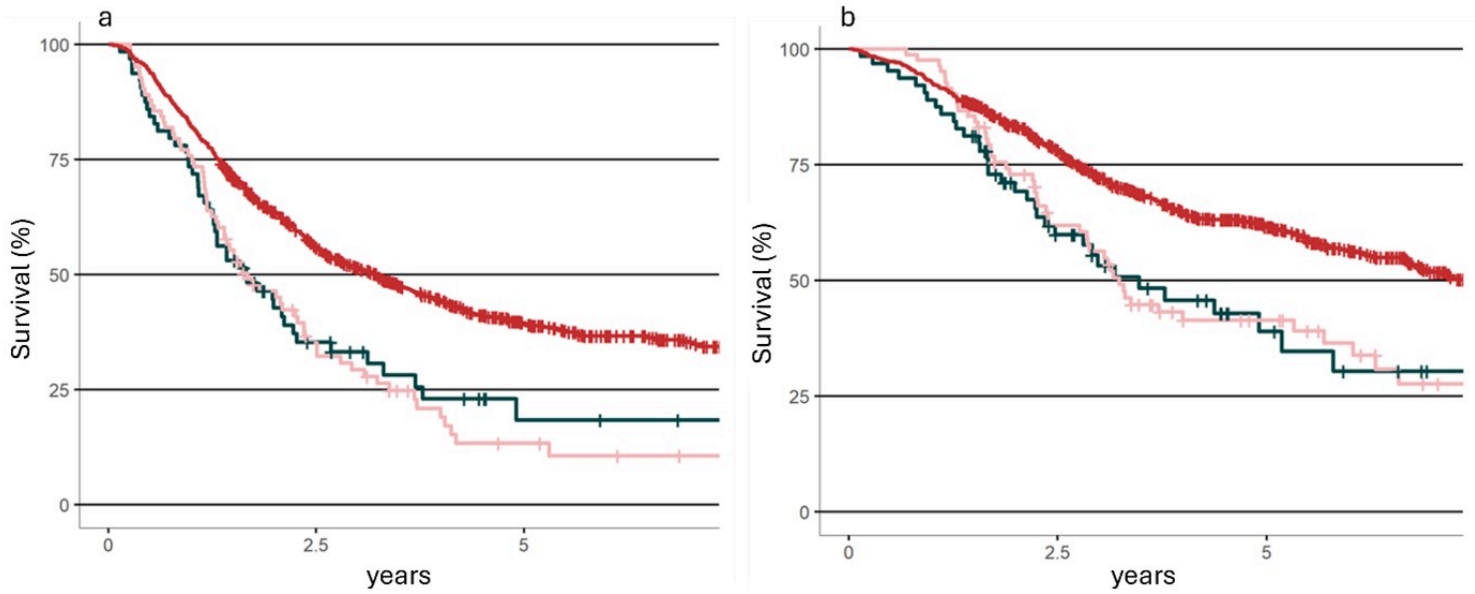


Figure 2

Event-free and overall survival independent of FIGO stage for patients with neoadjuvant systemic therapy but without adjuvant therapy (dark green), patients with neoadjuvant and adjuvant therapy (light red), and patients without neoadjuvant but with adjuvant therapy (red). (a) Event-free survival p<0.0001 (b) Overall survival p<0.0001

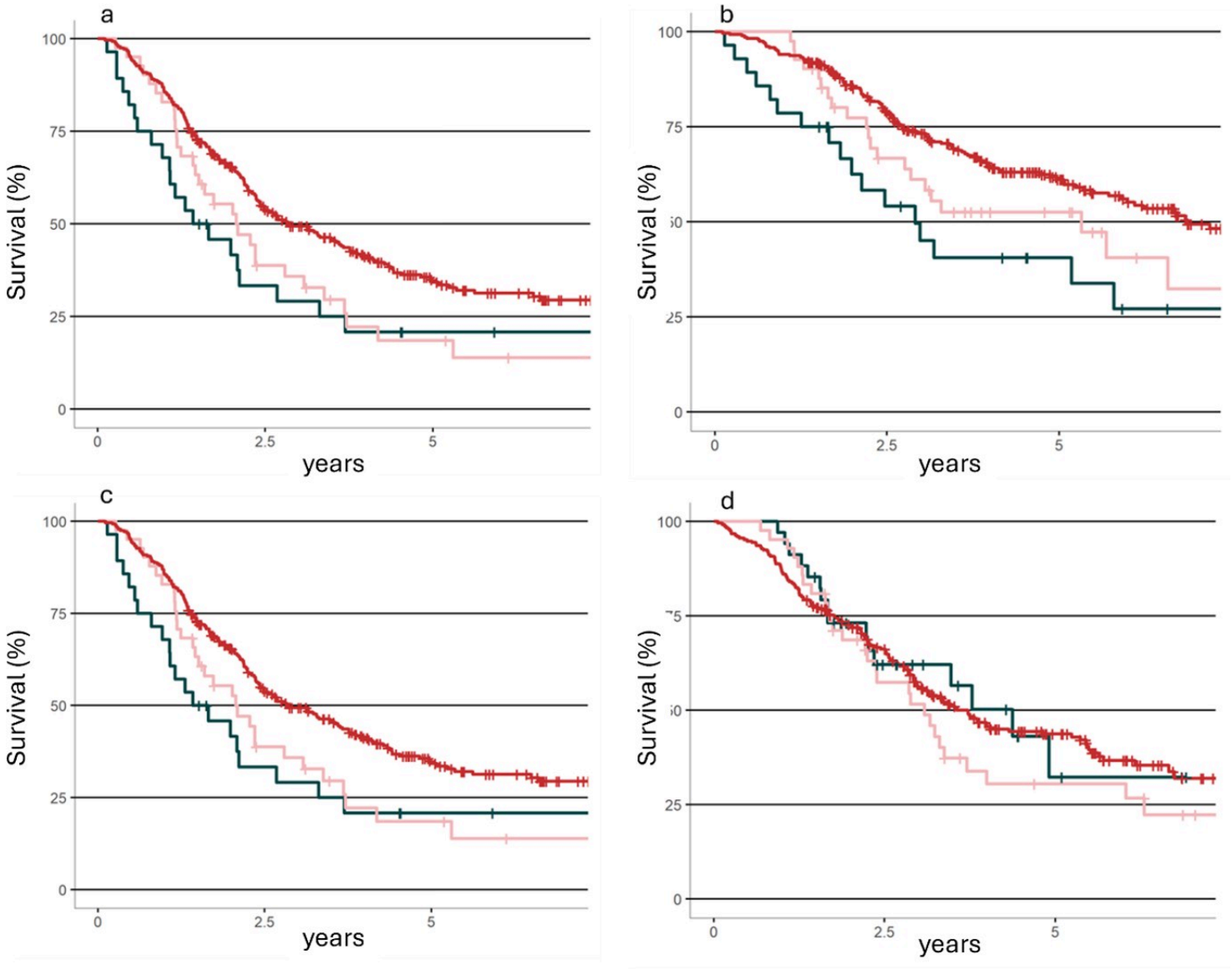


Figure 3

Event-free and overall survival for FIGO stages III and IV for patients with neoadjuvant systemic therapy but without adjuvant therapy (dark green), patients with neoadjuvant and adjuvant therapy (light red), and patients without neoadjuvant but with adjuvant therapy (red), (a) Event-free survival FIGO III p=0.008 (b) Overall survival FIGO III p=0.008, (c) Event-free survival FIGO IV p=0.37 (d) Overall survival FIGO IV p=0.47