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Prognostic Determinants in Secondary Ovarian Malignancy: A Retrospective Analysis of Clinical Features and Survival

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ABSTRACT

Background: *Secondary malignant involvement of the ovaries, designated here as secondary ovarian malignancy (SOM), arises from a wide array of extraovarian tumour sources, and both its frequency and the distribution of primary sites differ substantially across geographic regions and institutional types. This report characterizes the pathological findings and oncological outcomes of consecutive patients with histologically confirmed SOM who were managed surgically at a high-volume gynaecologic oncology unit.*

Methods: *Records of 806 women who underwent surgery for a suspected pelvic mass or ovarian neoplasm (2012-2016) were retrospectively analysed; 488 met the inclusion criteria for a definitive ovarian cancer diagnosis. Actuarial survival estimates were generated using the Kaplan-Meier method, and intergroup comparisons were performed using the log-rank test.*

Results: *Secondary ovarian tumours were identified in 79 women (16.2%), ranking second in frequency, only behind primary epithelial ovarian cancer. Non-gynecological primary sites accounted for 65.8% (n=52) of cases; endometrial (34.2%), colorectal (22.7%), and gastric (20.2%) carcinomas were the three most prevalent sources. Concurrent bilateral adnexal involvement was documented in 62% of cases, with a mean tumour diameter of 6.47 cm. Patients whose primary tumour was of a gynaecological origin were considerably older (62.3 vs. 52.8 years; p=0.007), suffered higher disease-related mortality (59.3% vs. 34.6%; p=0.036), and had a markedly abbreviated median survival (10.0 vs. 32.6 months; p=0.05) relative to those with non-gynaecological sources. Colorectal (46.4 months) and breast (45.0 months) primaries yielded the most favourable survival durations. Surgical extent and adjuvant treatment modality had no statistically significant bearing on outcomes.*

Conclusions: *Secondary ovarian malignancy is a clinically significant entity, accounting for nearly one in six of all ovarian cancers in this cohort. Prognosis is generally poor but varies considerably depending on the originating tumour. Determining the primary site with precision is foundational to appropriately selecting a surgical strategy and individualised systemic therapy.*

Keywords

Colon cancer, Kaplan-Meier survival, Krukenberg tumour, Oncological outcome, Ovarian metastasis, Secondary ovarian neoplasm, Uterine cancer.

Abbreviations

SOM: Secondary Ovarian Malignancy, TAH + BSO: Total Abdominal Hysterectomy and Bilateral Salpingo-Oophorectomy, CA: Cancer Antigen, GIS: Gastrointestinal System, FIGO: International Federation of Gynecology and Obstetrics, LVSI: Lymphovascular Space Invasion, OS: Overall Survival, CLDN18.2: Claudin 18.2, HER2: Human Epidermal Growth Factor Receptor 2, MMR: Mismatch Repair, MSI: Microsatellite Instability.

Introduction

Among all gynaecological malignancies, ovarian cancer has the greatest burden of mortality. GLOBOCAN 2022 projections

indicate that approximately 324,000 incident cases and over 206,000 deaths attributable to this disease occur globally each year [1]. U.S. data from the American Cancer Society for 2024 estimated 19,680 new diagnoses and 12,740 fatalities [2]. Even with improvements in cytoreductive techniques, molecularly targeted agents, and platinum-based regimens, the 5-year survival rate for stage III-IV disease persists below 30% [3].

Although approximately 90% of ovarian malignancies arise from the coelomic epithelium, the remaining fraction comprises germ cell tumours, sex cord-stromal neoplasms, and a diagnostically challenging category secondary (metastatic) ovarian tumours [4]. These lesions originate at an extraovarian primary site and disseminate to one or both ovaries via haematogenous, lymphatic, or transcoelomic pathways. Correctly categorising them as primary versus secondary disease has direct consequences for surgical planning, chemotherapy selection, and patient counselling.

Reported SOM frequencies range from 3% to 15% in Western series and approach 21% to 30% in Eastern and Asian series [5]. The principal primary tumour types also vary by geography: gastric carcinoma contributes nearly 30% of ovarian metastases in East Asian populations, whereas colorectal and breast carcinomas dominate in Western Europe and North America [6,7]. Institutions in geographically transitional zones, such as Turkey, which bridges Europe and the Near East, can be expected to display mixed epidemiological profiles.

Establishing the diagnosis of SOM is non-trivial: in approximately 40% of affected women, ovarian involvement is detected before the responsible primary tumour is identified, especially when the source is gastric or colonic [8]. Pathological clues favouring a secondary diagnosis include bilateral adnexal disease, compact tumour size (diameter < 10 cm), surface nodularity, and histomorphology that does not conform to recognised müllerian patterns [9,10]. Krukenberg tumours defined by signet-ring cell mucin-laden adenocarcinoma, typically of gastric, appendiceal, or colorectal derivation constitute a particularly virulent subgroup; published series place their median overall survival at < 14 months [11].

In general, SOM carries a worse prognosis than primary ovarian cancer, as it invariably reflects advanced or disseminated systemic disease. Across published cohorts, the median overall survival spans 9-30 months and is strongly shaped by the identity and extent of the primary tumour [12-14]. Cytoreductive surgery has shown some benefit in selected cases, notably those with colorectal or breast primaries; however, prospective randomised data are unavailable [15,16]. This investigation presents a detailed characterisation of the pathological profile, operative management, and oncological results of 79 consecutive patients with SOM treated at a tertiary referral unit. The findings are interpreted in light of recent advances in tumour imaging, predictive biomarkers, and novel molecularly targeted approaches, including CLDN18.2-directed therapy for gastric-origin ovarian metastases.

Materials and Methods

Study Design and Patient Selection

A retrospective cohort design was employed, drawing on the operative and pathological archives of the Department of Obstetrics and Gynecology at the Hacettepe University Faculty of Medicine, Ankara, Turkey. We reviewed consecutive records of 806 women who underwent surgery for a suspected pelvic mass or ovarian neoplasm between January 2012 and December 2016; 488 received a definitive ovarian cancer diagnosis (primary or metastatic) and were retained for analysis. The exclusion criteria were as follows: prior surgical or medical treatment of any gynaecological malignancy, fertility-sparing operative approach, and concurrent synchronous cancer confirmed at another anatomical site.

Ethical clearance was granted by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (decision no: 2019/04-43). As data collection was entirely retrospective and derived from routine clinical records, the committee waived the requirement for obtaining individual patient consent in accordance with applicable national regulations.

Operative Management

A gynaecologic oncologist performed every procedure via open midline laparotomy. Intact excision of the adnexal mass was performed whenever malignancy could not be excluded preoperatively, with immediate intraoperative frozen section histopathological assessment to guide the scope of surgery. For women with a pre-existing non-gynaecological cancer diagnosis who subsequently developed a pelvic mass on surveillance imaging, frozen section served to differentiate a new metastatic deposit from a coincidental primary ovarian tumour. If the frozen section result confirmed secondary disease, formal staging surgery was omitted, and the procedure was limited to total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH + BSO), with selective addition of omentectomy (when peritoneal or ascitic involvement was suspected) and appendectomy (when the appendix appeared abnormal). An inconclusive frozen section result prompted complete surgical staging: TAH + BSO combined with omentectomy, appendectomy, and bilateral pelvic-paraaortic lymphadenectomy. Women harbouring a primary endometrial carcinoma underwent the same comprehensive staging procedure. Radical type III hysterectomy with bilateral salpingo-oophorectomy and lymphadenectomy is the standard operation for cervical cancer.

Pathological Assessment

Dedicated gynaecological pathologists evaluated all surgical specimens. The recorded variables included histological type, differentiation grade, resection margin status, lymphovascular space invasion (LVSI), depth of myometrial invasion (relevant to endometrial primaries), and peritoneal cytology findings. Ovarian disease was designated as unilateral or bilateral. If the index primary could not be identified clinically, a directed immunohistochemical panel was applied, and a multidisciplinary tumour board rendered the definitive diagnosis. The disease stage

was assigned in accordance with the FIGO classification system in effect at the time of diagnosis.

Adjuvant Therapy and Surveillance Protocol

Postoperative systemic treatment was planned at weekly multidisciplinary gynaecologic oncology conferences. Chemotherapy regimens were chosen based on the histological identity of the primary tumour. Locoregional radiotherapy was incorporated when nodal or anatomical site-specific disease was documented, particularly for gynaecological primaries. Postoperative follow-up intervals were three-monthly for the initial two years, transitioning to six-monthly over the subsequent three years.

Statistical Methodology

All analyses were conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test evaluated the normality assumption for continuous variables; parametric (independent-samples t-test) or nonparametric (Mann-Whitney U test) comparisons were chosen accordingly. Fisher's exact test or Pearson 's chi-squared test was used for categorical variables. Overall survival (OS) was measured from the date of surgery until death from any cause or last clinical contact and was estimated using the Kaplan-Meier actuarial method; log-rank testing facilitated survival curve comparisons between groups. Median survival was read from the life tables. All reported p-values are two-tailed, and $p < 0.05$ was the threshold for statistical significance.

Results

Cohort Overview

Table 1: Clinicopathological profile of the 79 SOM patients.

Characteristic	n (%)
Primary ovarian cancer (reference group)	409 (83.8%)
All SOM	79 (16.2%)
Gynaecological (endometrial) primary	27 (34.2%)
Non-gynaecological primary	52 (65.8%)
Colorectal carcinoma	18 (22.8%)
Gastric carcinoma	16 (20.3%)
Pancreatobiliary carcinoma	5 (6.3%)
Appendiceal carcinoma	1 (1.3%)
Breast carcinoma	6 (7.6%)
Other confirmed primary	4 (5.1%)
Unknown primary site	2 (2.5%)
Bilateral adnexal involvement	49 (62.0%)
Mean metastatic tumour diameter (cm)	6.47 ± 3.2
Adjuvant chemotherapy only	50 (63.3%)
Chemoradiotherapy combination	26 (32.9%)
Alive at final follow-up	45 (57.0%)
Died of disease	34 (43.0%)
Mean follow-up (months)	13.3 ± 13.4 (range: 1-53)

The histological classification of the 488 confirmed ovarian cancer cases revealed 409 (83.8%) primary tumours 374 (91.5%) epithelial, 15 (3.7%) germ cell, and 20 (4.9%) sex cord-stromal alongside 79 (16.2%) secondary tumours. Of the 79 SOM cases, 27 (34.2%) had a gynaecological primary, all arising from the endometrium, and 52 (65.8%) had a non-gynecological primary. A full breakdown is provided in (Table 1 and Figure 1).

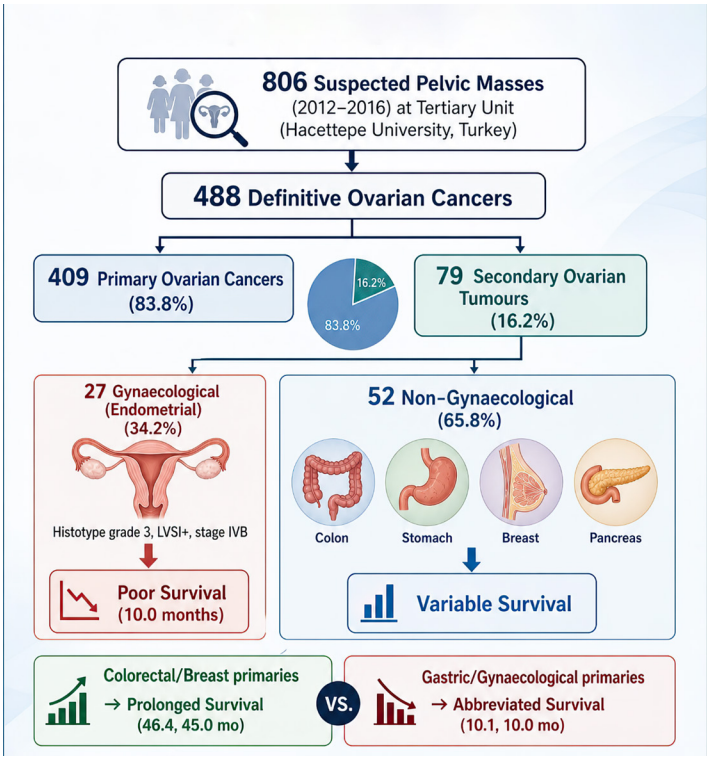

Figure 1: Study flow chart and determinants of secondary ovarian malignancy.

The age at surgery was nearly identical between women with primary ovarian cancer (mean 55.5 ± 14.2 years) and those with SOM (mean 56.3 ± 14.5 years; $p = 0.68$), and postmenopausal status was similarly distributed (73.6% vs. 74.7%; $p = 0.84$). The presenting complaints at the initial assessment were abnormal uterine bleeding (34%), unexpected findings on imaging (24%), pelvic or abdominal pain (18%), and bloating (12%). Formal staging surgery was performed in 50.6% of patients. Three patients (3.8%) succumbed to early postoperative complications before systemic therapy could commence, and the other 76 (96.2%) proceeded to adjuvant treatment. The median follow-up duration was 13.3 ± 13.4 months (range: 1.0-53.0 months), and 34 women (43.0%) died of the disease during the observation period (Figure 2).

Comparative Features by Primary Origin

Women with primary gynaecological conditions were significantly older at surgery (mean 62.3 vs. 52.8 years; $p = 0.007$) and were more frequently postmenopausal (96.3% vs. 65.4%; $p = 0.002$). Circulating tumour marker concentrations exceeded the upper reference range in every patient, regardless of primary origin CA-125:280.6 U/mL, CA 19-9:557.8 U/mL, and CA 15-3:48.0 U/mL but none of these markers distinguished gynaecological from non-

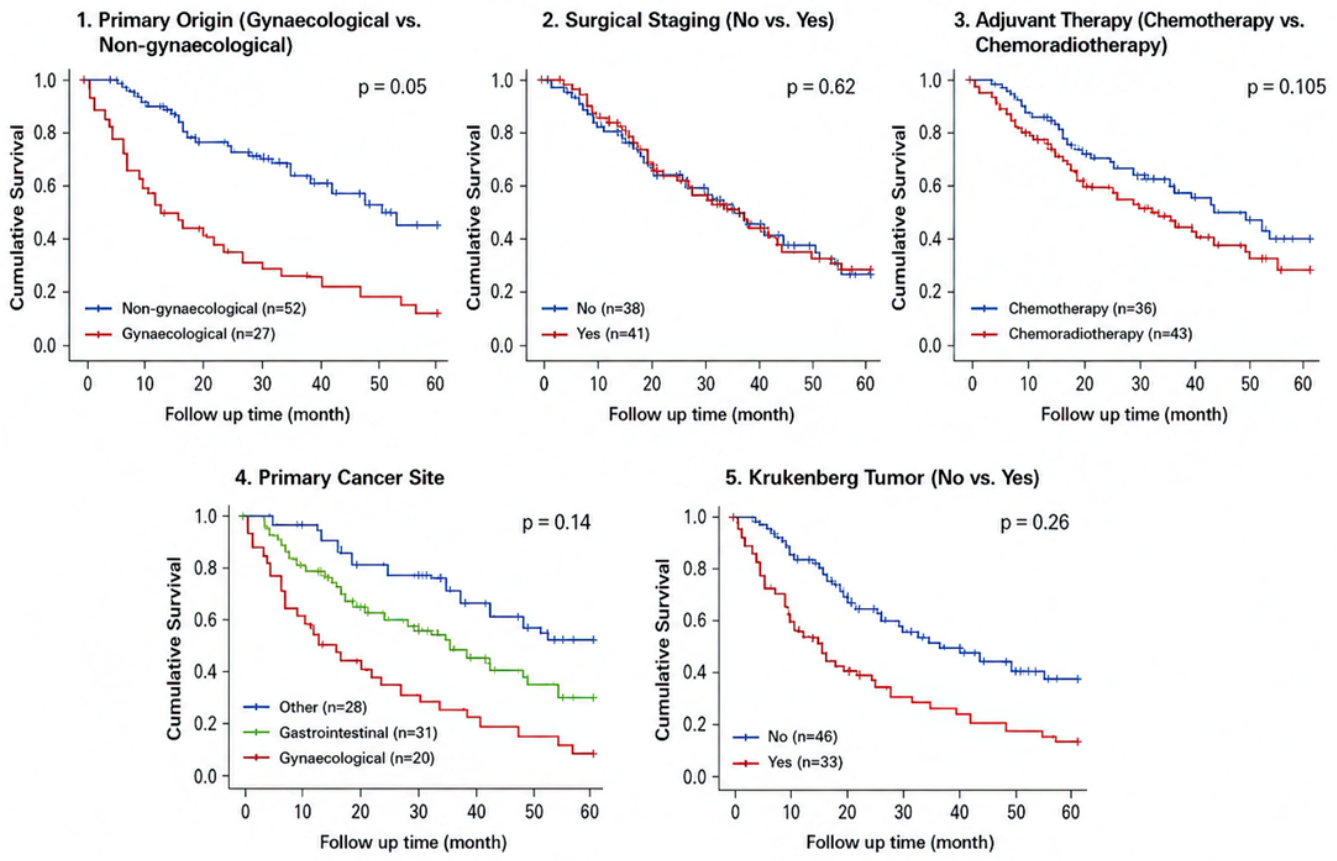

Figure 2: Survival analysis based on clinicopathological factors.

Table 2: Comparative clinical features: gynaecological versus non-gynaecological SOM.

Parameter	Gynaecological (n=27)	Non-gynaecological (n=52)	p-value
Age at surgery mean (years)	62.3 ± 11.1	52.8 ± 8.4	0.007
Postmenopausal, %	96.3%	65.4%	0.002
Serum CA-125 (U/mL)	178.8 ± 18.6	329.5 ± 25.8	0.494
Serum CA 19-9 (U/mL)	389.2 ± 35.6	629.0 ± 57.4	0.712
Serum CA 15-3 (U/mL)	60.1 ± 8.9	42.8 ± 6.7	0.597
Bilateral adnexal disease, %	48.1%	69.2%	0.067
Disease-related mortality, %	59.3%	34.6%	0.036
Median survival (months)	10.0 ± 3.5	32.6 ± 7.4	0.050

gynaecological diseases when group means were compared (all p > 0.05; Table 2).

In the non-gynecological subgroup, the most common impetus for clinical evaluation was an incidental adnexal mass on cross-sectional imaging (35%), followed by pain (27.5%) and progressive abdominal distension (20%). Every patient with a primary diagnosis of endometrial cancer presented with abnormal uterine haemorrhage. Among the breast cancer-associated SOM cases, abnormal imaging constituted the referral trigger in 83.3% of cases.

Pathological Profile of Endometrial Primaries with Ovarian Involvement

All 27 gynaecologically sourced SOMs originated from endometrial carcinoma. Non-endometrioid differentiation predominated (63.0%), and grade 3 tumours accounted for an equally large proportion (63.0%). Invasion extending to the deep myometrial layer was present in 77.8% of cases, while 74.1% demonstrated LVSI. Positive peritoneal cytology was observed in 55.6% of the specimens. Nearly half of the patients (48.1%) were categorised as having FIGO stage IVB, indicating haematogenous spread or extra-abdominal nodal disease. The primary endometrial

tumour measured 7.0 ± 4.1 cm on average (range: 1.5-18.0 cm), underscoring the substantial local tumour burden in this subset (Table 3).

Table 3: Pathological characteristics of endometrial carcinoma with ovarian metastasis (n=27).

Variable	n (%)
Histotype endometrioid	10 (37.0%)
Histotype non-endometrioid	17 (63.0%)
Histological grade 1-2	7 (25.9%)
Histological grade 3	17 (63.0%)
Grade undetermined	3 (11.1%)
Myometrial invasion superficial or absent	6 (22.2%)
Myometrial invasion deep (>50%)	21 (77.8%)
LVSI absent	2 (7.4%)
LVSI present	20 (74.1%)
LVSI status unknown	5 (18.5%)
Peritoneal cytology negative	12 (44.4%)
Peritoneal cytology positive	15 (55.6%)
Stage IIIA	7 (25.9%)
Stage IIIC1	3 (11.1%)
Stage IIIC2	4 (14.9%)
Stage IVA	2 (7.4%)
Stage IVB	11 (40.7%)
Primary tumour size mean ± SD (cm)	7.0 ± 4.1 (range: 1.5-18.0)

Survival Analysis

The median OS for the entire SOM group was 19.7 months. A statistically significant survival advantage was observed for patients with non-gynaecological primaries over those with gynaecological primaries (32.6 vs. 10.0 months; log-rank p = 0.05). Within the non-gynaecological group, gastrointestinal-origin cases had a median OS of 39.2 months, exceeding the 32.4 months recorded for non-gynaecological, non-GIS cases (p = 0.14). Within gastrointestinal primaries, survival was highest for colorectal (46.4 months) and progressively lower for pancreatobiliary (19.5 months), appendiceal (16.5 months), and gastric (10.1 months) disease. Breast cancer-associated SOM achieved a median OS of 45.0 months, second only to colorectal primaries.

Pairwise log-rank comparisons identified three significant survival contrasts: colorectal versus gynaecological primaries (p = 0.002), colorectal versus gastric primaries (p = 0.010), and colorectal versus appendiceal primaries (p = 0.029). Krukenberg tumours identified in 10 patients (12.7%), predominantly of gastric origin (n = 8) were associated with a numerically shorter median survival relative to non-Krukenberg SOM (9.9 vs. 20.5 months), although this did not reach statistical significance (p = 0.26). Complete operative staging was not associated with improved survival compared with limited procedures (18.1 vs. 39.7 months; p = 0.62), nor did the choice of adjuvant regimen (chemotherapy alone 31.7 months vs. combined chemoradiotherapy 11.6 months; p = 0.105) significantly alter outcomes.

Discussion

This five-year retrospective analysis of 488 women who underwent surgery for ovarian neoplasia revealed that secondary ovarian tumours constituted 16.2% of all cases, positioning SOM as the second most frequent ovarian malignancy category at our institution, behind primary epithelial cancer. Gastrointestinal tumours were the dominant extragonadal source, and endometrial carcinoma uniquely among gynaecological primaries emerged as the single most common tumour entity in the entire SOM cohort. Two-thirds of the metastatic cases had a non-gynological origin, mirroring broad trends in the published literature and reflecting distinctive regional and institutional factors.

A rate of 16.2% for secondary ovarian malignancy places our series at the upper boundary of Western-reported ranges (3-15%) and near the lower end of Eastern ranges (21-30%) [5,17]. This intermediate position is geographically plausible: Turkey and the South Caucasus region are situated at a biological and epidemiological crossroads, and the cancer phenotypes of these populations blend characteristics from both European and Asian cohorts. Lobo et al. [18] documented an SOM proportion of 26% in their pathological series, identifying the gastrointestinal system, breast, and female reproductive tract as the dominant source categories. In a large Chinese series, Zhang et al. [19] found that colorectal (38.4%) and gastric (34.5%) primaries predominated among non-gynecological cases, a pattern that our data partially replicate though with lower absolute proportions further supporting the influence of regional dietary habits and Helicobacter pylori exposure on gastric cancer incidence.

The prevalence of endometrial carcinoma as the most common primary individual source in our cohort differs from that in most Asian and Western institutional reports, in which gynaecological primaries collectively form a minority. We attribute this to the case-mix of our institution: endometrial cancer is the most frequently operated gynaecological malignancy in Turkey, and the systematic staging procedures undertaken for this tumour which include bilateral adnexal removal and pathological assessment ensure that ovarian deposits are reliably identified and recorded, whereas lower-volume settings may not apply equally rigorous staging protocols. Wang et al. [20] have highlighted the critical importance of distinguishing true synchronous endometrial and ovarian primaries from metastatic endometrial cancer with ovarian spread, which requires dedicated pathological criteria; in our series, all 27 cases were adjudicated as metastatic on histopathological grounds.

The 62.0% rate of bilateral adnexal involvement in our cohort is consistent with the prior literature, which cites bilaterality rates between 40% and 75% according to primary tumour type [10,21]. Non-gynaecological, predominantly gastrointestinal, cases exhibited higher bilateral rates (69.2%) than endometrial cases (48.1%), although this difference did not achieve statistical significance (p = 0.067). The imaging data of Karaosmanoglu et al. [21] support bilaterality as the most operationally useful radiological discriminator between primary and secondary ovarian

tumours; bilateral adnexal masses should therefore prompt systematic investigation for an extraovarian primary before definitive surgery is planned. Krukenberg tumours were observed in fewer than 13% of our SOM cases considerably lower than the 30-40% cited in some Asian series [11] a discrepancy that is attributable to the relative preponderance of endometrial cancer over gastric cancer in our cohort.

The unexpectedly poor survival outcomes among gynaecologically-sourced SOMs (median 10.0 months) stand in contrast to several published series in which endometrial primary disease typically confined to the pelvis or abdomen without distant spread is associated with more favourable oncological results [22,23]. In our cohort, this pattern is reversed, and the explanation lies squarely in the pathological severity of the endometrial tumours represented: 63% exhibited non-endometrioid histotypes, 63% were poorly differentiated (grade 3), 77.8% demonstrated deep myometrial invasion, and 74.1% showed LVSI all established determinants of adverse outcome regardless of ovarian status. The mean primary tumour diameter of 7.0 cm and the near-50% prevalence of stage IVB disease further illustrate that these cases represent particularly advanced and biologically aggressive neoplasms, which plausibly overcame any prognostic advantage that might otherwise attend a gynaecological primary.

Within the non-gynological subgroup, colorectal and breast cancers conferred the most prolonged survival (46.4 and 45.0 months, respectively), echoing the findings of Kajiyama et al. [6] and Li et al. [24]. Conversely, gastric primary SOM was associated with the shortest OS among all non-gynological subgroups (10.1 months), in line with the observations by Matsushita et al. [25], who attributed this to the intrinsically aggressive behaviour of diffuse-type gastric carcinoma and the challenges of achieving complete cytoreduction. Wang et al. [26] additionally demonstrated that among synchronous Krukenberg tumours, colorectal origin confers a more favourable course than gastric origin. From a future therapeutic perspective, Kim et al. [27] recently showed that CLDN18.2, a tight-junction protein present in approximately 40% of gastric adenocarcinomas, is expressed at comparable levels in their ovarian metastases, raising the prospect of zolbetuximab or analogous anti-CLDN18.2 agents in patients with Krukenberg tumours of gastric origin. Our median survival data for this subgroup lend urgency to this research direction. Separately, Braun et al. [28] confirmed that nearly 60% of breast cancer ovarian metastases display invasive lobular morphology and are virtually all oestrogen receptor-positive a molecular profile that explains the relatively prolonged survival observed in breast-origin SOM and underscores the importance of continued endocrine therapy after ovarian metastasectomy.

The surgical and adjuvant therapy analyses in our series produced no statistically significant survival differences, whether comparing complete staging versus limited resection (18.1 vs. 39.7 months; $p = 0.62$) or chemotherapy versus chemoradiotherapy (31.7 vs. 11.6 months; $p = 0.105$). The interpretation of these comparisons requires caution because the staging surgery group was disproportionately populated by patients with endometrial cancer, who had the worst prognosis, creating a confounder that may have masked the true surgical benefit. The findings of Yumru Çeliksoy et al. [29] are clinically relevant here: in a Turkish series in which 81% of adnexal masses in women with a history of gastrointestinal cancer proved to be ovarian metastases, meticulous preoperative multidisciplinary assessment was shown to be essential for appropriately limiting the surgical scope and avoiding unnecessary staging in patients with metastatic disease.

Several methodological constraints merit discussion. The retrospective single-institution design carries inherent risks of selection and information bias, and the enrolment window (2012-2016) predates the widespread integration of immune checkpoint inhibitors and targeted agents, notably PARP inhibitors, anti-VEGF therapy, and HER2-directed regimens, that have since reshaped the systemic treatment of multiple primary tumour types. The mean follow-up of only 13.3 months limits the reliability of long-term survival estimates and may understate actual event rates, particularly for indolent primaries, such as breast cancer. The absence of molecular data, including MSI/MMR status, HER2 amplification state, and BRCA germline results, precludes subgroup analyses that could inform biomarker-stratified treatment decisions. Multi-institutional prospective studies incorporating molecular characterisation are needed to generate more definitive guidance.

Conclusions

Secondary malignant involvement of the ovary represented a substantial proportion (one in six) of all ovarian cancers operated on at our institution and constituted a pathologically heterogeneous entity requiring careful multidisciplinary evaluation. Endometrial, colorectal, gastric, and breast carcinomas were the principal tumour sources. Contrary to reports from some other series, gynecological-origin SOMs in our cohort driven by endometrial tumours of high histological grade, deep myometrial invasion, and advanced FIGO stage carried higher mortality and shorter survival than non-gynecological cases, a finding that reflects unique institutional pathological characteristics rather than a universal biological law. Colorectal and breast primaries were associated with the most favourable survival. Neither surgical extent nor the choice of adjuvant regimen emerged as an independent determinant of OS, pointing to primary tumour biology and systemic disease burden as the dominant prognostic drivers. Identifying the primary site early and accurately remains essential for personalised treatment planning, and emerging agents, such as CLDN18.2-targeted therapy, may soon offer a new therapeutic option for the aggressive gastric-origin subset.

Statements and Declarations

Ethics Approval and Consent to Participate

Institutional ethical approval was obtained from the Hacettepe University Non-Interventional Clinical Research Ethics Committee (decision no: 2019/04-43). Given the entirely

retrospective nature of data collection, the committee authorised the waiver of prospective individual patient consent in accordance with applicable national and institutional guidelines.

Data Availability

De-identified data supporting the conclusions of this study are available from the corresponding author (A.I.) upon reasonable and written request.

Author Contributions

G.Z.: Acquired clinical and pathological data; contributed to manuscript drafting; participated in surgical care and patient follow-up. M.C.S.: Performed statistical analyses; provided methodological supervision; and critically revised the manuscript. A.I.: Conceived and designed the study; drafted and critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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