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Primary ovarian malignant melanoma: A systematic review of cases and pooled analysis

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HIGHLIGHTS

- Largest pooled analysis of primary ovarian malignant melanoma.
- Poor survival across all disease stages.
- Surgery is the most common management approach.
- Supports need for routine molecular profiling.
- Highlights need for investigation of novel therapies, including immunotherapy.

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ABSTRACT

Objective. Primary ovarian malignant melanoma is a rare malignancy arising from malignant transformation of a mature cystic teratoma of the ovary. Evidence is limited to case reports and case series. This systematic review and pooled analysis summarise clinical characteristics, management strategies and outcomes of this rare disease.

Methods. Systematic searches of Medline (PubMed), EMBASE, Scopus and Web of Science were conducted from inception to September 2025 identifying all case reports and case series reporting primary ovarian malignant melanoma. Data extraction and risk of bias assessments were performed in duplicate. Risk of bias was assessed using the Joanna Briggs Institute tool. Survival associations were analysed using Kaplan–Meier methods and Cox proportional hazards regression.

Results. Seventy-six studies reporting 92 patients were included. Mean age at diagnosis was 50.6 years (range 11–86). Abdominal distension (34/73, 46.6%) and pain (32/73, 44.4%) were the commonest presenting symptoms. Almost half were diagnosed International Federation of Gynaecology and Obstetrics stage I (34/70, 48.6%); no cases of stage II; 30% (21/70) were stage III and 15/70 (21.4%) stage IV. Surgery was performed in 78/79 (98.7%) patients. Adjuvant therapies included chemotherapy (35/63, 55.6%), immunotherapy (17/63, 27.1%), radiotherapy (9/63, 14.3%), and targeted therapy (3/63, 4.8%), including imatinib, vemurafenib and aflibercept regimes. Median overall survival declined with advancing stage (p-value <0.01); 62% of patients died (37/60), with 57.8% doing so within 12 months of diagnosis (21/37). In an unadjusted analysis, immunotherapy appeared associated with improved overall survival (Hazard Ratio [HR] = 0.38, 95% CI: 0.17–0.86, p-value = 0.02). This was not significant when restricted to stage 1 disease.

Conclusion. Primary ovarian malignant melanoma is associated with poor prognosis across all disease stages. Our findings are descriptive, limited by the rarity of the disease and quality of existing evidence. International

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collaborative studies, rare cancer registries, and molecular profiling are essential to improve understanding and management.

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1. Introduction

Malignant melanoma is an aggressive cancer arising from melanocytes, with approximately 330,000 incident cutaneous cases diagnosed globally each year [1]. While most malignant melanomas are cutaneous, they can also arise from mucosal sites including the mouth, nose, urogenital and digestive tract [2,3]. Primary ovarian malignant melanoma is an exceptionally rare subtype, arising from the malignant transformation of a mature cystic teratoma. Mature cystic teratomas are benign ovarian tumours containing cells from one or more of the three germ layers, with an incidence between 1.2 and 14.2 cases per 100,000 individuals [4,5]. Malignant transformation occurs in around 2% of mature cystic teratomas [6], with increasing risk post menopause [6]. Squamous cell carcinoma predominates (88%), followed by adenocarcinoma, fibrosarcoma, carcinoid tumours, and mixed tumours [7]. Primary ovarian malignant melanoma is extremely rare, accounting for 0.2%–0.8% of mature cystic teratomas [8,9].

Diagnosing primary ovarian malignant melanoma is challenging due to its rarity and non-specific imaging features. No consensus treatment protocol exists [7,10,11]. Existing literature is limited to case reports and small case series, with management mostly based on primary surgical resection [6,7,10] and variable use of adjuvant therapies, resulting in inconsistent oncological outcomes [8,12,13]. Reported oncological outcomes are poor and molecular characterisation of these tumours is almost entirely absent from the existing literature. Although checkpoint immunotherapies (CPIs) are highly effective in managing cutaneous melanoma, mucosal melanoma is under-represented in CPI trials and the role of immunotherapy in primary ovarian malignant melanoma remains unclear [11,14]. Similarly, whilst combined BRAF and MEK inhibitor therapy has demonstrated significant clinical benefit in melanoma patients with activating *BRAF* mutations, the relevance of targeted therapy in primary ovarian malignant melanoma is unclear given the lack of molecular profiling data [15].

Given the extreme rarity of this condition and the absence of prospective or comparative data, we performed a comprehensive systematic review of reported primary ovarian malignant melanoma cases, focusing on clinical characteristics, diagnosis and therapeutic management, with a pooled descriptive analysis of individual patient data to explore factors associated with survival.

2. Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [16] and was registered in PROSPERO (CRD42023457069).

Two reviewers (MO and LBE) independently conducted searches on Medline (PubMed), EMBASE, Scopus and Web of Science from inception to September 2025. The search strategy included terms "Primary" AND "Melanoma*" AND "ovar*", without using medical subject heading terms or restrictions on study design, country, or language. The truncation 'ovar*' was used to capture terms including ovary, ovarian and ovaries. Manual review of references was performed to identify additional studies. Title, abstract and full-text screening was conducted independently using Covidence. Discrepancies between reviewers were resolved, when necessary, by a third reviewer (KSK).

We included studies reporting data for individuals diagnosed with primary ovarian malignant melanoma arising from a mature cystic teratoma. Studies describing non-primary melanoma of the ovary or metastasis of melanoma to the ovary were excluded. All study formats providing individual patient data were deemed eligible for inclusion. Review articles, conference abstracts, sources without peer review and studies involving in vitro and animal models were excluded. Non-English articles were included following translation.

Two authors (AP and MO) independently extracted data including age, comorbidities, presenting symptoms and their duration, results of laboratory tests, primary diagnosis, imaging findings, staging, treatments and oncological outcomes. Discrepancies were resolved by a third author (KSK). Missing or unidentifiable data were excluded from analyses.

Two authors (AP and MO) independently evaluated the risk of bias using the Joanna Briggs Institute's critical appraisal for case reports and case series [17] consisting of eight distinct elements: patient demographics, medical history, health status, physical examination and diagnosis, concomitant therapies, post-intervention health status, and drug administration reaction interface. Studies were scored for each aspect as "Yes," "No," or "Unclear or Not/Applicable".

We employed descriptive statistics to present demographics and clinical characteristics. Continuous variables were expressed using means, while binary variables were represented as percentages. All

included studies with individual patient data are listed in Supplementary Table S1.

Cases were compared against the Cronje and Woodruff diagnostic criteria [18] to assess their agreement to the framework: (a) no extra-ovarian primary melanoma, (b) unilateral ovarian mass with teratomatous components, (c) alignment with reported demographics and symptoms, and, where available, (d) melanocytic junctional activity, which is 'supportive but not mandatory for diagnosis'. Cases in which criterion (d) was not reported were assessed using criteria (a)–(c) only. Staging data were standardised according to the International Federation of Gynaecology and Obstetrics (FIGO) ovarian cancer staging 2014 guideline [19].

Survival estimates were conducted using Kaplan-Meier survival curves and Cox proportional hazards models in statistical software R version 4.4.3, using *survminer* and *survival* packages, to describe patterns within the data. Overall survival (OS) was defined as the time from diagnosis to death. Progression free survival (PFS) was defined as the time from diagnosis to reported disease progression, recurrence or last follow up where progression was not reported. Subgroups were stratified by FIGO stage, surgical procedure, utilisation of adjuvant treatment, age, menopausal status and laterality of tumour. Statistical significance was set at p-value <0.05. Cases with missing or unidentifiable data were excluded from the analysis. Given the temporal heterogeneity of included studies and the retrospective nature of the individual patient data, all survival analyses were considered exploratory.

Data completeness varied across variables because of inconsistent reporting within the literature. A summary of available missing data for key variables is provided in Supplementary Table S2.

Upon request we will provide our data for independent analysis for the purposes of additional data analysis or for the reproducibility of this study in other centres.

3. Results

A full list of included case reports and series with extracted variables are provided in Supplementary Table S1. A total of 92 cases of primary ovarian malignant melanoma were reported in 76 studies between 1942 and 2025 (Fig. 1, Table S1). Patients had a mean age of 50.6 years (median: 50.0, age range: 11–86) with 43.5% (37/85) being pre-menopausal. (Table 1).

Presenting symptoms are detailed in Table 1. The most common symptoms were abdominal distention (34/73, 46.6%) and abdominal pain (32/73, 44.4%). Ten patients were asymptomatic (13.7%) (Table 1). Ethnicity and skin type was rarely reported. The geographic distribution of publication was broad, including studies from Asia [28], Europe [21], and the Americas [23], with single reports from South Africa and Australia (Table S1).

Initial diagnostic imaging most commonly included ultrasound (28/54, 51.9%), followed by Computed Tomography (18/54, 33.3%); additional modalities are summarised in Table 1. Immunohistochemical evaluation frequently included HMB-45, S-100,

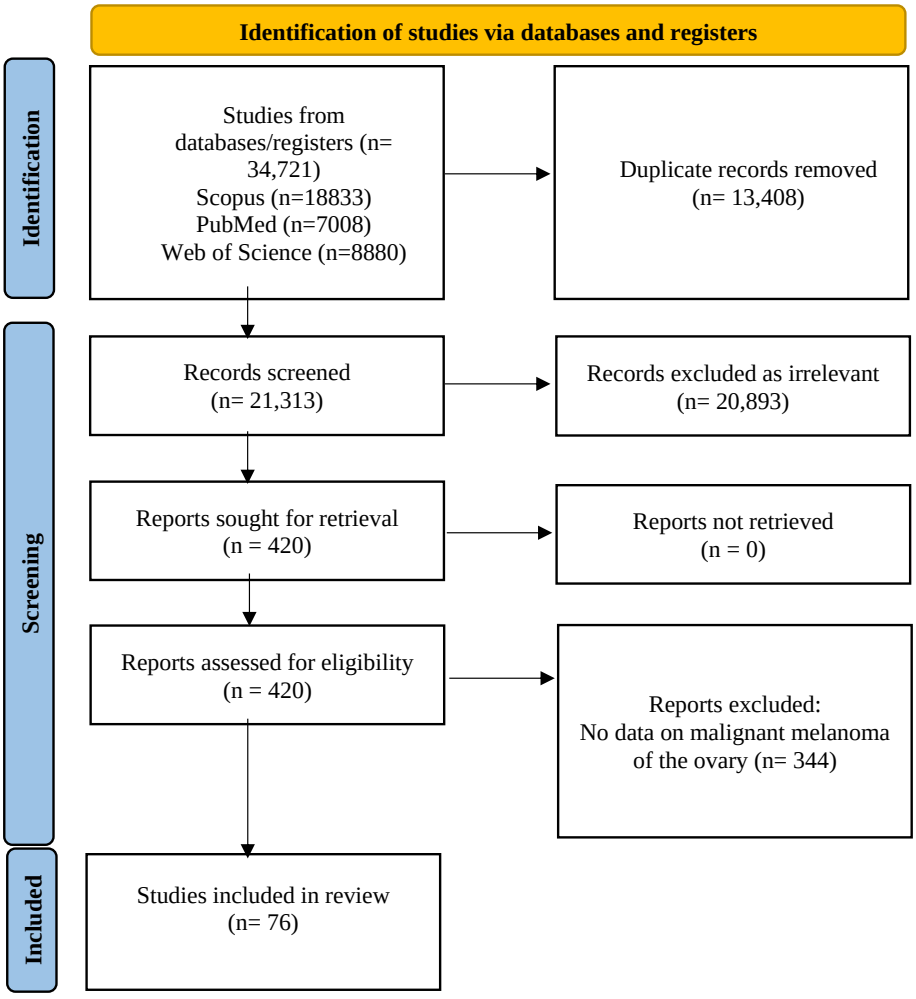


Fig. 1. PRISMA flow chart.

Table 1
Summary of characteristics of the included cases.[a]

Characteristic	n/N (%)
Age (years) (N=92)	
Mean (median, range)	50.6 (50.0, 11-86)
Menopausal tatus (N = 85)	
Pre-menopausal	37/85 (43.5)
Post- menopausal	48/85 (56.5)
Presenting symptoms (N = 73)	
Abdominal distension	34/73 (46.6)
Abdominal pain	32/73 (44.4)
Nausea and vomiting	8/73 (11.1)
Weight loss	5/73 (6.8)
Menstrual irregularities	4/73 (5.5)
Asymptomatic	10/73 (13.7)
Primary diagnostic modality used (N = 54)	
Ultrasound	28/54 (51.9)
Computed Tomography (CT)	18/54 (33.3)
MRI	3/54 (5.6)
X-ray	3/54 (5.6)
IV Urogram	2/54 (3.7)
Positive histological markers (N = 50)	
HMB-45	40/50 (80.0)
S-100	40/50 (80.0)
Melan-A	22/50 (44.0)
Vimentin	17/50 (34.0)
FIGO stage (N = 70)	
I	34/70 (48.6)
II	0/70 (0.0)
III	21/70 (30.0)
IV	15/70 (21.4)
Metastasis at diagnosis (N = 70)	
Yes	36/70 (51.4)
No	34/70 (48.6)
Location of distant metastasis (N = 70)	
Peritoneum	18/70 (25.7)
Omentum	12/70 (17.1)
Liver	8/70 (11.4)
Lymph nodes	7/70 (10.0)
Bowel	4/70 (5.7)
Lungs	3/70 (4.3)
Bones	2/70 (2.9)
Brain	1/70 (1.4)
Tumour l**aterality(N = 80)**	
Right	44/80 (55.0)
Left	30/80 (37.5)
Bilateral	6/80 (7.5)
Recurrence (N = 32)	
Yes	28/32 (87.5)
No	4/32 (12.5)
Site of recurrence (N = 32)	
Liver	12/32 (37.5)
Lung	8/32 (25.0)
Lymph nodes	6/32 (18.8)
Central nervous system	5/32 (15.6)
Bowel	4/32 (12.5)
Bone	4/32 (12.5)
Outcomes (N = 60)	
Alive	23/60 (38.3)
Deceased	37/60 (61.7)

[a] Abbreviations: CT, computed tomography; FIGO, International Federation of Gynaecology and Obstetrics; IV, intravenous; MRI, magnetic resonance imaging. Note: N varies across variables due to missing data. Percentages are calculated from available data only. Presenting symptoms, histological markers, location of metastasis and sites of recurrence are not mutually exclusive.

Melan-A and Vimentin, with all four markers positive in 7/50 cases (14.0%). Molecular profiling was rarely performed (5/92, 5.4%) (Table 1).

Among 70 patients with staging data FIGO stage I was most common (34/70, 48.6%), followed by stage III (21/70, 30.0%) and stage IV (15/70, 21.4%). No stage II cases were reported. Most patients had a unilateral mass, with bilateral disease observed in a minority (6/80, 7.5%). Size of the mass(es) was not consistently reported (Table 1). Presence or absence of distant metastases at diagnosis were reported for 70 patients and metastatic sites are summarised in Table 1.

Assessment using Cronje and Woodruff criteria indicated that 7/92 cases (7.6%) fulfilled one criterion, 35/92 cases (38.0%) met two, 30/92 cases met three (32.6%) and 20/92 cases (21.7%) satisfied all four (Table 2).

First line management was reported in 79 patients. Almost all patients underwent primary surgery (78/79, 98.7%). Most received definitive primary radical surgery (including total abdominal hysterectomy and bilateral salpingo-oophorectomy) or a 2-stage approach with primary isolated surgical resection of one or both adnexa followed by a second completion surgery after histological assessment (51/79, 64.6%) for staging or cytoreduction. The remaining patients had unilateral or bilateral salpingo-oophorectomy only (23/79, 29.1%). An omentectomy was performed in 33/74 patients (44.6%), and pelvic and/or para-aortic lymphadenectomy in 22/74 patients (29.7%). Both procedures were performed in 19/74 patients (25.7%). The type of omentectomy was not specified. Cytoreductive procedures including peritoneal stripping and bowel resection were performed in 10/77 (13.0%) patients. Cystectomy alone was performed in 5/77 patients (6.5%), four of whom subsequently underwent completion surgery in a 2-staged procedure. In three patients (3/79, 3.8%), surgery was abandoned due to inoperable disease. Data on intra-operative spillage, residual disease and surgical approach were inconsistently reported and could not be analysed separately (Table 3).

Data regarding oncological therapies were recorded in 63 patients. One patient received neoadjuvant chemo-immunotherapy (1/63, 1.6%). Adjuvant therapy was given to 39/63 patients (61.9%) all as part of combination treatment regimes. Chemotherapy was given to 35/63 (55.6%), external beam radiotherapy to 9/63 (14.3%), and immunotherapy to 17/63 (27.1%) patients. Sites of radiotherapy are detailed in Table 3. Among patients receiving immunotherapy ($n = 17$), all received it in combination with other therapies. Cytokine-based therapies were the most commonly used, with interferon administered to 12 patients (12/17, 70.6%). Interleukin-2 and Picibanil, were used in 2/17 (11.8%) and 1/17 (5.9%), respectively. Immune checkpoint inhibitors use included Ipilimumab (5/17, 29.4%), Pembrolizumab (3/17, 17.6%) and Nivolumab (3/17, 17.7%). Targeted therapy was given to three patients (3/63, 4.8%), including Imatinib (2/3, 66.7%) and combination Vemurafenib and Aflibercept (1/3, 33.3%). Three patients received neoadjuvant therapy before a secondary cytoreductive surgery for recurrent disease (3/63, 4.8%) (Table 3).

Follow-up data were available for 60 patients with a median follow-up period ranging from 1.2 to 54 months. Thirty-seven patients were reported to have died (37/60, 61.7%), and 21 of these died (57.8%, 21/37) within 12 months of diagnosis. Median overall survival (OS) for patients with FIGO stage I, III, and IV disease was 12.0 months (IQR: 7.5–21.5, range: 0.0–69.0), 9.5 months (IQR: 3.5–17.5, range: 2.0–63.0), and 2.5 months (IQR: 1.5–11.5, range: 1.0–24.0), respectively. Median progression-free survival for stage I, III and IV disease were 12.0 months (IQR: 6.0–24.0, range: 0.0–48.0), 4.0 months (IQR: 0.0–8.5, range: 0.0–54.0) and 0.0 months (IQR: 0.0–0.0, range: 0.0–3.0), respectively.

Patients with FIGO stage I disease had significantly improved overall survival compared to those with higher-stage disease (FIGO I:

Table 2
Distribution of POMM cases by number of Cronje and Woodruff diagnostic criteria fulfilled.[b]

Cronje & Woodruff Criteria Fulfilled	n/N (%)
1	7/92 (7.6)
2	35/92 (38.0)
3	30/92 (32.6)
4	20/92 (21.7)

[b] Criterion (d), melanocytic junctional activity, is considered supportive but not mandatory for diagnosis. Cases in which criterion (d) was not reported were assessed using criteria (a)–(c) only and were not penalised for missing criterion (d) data. Cases with evidence of extra-ovarian disease at presentation were not scored against criterion (a) due to diagnostic uncertainty in distinguising primary ovarian disease with metastatic spread from a seperate extra-ovarian primary.

Table 3
Summary of therapeutic approaches utilised for the included patients.

Therapeutic approach		n/N (%)
Surgical procedure (N = 79)		
Hysterectomy + bilateral salpingo-oophorectomy		
Either primary radical surgery or 2 stage completion procedure		51/79(64.6)
Unilateral or bilateral salpingo-oophorectomy only		23/79 (29.1)
Primary surgery: Cystectomy alone		
4 patients subsequently had staged completion surgery		5/79 (6.3)
Omentectomy		33/74 (44.6)
Pelvic and/or para-aortic lymphadenectomy		22/74 (29.7)
Both Omentectomy + Pelvic and/or para-aortic lymphadenectomy		19/74 (25.7)
Cytoreductive procedure (total abdominal hysterectomy + bilateral salpingo-oophorectomy +/− bowel resection +/− bowel resection +/− excision of all visible disease)		10/79 (12.7)
Biopsy only (inoperable disease)		3/79 (3.8)
Surgical procedure not specified		1/79 (1.3)
No surgery		1/79 (1.3)
Oncological treatment (N = 63)		
Neo-adjuvant therapy		
Chemotherapy + Immunotherapy		1/63 (1.6)
No neo-adjuvant therapy		62/63 (98.4)
Adjuvant therapy		
Chemotherapy		35/63 (55.6)
Radiotherapy		9/63 (14.3)
Site of radiotherapy	*Liver*	2/9 (22.2)
	Para-aortic	1/9 (11.1)
	Pelvic	1/9 (11.1)
	Spinal cord	1/9 (11.1)
	Brain	1/9 (11.1)
	Site not stated	3/9 (33.3)
Immunotherapy		17/63 (27.1)
Cytokine based therapies	Interferon	12/17 (70.6)
	Interferon alpha	5/12 (41.7)
	Interferon alpha-2B	2/12 (16.7)
	Unspecified	5/12 (41.7)
	Interleukin-2	2/17 (11.8)
	Picibanil	1/17 (5.9)
Immune checkpoint inhibitors	Ipilimumab	5/17 (29.4)
	Pembrolizumab	3/17 (17.6)
	Nivolumab	3/17 (17.7)
Targeted therapy		3/63 (4.8)
Type of targeted therapy	Imatinib	2/3 (66.7)
	Vemurafenib	1/3 (33.3)
	Aflibercept	1/3 (33.3)

12.0 months vs FIGO III: 9.5 months; FIGO IV: 2.5 months, p value = 0.001) (Fig. 2A). Among patients with FIGO stage IA disease, overall survival did not differ between those undergoing unilateral salpingo-oophorectomy or radical surgery (hysterectomy with bilateral salpingo-oophorectomy or complete staging) (21.3 vs 14.3 months, HR 1.85, 95% CI: 0.23–15.0, p-value =0.55) (Fig. 2B). Median overall survival was shorter in those undergoing surgery alone (7.0 months, IQR: 4.0–12.0, range 1.0–54.0) compared to those undergoing surgery plus adjuvant therapy (12.0 months, IQR 6.0–18.0, range 1.0–63.0) and both were superior to no treatment (1.0 months, IQR 0.0–2.0, range 0.0–2.0) (p-value <0.0001) (Supplementary Fig. 1A, B).

When stratified by stage, adjuvant therapy was not associated with improved overall survival for patients with early FIGO stage I disease (p-value =0.73) or FIGO stage III/IV disease (p = 0.62) (Fig. 2C, D). Cox proportional hazards regression demonstrated that the addition of adjuvant chemotherapy (n = 17) versus no chemotherapy (n = 33) and adjuvant radiotherapy (n = 18) versus no radiotherapy (n = 32) had non-significant hazard ratios (HR) of 1.0 (95% CI: 0.5–2.0, p-value =1.0), and 0.59 (95% CI: 0.23–1.50, p-value = 0.28) respectively. Corresponding Kaplan-Meier survival curves are shown in Supplementary Figs. 1C and 1D. In an unadjusted exploratory analysis, adjuvant immunotherapy (n = 17) vs no immunotherapy (n = 35) was associated with improved overall survival (median 14.0 months vs 6.0 months; p-value = 0.02; HR = 0.38, 95% CI: 0.17–0.86) (Fig. 2E). Of the 17 patients receiving immunotherapy, 11/17 had stage I disease (64.7%), 5/17 had stage III/IV (29.4%) and one patient's stage was not recorded. When analysis was restricted to patients with FIGO stage I disease, adjuvant immunotherapy was not significantly associated with improved overall survival (median 28 months vs 10 months; p-value = 0.22, HR = 0.45, 95% CI: 0.13–1.63) (Supplementary Fig. 2E).

Age and menopausal status were not associated with overall survival (p-value = 0.46, p = 0.35, p-value = 0.18) (Supplementary Fig. 2F, G). Bilateral tumours were associated with a significantly worse overall survival than unilateral tumours (p-value<0.001) (Fig. 2F).

The median follow-up period was 10.0 months (IQR 5.0–18.0). Information on disease recurrence was available in 32 cases (32/92, 34.7%), of which 28 experienced disease recurrence (28/32, 87.5%) and four did not (4/32, 12.5%). Some cases had recurrence at more than one site. Sites included the liver (12/32, 37.2%) lung (8/32, 25.0%), lymph nodes (6/32, 18.8%), central nervous system (5/32, 15.6%), bowel (4/32, 12.5%) and bone (4/32, 12.5%).

Quality assessment was performed using the Joanna Briggs risk of bias tool for case reports and case series. Using these criteria, 57 studies (57/76, 75.0%) were rated as 'low', 17 as 'moderate' (17/76, 22.4%), and two as 'high' (2/76, 2.6%) risk of bias according to their reporting quality using this tool. Twenty-three studies attained an optimal score (Table S3 and Table S4).

4. Discussion

4.1. Summary of main results

This systematic review and pooled analysis provides the largest review to date of primary ovarian malignant melanoma, synthesising 92 cases from 76 studies published between 1942 and 2025. This study provides a thorough synthesis of available evidence, enabling the generation of future research strategies.

We demonstrated that primary ovarian malignant melanoma predominantly affected middle-aged women, with an average age at diagnosis of 50.6 years. Age and menopausal status were not associated with survival. Ethnicity and skin type were rarely reported and although cases were reported globally, primary ovarian malignant melanoma, being a non-cutaneous malignancy, is unlikely to be related to sun exposure or skin type. Half of the patients presented as early stage (FIGO stage I; 34/70, 48.6%) and half presented at a late stage (FIGO stage III–IV; 36/70, 51.4%). The association between bilateral tumours and worse overall survival ($p < 0.001$) should be interpreted with caution, given only six of 80 patients had bilateral disease and the finding may reflect the advanced disease burden typically associated with bilateral involvement. Earlier-stage disease correlated with improved outcomes, whereas no clear survival signal was observed associated with surgical radicality or cytotoxic chemotherapy. Exploratory analyses suggested a potential association between immunotherapy and improved survival, which remained poor overall, however this finding is limited by the inherent heterogeneity of the data, which is likely confounded by stage distribution, treatment availability and selection bias. Metastatic patterns in advanced primary ovarian malignant melanoma in the available data appeared distinct from epithelial ovarian cancer, with our study demonstrating frequent parenchymal extra-abdominal recurrence, including lung, bone, and brain. Interestingly, no stage II cases were identified in the available cohort, which may reflect the tendency of primary ovarian malignant melanoma to disseminate haematogenously to distant parenchymal sites rather than by direct pelvic extension, although understaging in earlier historical cases cannot be excluded.

Unlike malignant germ cell tumours, primary ovarian malignant melanoma represents a secondary somatic malignancy that is histologically and clinically distinct [20]. As the ovary lacks native melanocytes, evidence of melanocytic differentiation within a teratoma is essential to confirm primary ovarian origin [21]. Distinguishing primary ovarian malignant melanoma from metastatic melanoma to the ovary remains a key diagnostic challenge and

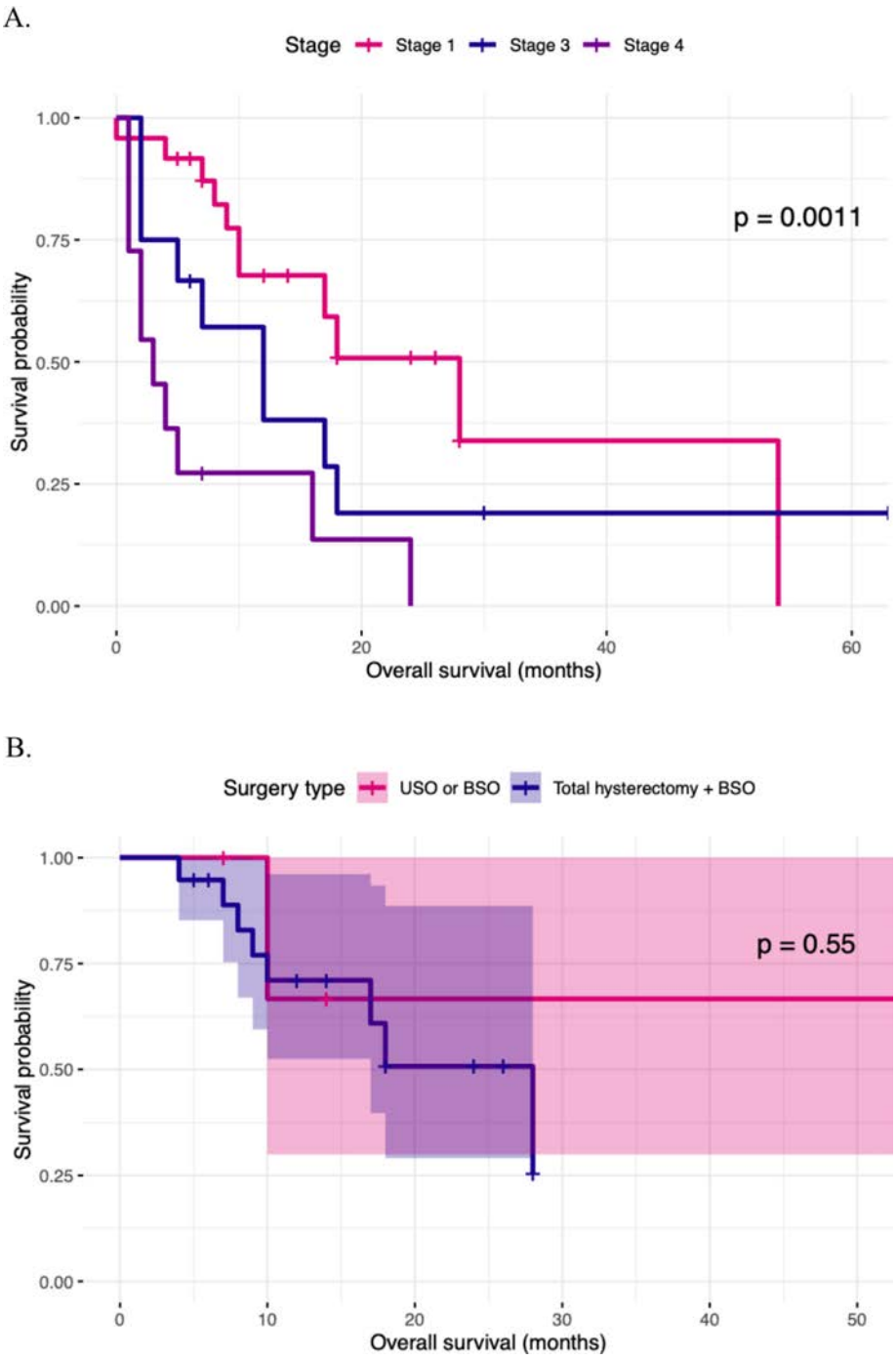


Fig. 2. Kaplan–Meier curves for overall survival A) FIGO stage (Stage 1 vs 3 vs 4) B) FIGO Stage IA Surgery Type (Unilateral salpingo-oophorectomy or Bilateral salpingo-oophorectomy vs total hysterectomy and bilateral salpingo-oophorectomy C) Stage I +/− Adjuvant therapy D) Stage III/IV +/− Adjuvant therapy E) Management: Immunotherapy vs no Immunotherapy F) Laterality of tumour (Bilateral vs right vs left).

diagnosis depends on thorough histopathological analysis and exclusion of an extra-ovarian primary [13]. Although immunohistochemical (IHC) markers (S-100, Melan-A and HMB45) supported diagnosis in over half of cases (50/92, 54.3%), reporting was inconsistent, reflecting the heterogeneity in diagnostic approaches. In our data, more than half of cases (50/92, 54.3%) fulfilled three or more Cronje and Woodruff diagnostic criteria, supporting wider adoption of these guidelines to improve diagnostic consistency [13].

Almost all patients underwent primary radical surgery, limiting conclusions regarding the efficacy of alternative strategies such as neoadjuvant chemotherapy, immunotherapy, or the safety of a fertility-sparing approach. Although our analysis did not demonstrate a significant benefit of radical surgery versus a fertility-sparing approach in stage IA disease; the very small number of patients undergoing unilateral or bilateral salpingo-oophorectomy ($n = 4$) and the lack of high-quality evidence preclude definitive conclusions or recommendations.

4.2. Results in the context of published literature

Consistent with previous studies, this pooled analysis demonstrates primary ovarian malignant melanoma is associated with a poor

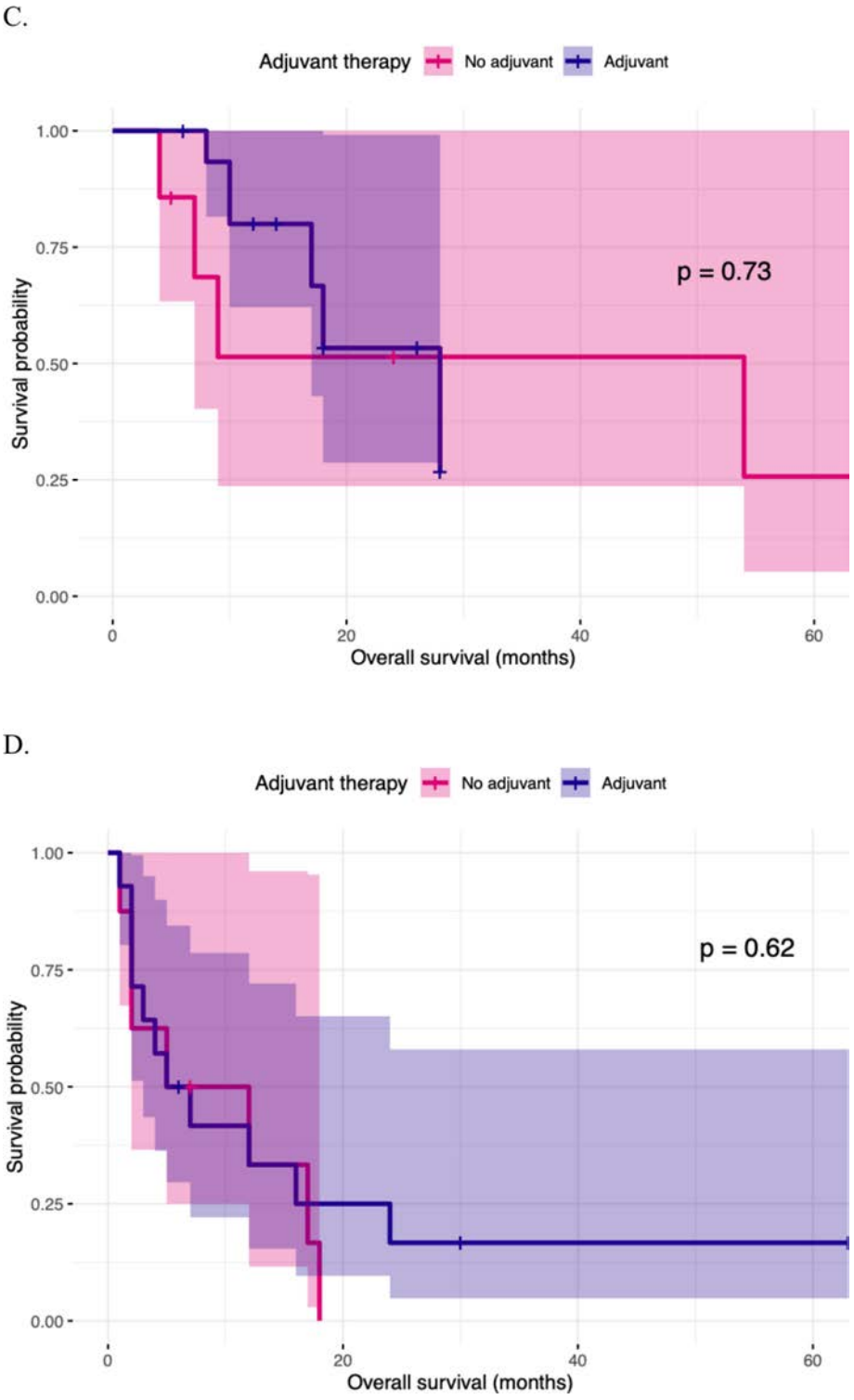


Fig. 2 (*continued*).

prognosis even for early-stage disease [13]. The largest previous case series by Paola et al. (2018) identified 49 patients, with primary surgery as the mainstay of treatment and only 35% receiving adjuvant therapy [13]. Poor oncological outcomes were observed, however, the effect of treatment on survival could not be determined due to stage effect, and lack of pooled analyses [13]. Although squamous cell carcinoma arising from a mature cystic teratoma, also carries an unfavourable prognosis, reported survival outcomes are more favourable than those observed for primary ovarian malignant melanoma. Specifically, median progression free and overall survival of 26.9 and 42.0 months and 5-year progression free and overall survival rates of 43.8% and 86%, respectively have been reported [22]. Similarly, stage I epithelial ovarian cancer has 5-year overall survival of 82% with adjuvant chemotherapy and 74% with observation [22]. These comparisons highlight the aggressive nature of primary ovarian malignant melanoma and need for more effective therapeutic strategies [23].

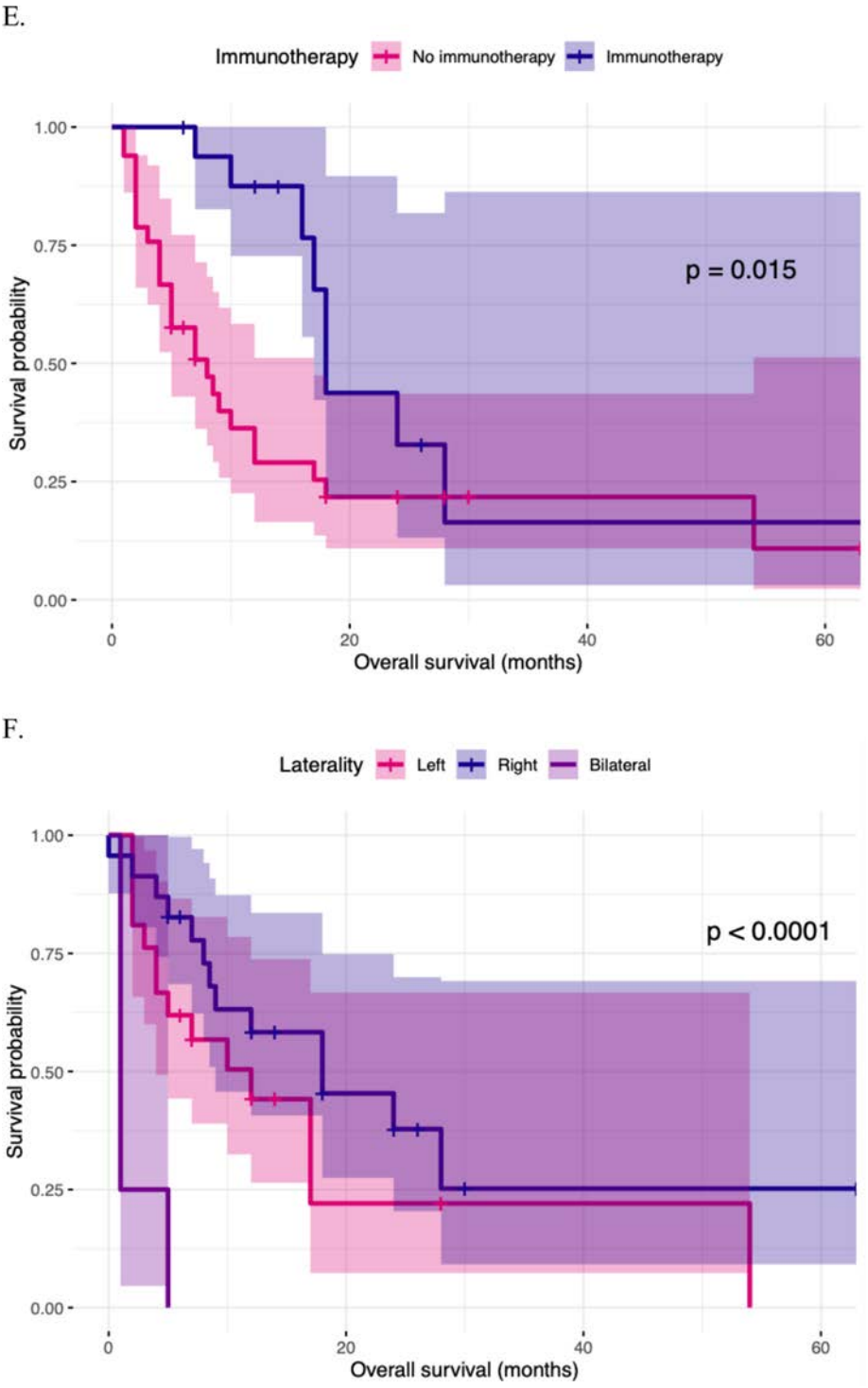


Fig. 2 (*continued*).

The heterogeneity of cytotoxic regimes and the absence of clear survival benefit from chemotherapy or radiotherapy limits meaningful interpretation in our analysis. Resistance to DNA-damaging agents, including platinum or alkylating chemotherapy, may reflect biological characteristics common to other melanoma subtypes, such as low mitotic index and frequent mutations in *BRAF* (B-Raf proto-oncogene, serine/threonine kinase), *NRAS* (neuroblastoma RAS viral oncogene homolog), *C-KIT* (KIT proto-oncogene, receptor tyrosine kinase) and *PTEN* (phosphatase and tensin homolog) genes, however comprehensive molecular profiling data for primary ovarian malignant melanoma are lacking [24]. Cutaneous melanomas typically develop within an immunosuppressive microenvironment which limits chemotherapy-induced apoptosis. Similarly, primary ovarian malignant melanomas arise within a mature cystic teratoma, a context not typically associated with chemosensitivity, sharing a similarly resistant phenotype, lacking the high proliferative index

and differentiation targets exploited by chemotherapy in epithelial tumours [25–28].

Exploratory unadjusted analyses suggested a potential association between adjuvant immunotherapy and improved survival. However, the immunotherapy cohort was highly heterogenous, comprising both older cytokine-based therapies (predominantly interferon and interleukin-2) and modern CPIs, which have substantially different mechanisms of action and efficacy profiles. Furthermore, this finding should be interpreted cautiously given the substantial imbalance in stage distribution, with a predominance of FIGO stage I disease among immunotherapy recipients. The association was not statistically significant when analysis was restricted to FIGO stage I disease (HR 0.45, p-value = 0.23), although this subgroup was limited by small sample size ($n = 11$) and events in this sub-analysis. While cytokine therapies such as interferon and interleukin-2 have historically demonstrated only modest benefit in melanoma [29], CPIs, alone or in combination, have substantially improved outcomes in cutaneous melanoma [15]. In this setting, the 3-year overall survival exceeds 50% with Programmed Death-1 (PD-1) monotherapy and combined PD-1 and Cytotoxic T-Lymphocyte Antigen-4 blockade [30], extending the median overall survival from 9 to 24 months [31]. The efficacy of CPIs in mucosal melanoma appears comparatively reduced, with lower response rates and survival reported in post hoc analyses of pivotal trials, including KEYNOTE-001/002/006 in the primary setting [32], and Checkmate-915 in the adjuvant setting [33]. We were unable to find any trials reporting on performance of CPIs in primary ovarian malignant melanoma specifically. Given the limitations of the available data including small sample size, early-stage over-representation and treatment heterogeneity, the observed association should be considered hypothesis generating rather than evidence of therapeutic benefit, although it may support further investigation of CPIs in both early stage and late stage/recurrence of primary ovarian malignant melanoma [34].

The near complete absence of molecular data represents a critical limitation of the current literature and barrier to improving diagnosis and management. Despite the known importance of molecular profiling in cutaneous melanoma, where mutations in *PTEN, BRAF, C-KIT* and *NRAS* guide targeted therapy [35], molecular profiling was only performed sporadically for primary ovarian malignant melanoma (5/92, 5.4%). In such a rare and biologically heterogenous disease, molecular features as likely to be more informative than clinicopathological variables alone, particularly given the limitations of the available data. In our analysis, the use of targeted therapy was rare. Only one patient received a BRAF inhibitor and anti-VEGF, which was in the relapse setting and combined with both cytokine-based and CPIs; the patient was alive 69 months after diagnosis (when follow-up ended) [36]. Two additional primary ovarian malignant melanoma cases received tyrosine-kinase inhibitors, both in the relapse setting. In one patient, second-line imatinib was given without reported KIT (CD117) expression, achieving disease stabilisation [37]. In a second case, imatinib was started for KIT-positive disease, and the patient died 10 months after treatment initiation [38]. No MEK inhibitors targeting NRAS mutations were reported. BRAF and MEK inhibitors in particular have revolutionised treatment outcomes in cutaneous melanoma and can be used alone or in combination with CPIs, with response rates exceeding 60% in cases harbouring BRAF mutations and improved progression-free and overall survival compared to monotherapy [39]. Importantly, BRAF inhibitors may paradoxically promote tumour growth in *BRAF* wild-type cases, highlighting the need for molecular guidance [40]. Targeting VEGF has shown some promise in mucosal melanoma [41,42]. The lack of genomic data not only restricts understanding of tumour biology but also limits application of targeted therapies and clinical trial design. Whole exome and genome sequencing of primary ovarian malignant melanoma could be beneficial in identifying common mutations and molecularly distinct subtypes to guide use of both existing and novel targeted therapies.

An additional concern is the lack of defined post-treatment surveillance protocols for primary ovarian malignant melanoma. This is particularly concerning given the high recurrence rates and limited utility of tumour markers such as CA125 [43]. Increased serum CA19–9 has been proposed as an adjunct to help distinguish a mature cystic teratoma from epithelial ovarian cancer [44]. In cutaneous melanoma, no serum marker is recommended for diagnosis or routine surveillance, while LDH serves only as a prognostic indicator in metastatic disease [45]. S100B is used selectively in some European centres with limited sensitivity and specificity, and circulating tumour DNA remains investigational [46]. Given the recurrence patterns observed in this cohort, cross-sectional imaging of the chest, abdomen and pelvis, with dedicated brain imaging, may have a role in surveillance strategies for primary ovarian malignant melanoma, consistent with approaches used in high-risk cutaneous melanoma, although supporting evidence remains limited [47].

4.3. Strengths and weaknesses

The main strength of this study is in its size and comprehensiveness, pooling 92 cases over eight decades to provide insights into primary ovarian malignant melanoma presentation, management and outcomes. This allows hypothesis generation and identifies knowledge gaps for future research.

The Joanna Briggs tool was utilised, which is designed specifically for the quality assessment of case reports and case series. Whilst the risk of assessment classified many studies as 'low risk' of bias, we acknowledge that the studies, being only case reports and series, are inherently low quality by nature and susceptible to a high degree of selection and conformation bias. However, given the rarity of the disease, this reflects the limitations of the existing evidence base rather than the strength of the data itself. The temporal heterogeneity of the studies, spanning over eight decades (1942–2025), likely influence staging accuracy, treatment availability, and reported outcomes further limiting comparability across cases. As such, all survival analyses should be interpreted with caution. Sensitivity analyses restricted to cases fulfilling all four Cronje and Woodruff diagnostic criteria were not feasible as only 20 cases met all four criteria, 12 of which were reported after 2000, limiting the statistical robustness of a subgroup analyses. Earlier cases prior to the 1980's may have underestimated metastases due to a lack of modern imaging. Another key limitation is the diagnostic uncertainty of the cases. Given the variability in histopathological reporting and incomplete information regarding the Cronje and Woodruff criteria across the cohort, misclassification of cases cannot be excluded. Key clinical parameters, including treatment toxicity, perioperative outcomes, as well as molecular profiling were inconsistently reported, in addition to details of surgery such as the approach (laparoscopic vs open) and presence of residual disease, which limits comparative analyses. Furthermore, most studies lacked follow-up data beyond 12–18 months, reducing insight into longer-term survival or recurrence.

4.4. Implications for practice and future research

Current management of primary ovarian malignant melanoma should move beyond extrapolating conventional treatment strategies used for epithelial ovarian cancer, as standard surgical and chemotherapeutic approaches appear be less efficacious. Future novel therapeutic approaches are needed, which may include immunotherapy. In any case, further investigation through international collaborative multicentre studies is needed. Given the rarity of this cancer, international registries, innovative trial designs, and implementation of molecular profiling as standard will be essential to understand optimal treatment strategies and develop novel therapeutics.

5. Conclusions

Primary ovarian malignant melanoma remains an exceptionally rare and aggressive malignancy with poor overall survival across all disease stages. From the available data, no clear survival benefit was observed with conventional surgery and chemotherapy, though this finding is limited by the quality and heterogeneity of the available evidence. Given the inherent limitations of the evidence base, these findings should be interpreted as descriptive, highlighting the urgent need for routine molecular profiling and co-ordinated international research to identify optimal management strategies and guide the development of novel therapies for this rare disease.

Transparency declaration

The lead/corresponding author (SB) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organisations.

Ethics approval and patient consent

Ethical approval was not required for this review.

CRediT authorship contribution statement

Anastasios Pandraklakis: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Amy Macdonald Shearer:** Writing – review & editing, Writing – original draft, Project administration, Formal analysis. **Laura Burney Ellis:** Writing – review & editing, Supervision, Project administration, Investigation, Formal analysis, Data curation. **Maria D. Oikonomou:** Writing – original draft, Formal analysis, Data curation. **Konstantinos Kechagias:** Writing – original draft, Methodology, Formal analysis, Data curation. **Baljeet Kaur:** Writing – review & editing. **Michael J. Seckl:** Writing – review & editing. **Christina Fotopoulou:** Writing – review & editing. **Sarah J. Bowden:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Maria Kyrgiou:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2026.05.024.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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