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REVIEW

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The complex clinical challenges of secondary ovarian tumors and cancer of unknown primary: diagnostic and therapeutic considerations

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Abstract

Favorable Carcinoma of Unknown Primary (CUP) types, representing approximately 20% of cases, are diagnosed through detailed histological, immunohistochemical, and imaging analyses that resemble known primary cancers. These include single-site or oligometastatic CUP, breast-like CUP, ovary-like CUP, head and neck-like CUP, prostate-like CUP, colon-like CUP and renal-like CUP. Patients benefit from site-specific treatments aligned with presumed primary sites, often leading to better prognoses. However, the remaining 80% of CUP cases are unfavorable, showing poor outcomes despite platinum-based chemotherapy, molecular targeted therapies and immunotherapy. Diagnosis of Secondary Tumors of Unknown Primary Origin (STOs) involves distinguishing primary tumor sites through molecular profiling and imaging. Cytoreductive surgery may offer survival benefits, particularly in ovarian metastases from colorectal cancer, although its role in gastric-origin STOs is less clear. Adjuvant chemotherapy, including platinum-based regimens, is considered beneficial but lacks robust evidence from randomized trials. Managing CUP and STOs requires a tailored approach based on tumor characteristics, site-specific treatments, cytoreductive surgery, and systemic therapies. Continued research and flexible treatment protocols are essential for optimizing outcomes in this complex and heterogeneous group of cancers.

Keywords

Cancer of unknown primary; Gene expression profiling; Cytoreductive surgery; Adjuvant chemotherapy; Krukenberg tumor; Metastasis

1. Introduction

Carcinoma of unknown primary origin (CUP) constitutes a heterogeneous array of cancers characterized by metastatic spread without an initially discernible primary tumor. This condition represents a minority, accounting for approximately 2% to 5% of all cancer diagnoses. Given the advancements in imaging modalities and targeted therapeutic approaches, determining the optimal extent of diagnostic evaluation for CUP poses a formidable challenge, necessitating a tailored approach guided by clinical presentation, histopathological findings, and the patient's treatment tolerance [1].

The propensity of tumors to metastasize to the ovaries has long been recognized. In 1896, Friedrich Ernst Krukenberg, a German gynecologist and pathologist, described a unique type of primary ovarian cancer, initially termed "fibrosarcoma ovarii mucocellulare carcinomatodes". This tumor's metastatic nature was later elucidated by Kraus, who introduced the eponym "Krukenberg tumor" approximately five years later [1]. Krukenberg tumors (KT) are histopathologically characterized as secondary ovarian tumors primarily composed of carcinomas containing a significant component (typically >10% of the tumor) of mucin-filled signet-ring cells [2]. However, this definition is not universally adopted, and caution should be exercised to avoid applying the designation "KT" indiscriminately to all metastatic tumors to the ovary. Gastric cancer, particularly the poorly cohesive/signet ring-cell type, is the most common origin of KT, accounting for up to 70% of cases [3]. Despite being among the most recognised secondary tumors of the ovary, Krukenberg tumors represent only approximately 10–25% of all secondary ovarian tumors. Ovarian metastases from various primary sites, such as colon, breast, small intestine, pancreatic cancer, malignant melanoma and others, frequently do not align with the histopathological definition of KT [4]. Detecting secondary tumors in the ovaries often precedes the diagnosis of the primary tumor, which may be small and asymptomatic at the time of discovery. This presents a significant challenge for clinicians and pathologists in achieving accurate diagnosis, crucial for appropriate treatment. While the prognosis for secondary tumors in the ovaries is generally poor, outcomes vary among different primary cancers. Also, metastasectomy may improve prognosis in selected cases [5].

In the first section, we will analyze and detail the diagnosis

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and site-specific treatments for favorable and unfavorable CUP and Secondary Tumors of Unknown Primary Origin (STOs). The paper concludes with a summary of key findings and implications, including the roles of cytoreductive surgery and emerging therapies in optimizing patient outcomes.

2. Epidemiology

Secondary tumors of ovarian origin (STOs) represent a significant proportion of ovarian malignancies, ranging between 10% and 25% [6]. The most frequent primary tumors leading to ovarian metastases originate from breast, colorectal, endometrial, stomach and appendix cancers. However, the prevalence of STOs varies greatly depending on several factors, including geographical location, patient demographics, diagnostic techniques, and the expertise of the examining pathologists.

For instance, in certain Asian countries, notably those with higher incidences of gastric cancer, STO rates tend to be elevated compared to their European counterparts, where gastrointestinal cancers are less predominant as sources of ovarian metastases. This geographical disparity underscores the influence of primary cancer types that are more common in specific regions.

Moreover, the age at which STOs are diagnosed often correlates with the origin of the primary tumor. For example, metastatic gastrointestinal tract tumors, such as those originating from the stomach or colon, are more frequently diagnosed in older patients. On the other hand, breast cancer metastases to the ovary typically affect younger individuals. This is consistent with the general age distribution of breast cancer, which often occurs at a younger age compared to gastrointestinal malignancies.

In general, patients with STOs tend to be younger than those diagnosed with primary ovarian cancer [7]. Among STO patients, those with Krukenberg tumors, which are metastatic tumors from gastrointestinal origins, particularly from gastric adenocarcinoma, represent the youngest subset. The younger age of these patients can be attributed to the earlier onset of primary tumors in this group, combined with increased ovarian vascularization in younger women, which facilitates the hematogenous spread of cancer cells to the ovaries. This enhanced vascularity in younger women might partly explain the predisposition to ovarian metastasis in certain cancers, especially those that spread via the bloodstream [7].

3. Prognosis

Patients with STOs typically face a poor prognosis, often reflecting advanced disease stages. Compared to primary ovarian cancer, STO patients exhibit significantly lower survival rates, with notable variations depending on the primary tumor [8]. Those originating from the genital tract generally do better than those from non-genital sources, such as the pancreas and small intestine, which carry the poorest prognosis. Prognostic factors include pre-operative serum Cancer antigen 125 (CA 125) levels, age at STO diagnosis, tumor size, site of metastasis, tumor histology, primary tumor origin, presence of peritoneal dissemination, the extent of cytoreductive surgery, and tumor laterality [9]. Additionally, mutations in genes like Decapentaplegic Homolog 4 (SMAD4) and Lysine methyltransferase 2D (KMT2D) are associated with reduced overall survival in ovarian metastases from colorectal cancer, suggesting the potential for somatic mutation profiling to offer additional prognostic insights [10].

4. Risk factors

CUP is a rare and aggressive cancer where the primary tumor site is not identified, and its causes remain elusive. However, several lifestyle and environmental factors have been identified that may increase the risk of developing this condition. One of the most significant risk factors is smoking, particularly heavy smoking. Research has shown that individuals who smoke 26 or more cigarettes per day are at a substantially higher risk of developing CUP compared to those who do not smoke [11]. This strong association emphasizes the detrimental role tobacco plays in cancer development, as smoking is a well-established risk factor for numerous cancer types. In the case of CUP, the harmful substances in tobacco likely trigger carcinogenesis in multiple areas of the body, making it difficult to locate the origin of the tumor.

Obesity, especially central obesity, has also been linked to an increased risk of CUP. Studies have found that individuals with larger waist circumferences—those in the highest quartile—face a 30% higher likelihood of developing CUP compared to individuals with smaller waist measurements. This association suggests that excess body fat, particularly visceral fat, may promote chronic inflammation or hormonal imbalances, creating an environment conducive to cancer development in various tissues [11]. While the connection between obesity and cancer risk is well-documented, the mechanisms by which it influences the development of CUP remain an area of ongoing research.

Alcohol consumption is another factor that has been investigated in relation to CUP risk. Though the association is weaker compared to smoking and obesity, some studies suggest that heavy alcohol use may still contribute to the risk. Alcohol can damage cells and lead to DNA mutations, which may play a role in cancer formation. However, the evidence is not as robust, and the specific link between alcohol and CUP requires further exploration.

Additionally, socioeconomic factors, such as education level, have been observed to influence the likelihood of developing CUP. Lower education levels have been loosely associated with a higher risk of CUP, potentially due to disparities in access to healthcare, health literacy and lifestyle choices. Individuals with lower education levels may be more likely to engage in risky behaviors, such as smoking and poor dietary habits, which can increase cancer risk [11]. This association highlights the complex interplay between socioeconomic status and health outcomes, further complicating the understanding of CUP.

In summary, the development of CUP is influenced by a variety of risk factors, including heavy smoking, obesity, alcohol consumption and lower socioeconomic status. These factors contribute to an increased likelihood of cancer formation, but their precise role in CUP remains difficult to determine due to the enigmatic nature of the disease. Ongoing research is es-

sential to better understand the underlying mechanisms driving these associations and to develop more effective strategies for prevention and early detection.

5. Pathogenesis

The mechanism by which extra-ovarian tumors metastasize to the ovaries remains unclear, with proposed pathways including lymphatic, hematogenous and transcoelomic dissemination [12]. Different tumors appear to utilize distinct pathways; for instance, colon cancer commonly spreads hematogenously, while gastric cancer tends to metastasize via retrograde lymphatic spread [13]. Immunohistochemical analyses support these observations, revealing varying vascular and lymphatic invasion rates in ovarian metastases from different primary cancers. The rich mucosal lymphatic network in the stomach and anatomical characteristics of the lymphatic system contribute to these diverse metastatic routes [14]. Gastric cancer cells metastasize easily to the ovaries via the receptaculum chyli and urogenital lymph vessel trunks due to their proximity. Gastrointestinal cancers may also obstruct retroperitoneal lymphatic nodes, causing lymph flow reversal into the ovaries. While transcoelomic dissemination is not a primary pathway for secondary ovarian tumor development, metastatic routes may combine, particularly in advanced gastrointestinal tumors [14].

6. Metastatic organotropism and role in STO

Metastatic organotropism, the preferential spread of tumors to specific secondary sites, is a longstanding phenomenon with complex molecular mechanisms [15]. While various factors influence this process, including tumor cell attraction, adhesion, survival, angiogenesis and micro-RNA (miRNA) loss, specific markers for ovarian metastasis remain elusive [16]. Studies have identified mutations in genes like Kirsten rat sarcoma viral oncogene homolog (KRAS), SMAD4 and Neurotrophic receptor tyrosine kinase 1 (NTRK1) in ovarian metastases from colorectal cancer, but their role in organotropism is unclear. Differences in mutation profiles between primary colorectal tumors and matched ovarian metastases suggest the presence of specific sub-clones with ovarian homing ability [17]. Although high-grade serous ovarian cancers likely originate in the fallopian tube fimbria, shared molecular patterns with secondary ovarian tumors warrant further investigation for potential treatment implications, such as prophylactic bilateral oophorectomy based on primary tumor characteristics [18].

7. Clinical signs

STOs, much like primary ovarian cancer, tend to remain asymptomatic during their early stages, which often results in a delayed diagnosis when the disease has already progressed to an advanced stage. This lack of early symptoms makes it challenging to detect the condition before the tumor reaches a considerable size. When symptoms do arise, they are generally non-specific and may be easily attributed to less serious conditions, further complicating early diagnosis. Among the most commonly reported symptoms are abdominal pain, which occurs in approximately 42% of patients, and postmenopausal bleeding, reported by about 18% of individuals at the time of diagnosis. These symptoms are not unique to STOs, contributing to the difficulty in distinguishing between primary and secondary ovarian malignancies.

Other non-specific symptoms include weight loss, experienced by 6% of patients, and increasing abdominal girth, which affects around 15%. The latter is often a result of the growing tumor mass or fluid accumulation in the abdominal cavity, known as ascites. Although ascites is present in about 39% of STO cases, it is notably less common compared to primary ovarian cancer, where ascites is a more frequent finding [19, 20]. This difference in the prevalence of ascites between primary and secondary ovarian tumors may help guide diagnostic considerations in clinical practice.

Additionally, some patients with secondary ovarian tumors may experience hormonal changes due to the tumor's ability to produce hormones. These hormonal effects can lead to irregular vaginal bleeding and changes in menstrual habits, even in postmenopausal women. In more severe cases, the hormonal imbalance may cause hirsutism (excessive hair growth) and virilization (the development of male characteristics), which can be distressing for the patient.

One unique presentation associated with STOs that originate from the appendix is pseudomyxoma peritonei, a rare condition where mucinous tumors spread within the abdominal cavity, causing a build-up of mucus [20]. This condition can lead to significant abdominal distention and discomfort, requiring careful management.

Overall, the clinical signs of STOs are often indistinguishable from those of primary ovarian cancer, contributing to the difficulty in differentiating between the two. However, the presence of specific features, such as the pattern of ascites or hormonal effects, may provide clues to the nature of the tumor's origin. Despite these subtle differences, both primary and secondary ovarian tumors present with a broad range of symptoms, most of which are non-specific, necessitating a thorough diagnostic approach to accurately determine the tumor type and origin.

8. Diagnosis

The diagnostic challenge of distinguishing STOs from primary ovarian cancer is paramount, as up to 40% of cases present without a known primary tumor. Accurate diagnosis is crucial for appropriate treatment [21]. The United States National Cancer Institute (NCI), National Comprehensive Cancer Network (NCCN), and the European Society of Medical Oncology (ESMO) have published clinical guidelines for diagnosing CUP to rule out metastasis-related cancers. In 2010, the National Institute for Clinical Excellence (NICE) recommended forming a dedicated multidisciplinary team including oncologists, palliative care physicians, and nurse specialists to manage CUP patients. However, this approach has not significantly improved performance status or survival rates [22].

The initial clinical workup for CUP involves a

thorough medical history, physical examination (including genitourinary, rectal, and breast examination for women), and laboratory tests. Imaging includes computed tomography (CT) scans of the abdomen, chest, and pelvis. Positron emission tomography (PET)/CT and multiparametric 3-tesla magnetic resonance imaging (3T-MRI) (Multiparametric (MP)-MRI) are equally effective for diagnosing neck lymph node metastasis, with whole-body PET/CT being the preferred method for assessing overall disease. MP-MRI evaluates local soft tissue involvement after positive PET/CT results, aiding in tumor staging and prognosis. Histopathological examination, ideally with immunohistochemistry, is necessary for definitive diagnosis, although the primary tumor remains unidentified in approximately 15% of cases despite extensive evaluation. Immunohistochemistry identifies specific markers such as caudal-related homeobox protein (CDX2), homeobox protein Nkx-3.1 (NKX3-1), paired box gene 8 (PAX8), special Adenine-Thymine (AT)-rich sequence-binding protein 2 (SATB2), thyroid transcription factor 1 (TTF-1), and splicing factor 1 (SF1), focusing on lineage-restricted transcription factors for diagnostic accuracy [23].

9. Imaging methods

Imaging methods play a crucial role in assessing the extent of disease and identifying potential primary tumor sites in cases of STOs. Computed tomography (CT) scanning of the chest, abdomen, and pelvis with contrast is standard for initial evaluation. It locates the primary tumor, assess disease extent, and select the optimal biopsy site [24, 25]. However, conventional imaging techniques, including CT, ultrasound (US), and magnetic resonance (MR) imaging, are not reliable in distinguishing primary ovarian cancer from STOs [26]. Additionally, 2-[fluorine-18]-fluoro-2-deoxy-d-glucose positron emission tomography integrated with CT (18F-FDG PET/CT) does not differentiate between the two [27]. While PET/CT offers superior sensitivity, limitations such as the detection of smaller lesions and tumors with low FDG uptake exist [28, 29]. Limited data from prospective trials suggest no clear diagnostic advantage of PET/CT over CT alone in patients with multiple metastases of unknown primary origin [30]. Consequently, PET/CT is not routinely recommended for STO diagnosis but may be considered for local or regional therapy planning in select cases.

10. Role of tumor markers

While CA 125 is elevated in a majority of primary epithelial ovarian cancer cases and in a substantial portion of STOs, its pre-operative levels do not differentiate between primary and secondary ovarian malignancies. Furthermore, CA 125's sensitivity in detecting STOs is notably lower than in primary ovarian cancer, limiting its utility in primary diagnostics. However, the CA 125/Carcinoembryonic antigen (CEA) ratio may aid in distinguishing primary ovarian tumors from colorectal carcinoma metastases [1]. Elevated CA 125 and CA 19-9 levels pre-operatively may be associated with a poorer prognosis. The routine use of epithelial tumor markers in the primary diagnosis of STOs is not recommended due to their limited specificity and lack of prospective clinical trials [1]. Nonetheless, tumor markers may offer valuable insights into treatment response.

11. Role of endoscopy

Endoscopic methods are not routinely recommended for patients with cancer of CUP unless specific symptoms or abnormalities suggest gastrointestinal (GI) tract involvement. However, given that most STOs originate from the GI tract, endoscopic investigation is a reasonable approach, offering a non-invasive means to obtain histopathological specimens. In regions with high incidences of gastric and colorectal cancer, such evaluations (esophagogastroduodenoscopy and/or colonoscopy) should be considered frontline diagnostic tools for STOs unless GI origin is ruled out histopathologically.

12. Histopathological diagnosis

12.1 Gross features

Metastases to the ovaries are typically smaller and contain cysts, with most STOs measuring less than 10 cm in diameter. Metastases from breast cancer tend to be smaller, while those from the GI tract, especially colon cancer, may resemble primary ovarian tumors and are often larger. Bilateral involvement is more common in STOs, particularly in KT, affecting both ovaries in over 80% of cases. However, metastases from colorectal carcinoma tend to be unilateral. Assessing tumor size and bilateralism intra-operatively may aid in distinguishing primary ovarian tumors from STOs [31]. Additionally, bilateral involvement may indicate a poorer prognosis. Generally, features favoring metastases include small size, bilateralism, nodular growth pattern, and tumor presence on the ovarian surface or in the superficial cortex [32].

12.2 Histology

Histologically, STOs typically mirror the primary tumor, with mucinous adenocarcinoma being the most common finding. Signet-ring cell morphology predominates in metastases from gastric cancer [3], while invasive ductal carcinoma is prevalent in breast cancer metastases, including Krukenberg tumors. Metastatic endometrial malignancies are primarily adenocarcinomas, whereas squamous cell carcinomas are common in cervical metastases. Rarer histological types include metastatic sarcoma, melanoma and lung cancer. Adenocarcinomas with mucinous features can pose a diagnostic challenge, often mistaken for primary ovarian neoplasms. Intra-operative frozen section biopsy aids in surgical planning, but definitive diagnosis may require immunohistochemistry to distinguish primary ovarian carcinomas from STOs [6]. Histological features favoring metastases include infiltrative growth pattern, stromal desmoplasia, nodular growth, involvement of ovarian surface and cortex, and hilar and lymphovascular space involvement [32].

12.3 Role of immunohistochemistry

The pathologists follow a systematic approach to identify the tumor type, subtype and possible site of origin. Most CUPs are

carcinomas, with adenocarcinomas (60%) and poorly differentiated carcinomas (30%) being the most common, followed by squamous (5%) and neuroendocrine carcinomas (5%). Initial immunohistochemistry (IHC) testing rules out tumor types with specific treatment options, such as lymphoma, melanoma, germ-cell tumors and sarcoma. For epithelial carcinomas, keratin expression (Cytokeratin 7 (CK7) and CK20) is used to predict the primary site. CK7 is found in certain simple epithelia, while CK20 is more restricted. However, exceptions exist, as some cancers show variable or overlapping keratin expression patterns. After determining the CK7/CK20 profile, site-specific markers are assessed, including both cytoplasmic and nuclear transcription factors [33].

12.4 Key site-specific markers

1. CDX2: A nuclear transcription factor predominantly expressed in gastrointestinal (GI) carcinomas, especially colorectal adenocarcinomas, and some neuroendocrine tumors of the GI tract. CDX2 is also found in carcinomas of the pancreas, biliary tract, and certain ovarian, bladder and pulmonary adenocarcinomas.

2. SATB2: Another marker for GI origin, particularly useful for distinguishing ovarian mucinous carcinomas from lower GI metastases.

3. GATA binding protein 3 (GATA3): A highly sensitive marker for breast and urothelial carcinomas, also expressed in some endometrial, pancreatic, salivary gland and other tumors.

4. TTF-1: This transcription factor is strongly associated with lung adenocarcinomas and neuroendocrine carcinomas, though its expression is less specific in high-grade neuroendocrine carcinomas. TTF-1 is also occasionally found in ovarian, endometrial, and colorectal cancers.

5. Napsin A: Typically co-expressed with TTF-1, Napsin A is highly specific for pulmonary adenocarcinomas but also found in renal cell, endometrial, and ovarian carcinomas.

6. PAX8: A marker critical for identifying carcinomas of the thyroid, kidney and Müllerian system. PAX8 is strongly expressed in non-mucinous ovarian and endometrial cancers but is absent in mammary carcinomas.

This stepwise IHC approach, focusing on specific gene expression patterns, is essential in determining the primary site of CUP, particularly when dealing with well-differentiated tumors [33].

Immunohistochemical (IHC) evaluation is essential in ovarian tumors, providing additional diagnostic insights beyond morphology assessment. Cytokeratin 7 (CK7) positivity and cytokeratin 20 (CK20) negativity are typical of primary ovarian carcinomas, with CK7 being consistently positive (90–100%). Markers like Wilms tumor 1 (WT1) and CA 125 are associated with primary ovarian carcinoma, showing variable expression across histologic subtypes. Progesterone receptors (PRs) and estrogen receptors (ERs) exhibit variable expression patterns depending on tumor type, with ERs more commonly expressed than PRs. Notably, ERs and PRs are also present in breast carcinoma and other tumors of the female genital tract.

The primary challenge in differential diagnosis lies in distinguishing metastatic colorectal cancer (mCRC) from primary ovarian endometrioid or mucinous adenocarcinomas. Primary ovarian endometrioid adenocarcinomas typically show diffuse positivity for CK7 and CA 125, while mCRC exhibits a converse immunophenotype with CK20+, CEA+, CDX2+, CK7−, and CA 125−. Distinguishing primary ovarian mucinous carcinoma from mucinous mCRC is more complex, with overlapping immunophenotypes [34]. Additional markers like β-catenin, Mucin 5AC (MUC5AC) and Dipeptidase 1 (DPEP1) aid in discerning primary mucinous ovarian cancer from ovarian metastasis of GI cancers. If combined with other IHC markers (CDX2 and CK7), together with a single clinical factor (tumor size), DPEP1 can provide an accuracy of 93% [35]. In cases of breast cancer presenting with adnexal mass, Gross cystic disease fluid protein 15 (GCDFP-15) and vimentin staining are employed, alongside markers like mammaglobin, GATA3, WT1, CA 125 and PAX8, to differentiate between breast carcinoma and primary ovarian carcinoma [36]. Specific IHC markers further aid in distinguishing metastases from renal cell carcinoma (CK7−, Cluster of differentiation 10 (CD10)+, Renal cell carcinoma (RCC)+) [37], cervical carcinoma (p16+, ER−, PR and positive Human papilloma virus (HPV) status) [38], and malignant melanoma (S-100, Melanoma-associated antigen recognized by T cells (MART-1), Human melanoma black 45 (HMB-45) and SRY-box transcription factor 10 (SOX10)) [39]. However, it's important to note that no single antibody is entirely specific or sensitive, necessitating the use of antibody panels for accurate tumor typing. The immunophenotypes of selected primary and secondary ovarian tumors are listed in Table 1 (Ref. [40–46]).

13. Stepwise approach for CUP

Cancer classification traditionally relies on anatomical location and tumor morphology, guiding patient management. Biomarkers for CUP mainly aim at establishing cancer type, subtype, and site through methods like IHC and molecular profiling (Table 2). Prognostic and predictive biomarkers may gain significance as targeted therapies evolve. The common metastatic biopsy sites include solid organs (liver, lung, bone, brain), lymph nodes (cervical, inguinal, axillary), and serous cavities (peritoneal, pleural) [47, 48]. Biopsy confirms malignancy and follows a stepwise approach to identify tumor type, subtype, and likely origin site, often utilizing IHC. They typically presents as carcinoma, but other tumor types like lymphoma, melanoma, and sarcoma should be considered [49]. Adenocarcinoma, squamous carcinoma, neuroendocrine carcinoma, and poorly differentiated carcinoma are common subtypes, with adenocarcinoma and poorly differentiated tumors comprising around 90% of CUPs. Adenocarcinoma primarily originates from the lung and pancreas, followed by colon, stomach, esophagus, breast, ovary and prostate. Metastatic sites can aid diagnosis and prognosis categorization, with loco-regional lymph node involvement suggesting a better prognosis and multiple liver metastases indicating a worse prognosis. Specific treatments are available for certain CUP subtypes, such as lymphoma, neuroendocrine carcinoma, colorectal adenocarcinoma, and other "good prognosis" cases. Optimal tumor classification by pathologists is crucial for identifying treatable and/or favorable prognosis tumors. Flexibility in diagnostic approaches is necessary to adapt to

TABLE 1. IHC profile of primary versus secondary ovarian carcinoma.

Tumor Type	Positive	Negative
Primary ovarian carcinoma		
Serous [40]	CK7, CA 125, HAM56, PAX8	CK20
Mucinous [40]	CK7, CK20, MUC5AC, HAM56, CEA, PAX8	CA 125
Endometrioid [41]	CK7, CA 125, HAM54, ER, PR, PAX8	CK20, CEA
Metastatic carcinoma		
Colorectum [42, 43]	CK20, CEA, CDX2	CK7, CA 125, MUC5AC, HAM56
Appendix [44]	CK20, MUC5AC, CEA	CK7, CA 125
Stomach [44]	CK7, CK20, MUC5AC	CA 125, HAM56
Breast [44]	GCDFP15, mammaglobin, GATA3, ER, PR	vimentin, WT1, CA 125
Pancreas [44]	CK7, CK20, MUC5AC, CEA, CA 19-9	CA 125, HAM56, DPC4
Renal cell carcinoma (clear cell) [45]	vimentin, AE1/AE3, CD10, RCC, PAX8	CK7, CK20, 34βE12
Cervical carcinoma [46]	p16, CEA, HPV infection	ER, PR

CK: Cytokeratin; CA 125: Cancer antigen 125; PAX8: paired box gene 8; MUC5AC: Mucin 5AC; CEA: Carcinoembryonic antigen; CD: Cluster of differentiation; ER: estrogen receptors; PR: Progesterone receptors; CDX2: caudal-related homeobox protein; GCDFP15: Gross cystic disease fluid protein 15; GATA3: GATA binding protein 3; RCC: Renal cell carcinoma; HPV: Human papilloma virus; WT1: Wilms tumor 1; HAM56: Macrophage Antibody; DPC4: Deleted in Pancreatic Carcinoma 4; AE1/AE3: Pan cytokeratin.

TABLE 2. Stepwise approach for carcinoma of unknown primary.

Step 1: Identify broad cancer type	
Carcinoma	Cytokeratin and other epithelial markers like AE1/AE3, CK7, CK20, EMA
Melanoma	S-100, Melan-A, HMB-45
Lymphoma/leukaemia	CD20, CD3, CD138, CD30
Sarcoma	vimentin, actin, desmin, S-100, c-kit
Step 2: If carcinoma or related then identify the subtype	
Adenocarcinoma	CK7, CK20, PSA
Squamous carcinoma	CK5, p63
Neuroendocrine carcinoma	Chromogranin, CD56, synaptophysin, TTF-1
Solid organ carcinoma	
Kidney	RCC, CD10, PAX8, Napsin A
Liver	Hepar1, CD10, glypican-3
Thyroid	TTF-1, thyroglobulin, PAX8
Adrenal	Melan-A, inhibin
Germ cell tumour	OCT4, PLAP, HCG, AFP
Mesothelioma	Calretinin, mesothelin, WT1
Step 3: If adenocarcinoma, then predict possible primary site, *e.g.*, colon, stomach, breast, ovary, pancreas	See Table 1

Bolded indicates a large category. CK: Cytokeratin; HMB-45: Human melanoma black 45; CD: Cluster of differentiation; PSA: Prostate-specific antigen; TTF-1: thyroid transcription factor 1; PAX8: paired box gene 8; AE1/AE3: Pan cytokeratin; EMA: Epithelial membrane antigen; OCT4: Octamer-binding transcription factor 4; PLAP: Placental alkaline phosphatase; HCG: Human chorionic gonadotropin; AFP: Alpha-fetoprotein; WT1: Wilms tumor 1.

emerging therapies and evolving tumor classifications.

14. Classification of CUP

International guidelines for cancer treatment are primarily based on identifying the primary tumor site. In the absence of this, CUP patients are treated according to

their clinicopathological characteristics. They are categorized into two prognostic subgroups: favorable (15–20%) and unfavorable (80–85%) [50].

Favorable CUPs share common features with known tumor types, including similar metastatic patterns, treatment responses, and prognoses. These patients are treated as if they have a specific tumor type, showing higher chemosensitivity and longer life expectancy (15–20 months), with long-term disease control in 30–60% of cases. Examples include patients with cervical lymph node metastases from squamous cell carcinoma or peritoneal carcinomatosis from papillary serous carcinoma.

Unfavorable CUPs constitute the majority, with a median survival of 6–10 months. The French CUP Group (Groupe d'Etude Français des Carcinomes de site Primitif Inconnu (GEFCAPI)) developed a prognostic model for these cases, based on performance status and pre-treatment serum lactate dehydrogenase (LDH) levels. Patients with good performance status (0–1) and normal LDH levels, treated with a platinum-based chemotherapy regimen combined with gemcitabine or taxane, show a median survival of 12 months. However, patients with poor performance status ($\geq$2) and elevated LDH have a much worse prognosis, with a median survival of just 4 months. In such cases, treatment focuses on palliative care, symptom control or low-toxicity chemotherapy [50].

A meta-analysis revealed that no chemotherapy agent, whether in monotherapy or combination regimens (platinum, taxane, gemcitabine, irinotecan, *etc.*), significantly improved survival in CUP patients. Current NCCN guidelines list multiple chemotherapy regimens for adenocarcinoma and squamous histology, but these recommendations are largely based on limited clinical evidence [50].

Identifying the tumor's origin or using personalized medicine approaches may help optimize treatment choices and improve outcomes for CUP patients.

15. Molecular analysis

Gene expression profiling aids in identifying primary tumors in CUP using mRNA or miRNA assessment via Reverse transcriptase polymerase chain reaction (RT-PCR) or microarray. Two assays identify the primary site in 80% of cases, with promising clinical utility backed by survival benefits in phase II trials. Molecular profiling helps differentiate primary ovarian tumors from STOs when IHC is inconclusive, employing single nucleotide polymorphism (SNP) assays and transcriptomic analysis. SNP array analysis effectively distinguishes primary ovarian tumors from STOs, even without primary tumor tissue specimens. Array-based comparative genomic hybridization helps diagnose ovarian and endometrial tumors, enhancing accuracy in ambiguous cases [51–53].

16. Liquid biopsy

The urgency to enhance diagnostic protocols for CUP origin, coupled with the critical condition of patients at diagnosis, has driven the exploration of less invasive diagnostic methods such as liquid biopsy. This technique analyzes tumor-derived elements like circulating tumor cells (CTCs) or circulating tumor DNA (ctDNA) in biological fluids, offering several advantages over traditional tissue biopsies, which are invasive, provide limited snapshots of tumor diversity, and can be compromised by preservation techniques.

Liquid biopsies reflect the genetic diversity of all tumor sites by analyzing CTCs and ctDNA, offering more comprehensive molecular insights. This makes it particularly suitable for implementing personalized medicine strategies, assessing prognosis, and monitoring treatment response and disease recurrence. Despite its potential, the current use of liquid biopsy in CUP management is limited due to few studies involving CUP patients directly.

Initial liquid biopsy applications focused on detecting tissue-of-origin via specific markers on CTCs but were less effective for poorly differentiated tumors. Techniques such as the Food and drug administration (FDA)-approved CellSearch System have demonstrated the potential of CTC counts as prognostic biomarkers in various cancers, with studies showing a significant presence of CTCs in over half of CUP patients, which tends to decrease post-chemotherapy.

Moreover, comprehensive genomic analysis of ctDNA has identified actionable genetic mutations in a significant proportion of CUP cases, with mutations in major pathways like Mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K) and cell cycle regulation commonly observed [40].

17. Treatment

17.1 Classification and management of favorable CUP

Favorable CUP types are those with characteristics similar to cancers with known primaries, typically showing better prognoses. About 20% of CUP patients fall into these favorable subtypes, which benefit from site-specific treatments tailored to the presumed primary site [41]. These include:

1. Single-Site or Oligometastatic CUP: Defined by one metastatic deposit or limited metastatic disease treatable with local ablative therapy, such as surgery or radiotherapy. Imaging, including PET-CT and brain MRI, confirms a limited number (no more than five) of metastases without diffuse organ involvement.

2. Breast-Like CUP (Women with Isolated Axillary Lymph Node Metastases): Diagnosed in women with axillary lymph node metastases resembling breast cancer histologically, without a detectable breast primary. Management includes axillary lymph node dissection and targeted breast therapy (radiation or mastectomy), with systemic therapy similar to nodal-positive breast cancer treatment protocols.

3. Ovary-Like CUP (Women with Peritoneal Carcinomatosis): Characterized by serous papillary adenocarcinoma, resembling ovarian cancer. Treatment parallels stage III/IV ovarian cancer protocols, including surgical debulking followed by carboplatin-paclitaxel chemotherapy, and possibly Poly (ADP-ribose) polymerase (PARP) inhibitor maintenance.

4. Head and Neck-Like CUP (Squamous-Cell Carcinoma in Cervical Lymph Nodes): Managed by attempting to identify the primary through extensive imaging and biopsies, includ-

ing panendoscopy and tonsillectomy. Treatment typically involves surgery and/or radiotherapy, potentially combined with chemotherapy, depending on the disease volume.

5. Prostate-Like CUP (Men with Blastic Bone Metastases and/or Prostate-specific antigen (PSA) Expression): Treatments are aligned with those for metastatic prostate cancer, focusing on therapeutic approaches that target PSA and bone metastases characteristics.

6. Colon-Like CUP (Adenocarcinoma with GI Histological Profile): Identified by specific immunohistochemical markers (CK7-negative, CK20-positive, CDX2-positive). Treatment typically involves colorectal cancer chemotherapy regimens, such as folinic acid, oxaliplatin and 5-fluorouracil (FOLFOX) or folinic acid, fluorouracil, and irinotecan hydrochloride (FOLFIRI), adjusted based on microsatellite stability.

7. Renal-Like CUP (Carcinoma with Renal-Cell Histology): Even without detectable renal lesions, if histological and immunohistochemical profiles match renal-cell carcinoma, renal-specific treatments, including tyrosine kinase inhibitors and immune checkpoint inhibitors, may be appropriate.

These subtypes are not universally recognized in all guidelines, particularly those historically associated with extragonadal germ cell tumors or poorly differentiated carcinomas with midline distribution. The classification of CUP into favorable subtypes is pivotal as it allows for more targeted and potentially effective treatments, significantly impacting patient outcomes [41].

17.2 Management of unfavorable carcinoma of unknown primary (CUP)

Unfavorable CUP, constituting approximately 80% of all CUP cases, typically shows a poor prognosis despite treatment. The standard care involves platinum-based chemotherapy (ChT) regimens, as randomized trials have not conclusively shown these to be superior to supportive care alone. The primary goals for these patients are modest survival benefit and quality of life preservation [41].

Chemotherapy Protocols: Widely accepted platinum-based doublets include combinations with taxanes or gemcitabine. Comparative studies suggest that cisplatin-gemcitabine has a better efficacy-toxicity ratio than cisplatin-irinotecan. Other regimens like carboplatin-paclitaxel have shown meaningful activity but without statistically significant superiority over alternatives in randomized trials.

Molecular Targeted Therapy and Immunotherapy: Molecular profiling using panel Next generation sequencing (NGS) identifies diverse actionable mutations, with Tumor protein 53 (TP53) being the most common. Treatments are advised based on molecular targets, such as NTRK inhibitors (larotrectinib, entrectinib) for NTRK fusion-positive cancers, and targeted therapies for known genetic markers like Raf Murine Sarcoma Viral Oncogene Homolog B (BRAF) V600E and Rearranged during Transfection (RET). ICIs are considered in second-line treatments for patients with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR), as pembrolizumab has FDA approval for these conditions. For high tumor mutational burden (TMB-H) or programmed death ligand 1 (PD-L1)-high CUPs, ICIs are also recommended based on their efficacy in other cancer types.

Surgery: Cytoreductive surgery is considered for isolated peritoneal carcinomatosis, especially in cases suggestive of ovarian or colon-like CUP, without Hyperthermic intraperitoneal chemotherapy (HIPEC) due to the lack of supportive data. Given the challenging nature of unfavorable CUP, enrollment in clinical trials is encouraged to explore new therapeutic options and improve patient outcomes [41].

The treatment of STOs lacks uniform guidelines due to their heterogeneous nature and rarity, rendering prospective randomized clinical trials impractical. Management should prioritize thorough diagnostics to determine the primary tumor site, its biological features, and disease extent. Treatment for identified primary tumors should align with histological type and stage. Key questions in STO management include the role of cytoreductive surgery and adjuvant chemotherapy post-metastasectomy.

18. Role of cytoreductive surgery in STO

While the role of cytoreductive surgery in STOs lacks extensive prospective trial data, retrospective studies suggest a potential survival benefit in select patient sub-groups. The primary tumor site appears to be a crucial factor, with ovarian metastases from colorectal cancer (CRC) showing the most consistent survival benefits [42]. Patients with pelvic-confined disease generally fare better than those with extra-pelvic metastases [43]. Optimal cytoreduction in metastatic CRC confined to the ovaries may even result in higher 5-year survival rates compared to optimally resected isolated pulmonary or liver metastases [44]. The role of cytoreductive surgery in gastric cancer-associated secondary tumors of unknown primary origin (STOs) is uncertain. While some studies suggest a survival benefit, others report contradictory results [45, 46]. STOs originating from gastric cancer typically have a poorer prognosis and are often associated with lower performance status and other complications, making surgery challenging. Metachronous STOs may offer better feasibility for complete resection and improved survival compared to synchronous cases. Cytoreductive surgery may be considered in metachronous STOs confined to the ovaries in patients with good performance status. For synchronous metastases, the benefits are less clear, but combining surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) could potentially offer a survival advantage with manageable risks [54]. Decisions regarding cytoreductive surgery should be tailored to individual patients, considering all relevant factors.

The role of metastasectomy in secondary tumors of breast cancer origin remains unclear, with no significant survival benefit observed in ovarian metastases. While debulking surgery for abdominal/pelvic masses shows a trend toward improved survival when complete resection is achieved, it lacks statistical significance. Evidence does not support routine metastasectomy in breast-origin STOs. In line with primary ovarian cancer, the extent of cytoreductive surgery significantly impacts prognosis, with superior survival seen in patients with minimal residual disease, particularly in primary colorectal cancer. Aggressive debulking surgery is advocated, with bilateral oophorectomy recommended even for unilateral metas-

tases to prevent future resections [54]. Combined ovarian and extraovarian metastases indicate poorer prognosis and reduced feasibility of optimal cytoreduction, although select patients with extensive colorectal metastases may benefit. Patients with good performance status, ovarian-limited metastases, colorectal primary tumors, and potential for minimal residual disease are candidates for cytoreductive surgery. However, the decision should be individualized, especially for STOs of gastric origin, considering factors like disease extent and patient suitability. Study limitations, including selection bias and retrospective design, underscore the need for prospective research to validate these findings.

19. Adjuvant chemotherapy

Adjuvant chemotherapy following cytoreductive surgery in STOs has shown potential to prolong survival. Platinum-based regimens offer benefits in gastric cancer, although the choice between intravenous and intraperitoneal administration lacks significant impact on overall survival (OS). Combined hyperthermic intraperitoneal chemotherapy (HIPEC) and systemic chemotherapy demonstrate superior OS compared to systemic chemotherapy alone [55]. Limited data exists regarding adjuvant chemotherapy following metastasectomy in colorectal-origin STOs, but experiences with lung or liver metastases support its use [56]. Regimens containing 5-fluorouracil (5FU)/leucovorin (LV) show improved progression-free survival (PFS), with triplets containing oxaliplatin yielding better outcomes than 5FU/LV alone [57–60]. However, triplets with irinotecan do not offer additional benefits over 5FU/LV in the adjuvant setting post-resection of primary colorectal cancer. Although adjuvant chemotherapy post-metastasectomy appears beneficial, its use remains contentious due to the absence of randomized prospective trials.

20. Conclusion

Metastasis to the ovaries from diverse primary tumor sites is common, indicating multiple potential metastatic pathways, such as lymphatic, bloodborne and transcoelomic dissemination. Different primary tumors likely utilize distinct preferential metastatic routes. CUP management should prioritize distinguishing favorable subtypes, which show better responses to site-specific therapies and have improved prognoses. For unfavorable CUP, treatment aims at preserving quality of life, with chemotherapy and emerging molecular therapies providing modest benefits. Liquid biopsies and advanced molecular profiling hold potential for enhancing personalized care. Continued research and flexible treatment protocols are crucial for optimizing patient outcomes in this complex and heterogeneous group of cancers. Managing CUP with secondary ovarian metastases requires a tailored approach. While gene expression profiling aids in identifying the primary tumor site, cytoreductive surgery may benefit select patients with favorable characteristics. Adjuvant chemotherapy shows promise but lacks robust evidence. Further research, including prospective trials, is needed to refine treatment strategies for this complex condition.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

SG, SA and DSK—designed the research study. SG and SA—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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