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CUP Syndrome – Cancer of Unknown Primary

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

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CUP Syndrome – Cancer of Unknown Primary

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1 Summary

CUP syndrome (= cancer of unknown primary, cancer with an unknown primary tumor) represents a very heterogeneous clinical setting. It is defined as a histologically or cytologically confirmed malignancy with an unknown primary tumor after completion of standardized primary diagnostics (basic program plus extended individual diagnostics plus clinical pathways, see chapter 4.2).

The treatment of CUP syndrome is based on defined subtypes characterized by location, histology, immunohistology, molecular tumor profile, as well as comorbidity, gender, and risk factors (primarily smoking). Curative therapy may be possible for subtypes with a favorable prognosis.

This guideline has been updated in line with the 2022 ESMO guideline [20]. However, due to relevant new developments, it goes significantly beyond this guideline.

2 Basics

2.1 Definition and basic information

The term CUP syndrome (= cancer of unknown primary) refers to a diverse oncological clinical setting. It is defined as a

- histologically or cytologically confirmed malignant tumor
- tumor of unknown/uncertain origin after completion of standardized basic diagnostics and extended diagnostics following clinical and histopathological diagnostics

2.2 Epidemiology

The incidence has been declining in Western industrialized countries since the turn of the century and is now 4–15/100,000 inhabitants/year, corresponding to 1–3% of all malignancies [1]. However, the number of patients with histologically/cytologically confirmed disease in registry databases is small, at only 20–60%; in addition, diagnostic measures are incomplete in some cases. In cancer registry data, it is difficult to distinguish between definitive and provisional CUP diagnoses and inaccurately documented cases.

In the current German nationwide cancer registry data (2021-2023), approximately 3,760 new cases of cancer with unknown primary tumors reported annually by clinics or pathology departments are confirmed by the histology of a metastasis (confirmed CUP). In addition, there are approximately 1,500 cases coded with ICD-10 C80.0 each year in which the diagnosis was

solely confirmed clinically or by a death certificate (DCO cases), or is not known in the registry; such cases can be referred to as possible CUP. Overall, a total of 3,720-5,260 cases per year can currently be assumed, which corresponds to around 1% of all new cancer cases. The median age at onset for confirmed CUP is 71 years for men and 73 years for women, with men developing the disease slightly more often than women (m:w approx. 1.15:1). In 46% of confirmed CUP cases, adenocarcinoma is reported, in 17% squamous cell carcinoma, and in 14% a neuroendocrine tumor or neuroendocrine carcinoma. Approximately three-quarters of affected patients die within the first year after diagnosis, and after 5 years, around 10% remain alive. The prognosis for CUP with squamous cell carcinoma is significantly better, with more than 30% still alive after 5 years. Overall, mortality is high in relation to incidence; the causes-of-death statistics show 5,286 deaths (2% of all cancer deaths) for C80.0 in Germany in 2023, although a certain degree of uncertainty can be assumed here as well.

2.3 Pathogenesis

The etiology and pathogenesis of CUP syndrome are not yet fully understood scientifically. The principal question of whether CUP represent a heterogeneous group of different metastatic tumor entities that only share the lack of a proven primary tumor, or whether they represent a separate entity with characteristic biological features, remains open [78, 81]. The fact that most treatment studies targeting the presumed primary tumor were negative [71, 72] and that a tumor stem cell model was able to reproduce the CUP phenotype with early and disseminated metastasis and growth factor-independent proliferation in experiments [5] supports the idea that CUP syndrome is a distinct biological entity.

Presumably, the pro-metastatic signature, the microenvironment, or the selection pressure of the immune system give metastases a growth advantage over the primary tumor [81]. There is also a debate as to whether a malignancy can manifest primarily as a metastatic disease ("primary metastatic cancer") even without an existing primary tumor [76].

2.4 Risk factors

A recent meta-analysis summarizes the risk factors for CUP [85]: smoking undoubtedly increases the incidence, with a hazard ratio between 1.7 and 3.7. Several, but not all, studies show an increased risk in individuals with diabetes mellitus and those with regular alcohol consumption. There is inconclusive evidence for obesity, dietary habits (meat consumption), family history, and socioeconomic status.

2.5 Prevention and early detection

Due to the nature of the disease with an unknown primary tumor, there are no specific measures for prevention or early detection, apart from the avoidance of the above-mentioned nutritional habits..

3 Clinical picture

3.1 Symptoms

CUP syndrome is a multifaceted clinical setting. Multiple manifestations are possible and must be distinguished. Clearly discernable subgroups can be identified that require specific therapy.

4 Diagnosis

4.1 Diagnostic criteria (histology, primary tumors, and classification)

4.1.1 Histology, immunohistochemistry, molecular genetics, immunogenicity

The proportional distribution of histological subtypes of CUP syndrome is summarized in Table 1.

Table 1: Histological subtypes in CUP syndrome [3]

Histology	%
Adenocarcinoma (well to moderately differentiated)	40
Undifferentiated carcinoma	15
Squamous cell carcinoma	15
Small cell/neuroendocrine carcinoma	3
Other	1-3

Histomorphology and characterization using immunohistological markers and molecular methods are of paramount importance. The clinical and radiological presentation should be discussed with the pathologist in order to obtain the best possible information in a material- and time-saving manner. However, precise classification of the primary tumor is not always possible due to overlapping and aberrant expression of structural proteins in the tumor tissue; in almost all cases, however, a therapeutically relevant differential diagnosis of possible primary tumors can be made.

Correct lineage assignment is essential for therapy: carcinoma vs. non-carcinoma (e.g., hematological tumors, sarcomas, melanomas, etc.). In the case of carcinomas, tissue differentiation (e.g., adenocarcinoma, squamous cell carcinoma, undifferentiated carcinoma, neuroendocrine carcinoma) is also important. The cytokeratin pattern can provide important information in this regard [9, 10, 11, 28]. Table 2 provides an overview of lineage assignment and tumor type as well as the most important immunohistochemical markers for further specification. Extensive details can be found in the current ESMO guidelines [20]. Markers for the detection of immune checkpoint blockade-sensitive tumors are part of the diagnostic process (e.g., PD1/PDL1, MMR proteins) [12, 13, 14]. Molecular signatures [e.g., microsatellite status, tumor mutational burden (TMB), smoking signature, etc.] are already providing new insights into tumor biology and hold out the prospect of more in-depth specification in the near future. Chromosomal instability together with homologous recombination deficiency (HRD) could become potentially important new biomarkers for CUP in the future [80, 88]. Broad and comprehensive molecular next-generation sequencing (NGS) (see Onkopedia guideline on precision oncology) has been included as a recommendation in the ESMO guidelines and should be performed if available and relevant for treatment decisions [20].

Table 2: Selection of important immunohistochemical markers

Line	Screening marker	Tumor type	Expression pattern	Organ assignment according to additional markers
Epithelial differentiation	Broad spectrum keratin (e.g., Pan CK AE1/AE3, OSCAR)	Carcinoma	CK 7+, CK 20-	Lung (TTF1, SMARCA4, synaptophysin) Breast (GATA3, Sox10, TRPS1, ER, PR, Her2) Upper GI tract/pancreaticobiliary (CDX2, CK19, BAP1, ARID1a, CK19) Ovarian, endometrial (Pax8, WT1, ER, PR) Thyroid (TTF1, thyroglobulin, Pax) Salivary gland (Sox10, S100, GATA3, AR, Her2) etc.
			CK 7-, CK 20+	Colorectal (CDX2, SATB2) Merkel cell carcinoma (synaptophysin, MCPyV) Rare upper GI (CDX2) etc.
			CK 7+, CK 20+	Bladder (GATA3, p63) Upper GI tract/pancreaticobiliary (CDX2, CK19, BAP1, ARID1a, CK19) including
			CK 7, CK 20	Liver (arginase1, HepPar1), Kidney (Pax8, Pax2, CD10, AMACR, RCC) Prostate (NXK3.1, PSMA, PSA)
Hematolymphoid differentiation	CD45 (LCA)	Lymphomas, leukemias	CD3, CD20, CD79a, CD30, etc.	Hematopathology consultation
Neuroectodermal differentiation	Sox10, S100, CD271	Melanoma	Melan A, HMB45, tyrosinase	Melan A, HMB45, tyrosinase are lost during dedifferentiation
Mesothelial differentiation	Calretinin	Mesothelioma	WT1, D2-40, CK5/6, BAP1	Mesothelioma
Mesenchymal neoplasia	Pan CK AE1/AE3, Sox10, Desmin, SMA, CD34	Depending on screening	Adipocytic, myogenic, fibroblastic, myofibroblastic, vascular	Consultation with soft tissue and bone specialist
Neuroendocrine differentiation	Synaptophysin, INSM1	Morphology and Ki67		e.g., GI tract (CDX2) e.g., pancreas (ISLET1)
Germ cell tumor Differentiation	SALL4	Germ cell tumor		Seminomas (OCT3/4, CD117, D2-40) Embryonal carcinoma (OCT3/4, CD30) Yolk sac tumor (AFP, Glypican-3) Choriocarcinoma: (β-HCG, GATA3, inhibin)

Molecular characterization using tests to detect gene expression, DNA methylation, or microRNA patterns allows the identification of the possible primary tumor with 85-90% accuracy [15, 16, 17]. Randomized studies have not shown improved survival based on such classification [18, 71, 72]. The only positive study [86] links such classification with individually targeted therapy in a very heterogeneous group of patients, so that no improvement in prognosis can be inferred from the tumor-of-origin test alone. Overall, these tests cannot be recommended as standard practice.

The use of NGS panel tests or other large-scale sequencing platforms to create a molecular signature and examine tumor tissue for actionable targets, i.e., therapeutically relevant driver mutations, is internationally recommended for patients in whom a therapeutic consequence is possible or expected and is part of standard diagnostics for all patients in good general condition (see Onkopedia guideline on precision oncology) [19, 20]. Genetic alterations are found in more than 85% of cases, and molecular tumor boards can provide well-founded treatment recommendations based on this diagnosis for approximately one-third of patients. The data published to date from the CUPISCO study (phase II study with 636 patients included) show that the use of targeted therapy in the first line, based on a broad molecular genetic analysis performed at initial diagnosis, enables longer progression-free survival than standard platinum-based chemotherapy in patients with previously untreated, unfavorable CUP [21].

Microsatellite instability or deficiency of mismatch repair enzymes and TMB-high (≥10 mutations/megabase) in CUP are well established markers for possible sensitivity to immune checkpoint blockade. PD-L1 expression appears to play a minor role in comparison, however, no cut-off for relevant PD-L1 expression has been defined based on the currently available data [12, 22, 23].

Various artificial-intelligence-supported diagnostic tools that use image and molecular data can predict the origin of the primary tumor in around 60-80% of cases in line with the clinical and histological picture [87;95]. This is by no means sufficient for current routine practice. It remains to be seen whether such tools can be used in clinical practice in the future.

4.1.2 Primary tumors

The reliable identification of the primary tumor during the course of the disease remains a rare exception (<10%). Historical autopsy series are no longer helpful in identifying common possible primary tumors. The best assignment to a working diagnosis is provided by the characterization of the tumor material (see chapter 4.1.1.). For treatment, it may be relevant to exclude or detect a late recurrence of a previous tumor disease as reliably as possible – this is particularly important in the case of breast and kidney carcinomas. Comparative NGS of previous malignancies and suspected CUP syndrome can help to avoid misinterpreting recurrences of previous malignancies as CUP [78].

CUP syndromes with cervical lymph node metastases in the upper and middle third of the neck represent a special form. Here, diagnosis of the primary tumor is more frequently successful in HPV-positive tumors [24], see Table 3.

Table 3: Primary tumors in cervical lymph node metastases

Location of the primary tumor	%
Human papillomavirus (HPV)-positive: Oropharynx (tonsils or base of tongue)	80 to >90
HPV-negative: Head and neck tumors	60
Lungs	15
Thyroid	5
All others combined, including Epstein-Barr virus (EBV)-associated nasopharyngeal carcinomas	<5

4.1.3 Distribution

The distribution pattern of metastasis in patients with CUP syndrome is shown in Table 4.

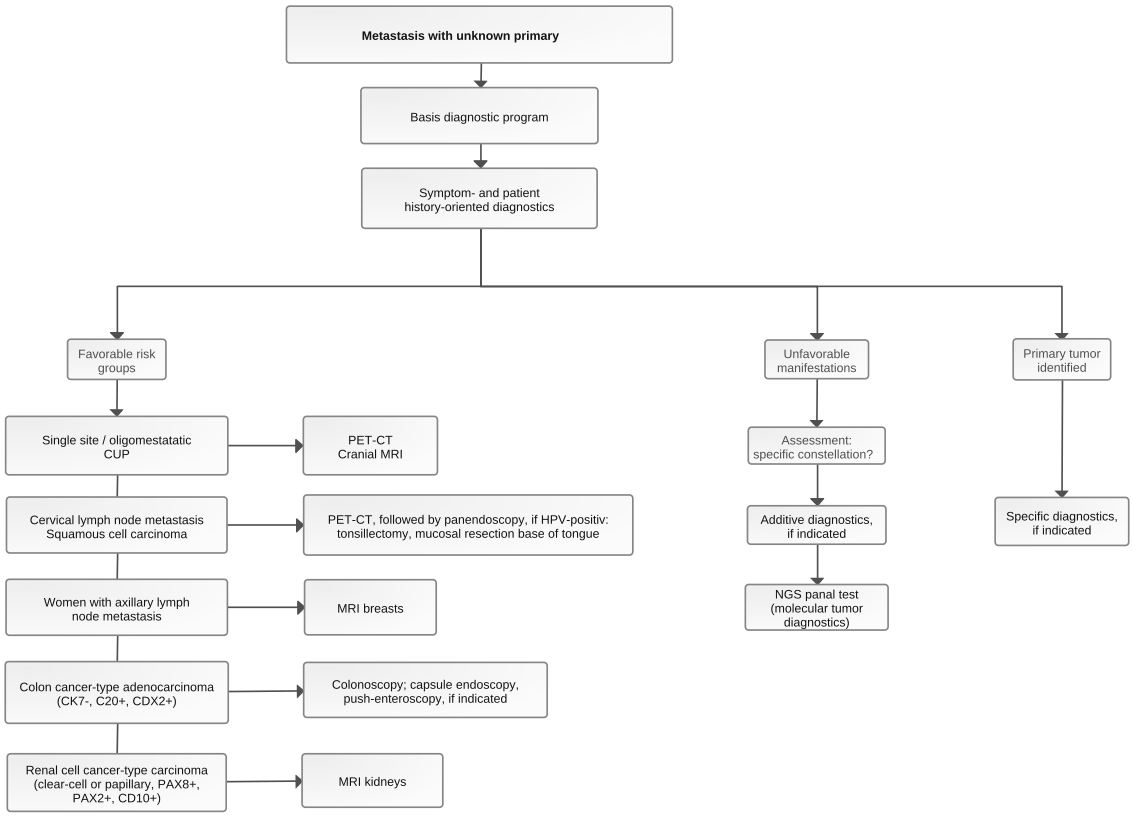
Table 4: Pattern of involvement in CUP [3]

Pattern of involvement	%
Primarily localized (solitary/oligometastasis or involvement of only one lymph node region)	15
Primarily disseminated	75
Lymph nodes	40
Liver	30
Skeleton	25-35
Lungs	30
Pleura	5
Peritoneum	5
CNS	5
Adrenal glands	~ 6
Skin	~ 4

4.2 Diagnostics

Diagnostic procedures are prognosis- and therapy-oriented. This includes staging and documentation of defined entities with a more favorable prognosis (see Table 7 and Figure 1), establishing a working diagnosis, and identifying the primary tumor.

Figure 1: Diagnostic algorithm for CUP



Histological (not just cytological) diagnostics are essential. Histology, immunohistology, and molecular biology provide information of crucial therapeutic relevance by narrowing down the lineage assignment and enabling a more precise differential diagnosis of possible primary

tumors, as well as better therapy planning. Material for histology must therefore be obtained **early on** as part of the primary diagnostics [94].

4.2.1 Initial diagnosis

4.2.1.1 Basic program

The diagnostic process begins with a basic diagnostic program, see Table 5.

Table 5: Basic diagnostic program for CUP syndrome [10, 19, 20]

Diagnostic procedures	Comments
Medical history	
Physical examination	In men, including testicular palpation In women, including examination of the breasts
Tissue sample	Histology! Sufficient material for immunohistology and molecular analysis
CT thorax CT abdomen with true pelvis	Better: PET-CT at an early stage
PET-CT	For head and neck CUP For solitary metastasis or oligometastasis with the prospect of local ablative treatment (tumor board decision required)
Gastrointestinal endoscopy	For suspected primary gastrointestinal cancer
Gynecological examination Mammography and breast ultrasound Vaginal sonography if indicated	For women
Laboratory tests including tumor markers	Laboratory values including white blood count and differential, serum lactate dehydrogenase (LDH), albumin, alkaline phosphatase Tumor marker alpha fetoprotein (AFP) For men, additionally: prostate-specific antigen (PSA), human chorionic gonadotropin (β-hCG)

These basic diagnostic procedures allow for a quick search for common primary tumors, preliminary staging, and - if not clinically obvious - determination of the optimal location for obtaining a tissue sample. It is not advisable to examine asymptomatic regions beyond the basic program. Repeated diagnostics during the course of the disease do not improve the identification of a primary tumor. Only rarely does the primary become symptomatic during the course of the disease and is then detectable (<10%).

A PET-CT scan **at the beginning** of the diagnostic process is desirable, but, apart from cervical lymph node metastases with an unknown primary tumor, is not accepted for reimbursement by the regulatory agency (“G-BA”) in Germany and is currently not recommended by international guidelines [10, 19, 20]. PET-CT enables rapid staging, often eliminating the need for additional cross-sectional imaging with CT and/or MRI, and facilitates more targeted further diagnostics. A recent meta-analysis including 32 studies shows a 54% detection rate for the primary tumor, which is highly dependent on the organs affected. The highest probability is for CNS metastases (pooled detection rate 74%), and the lowest for peritoneal carcinomatosis and lymph node metastases (37-38%) [92]. Another meta-analysis of 20 studies concludes that PET-CT only finds therapy-relevant findings in one-third of patients [25]. The primary tumor is identified in 18-28% of cases, and previously unknown metastases are found in 10-19% of cases. As mentioned, there is currently no uniform recommendation for PET-CT in international guidelines and consensus recommendations [19].

The ESMO guideline recommends the use of PET-CT in all cases of cervical lymph node metastasis (**before** panendoscopy) as well as in cases of solitary metastasis or oligometastatic dis-

ease if there is the prospect of locally ablative therapy with curative-intent treatment including surgery and/or radio(chemo)therapy [20]. This is to rule out possible further metastases before local treatment. Before ordering a PET-CT, it is advisable in Germany to obtain an explanatory tumor board decision and, if necessary, submit a cost coverage application to the health insurance company, which should be done with reference to the ESMO guideline and the present Onkopedia guideline.

4.2.1.2 Further diagnostics: Stage I

Additional examinations are performed specifically based on the patient's medical history, findings, and working diagnosis. Above all, it is important to look for therapeutically relevant, prognostically favorable groups, see Table 7. Further diagnostic procedures in stage I are based on the patient's medical history, the location of tumor manifestations, and the histology. Recommendations are summarized in Table 6.

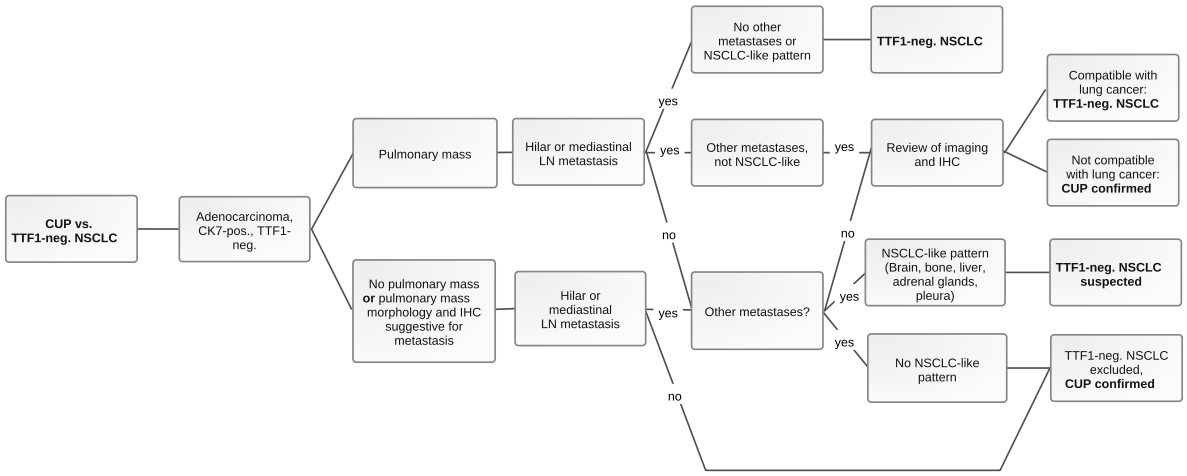
Table 6: Further diagnostics for CUP syndrome

Manifestation	Comments
Locally confined (solitary metastasis or oligometastatic disease)	• Intensive locoregional exploration • PET-CT [10, 20] • Cerebral MRI
Involvement of cervical lymph nodes	• PET-CT **before** panendoscopy [20, 26] • Panendoscopy, for HPV-positive tumors with base of tongue, mucosal resection and ipsilateral or bilateral tonsillectomy [26] • Endoscopic narrow-band imaging where possible
Axillary lymph node involvement in women	• Bone scintigraphy • MRI of the breasts [19, 20, 90]
Neuroendocrine tumors (grade I-III)	• 68-gallium somatostatin receptor PET-CT [57] • Exploratory laparoscopy/laparotomy if R0 resection of the metastasis(es) appears feasible [27]
Histology and immunohistochemistry indicating upper gastrointestinal or pancreaticobiliary adenocarcinoma	• Gastroscopy, endoscopic ultrasound (including distal esophagus and stomach wall), MRI of pancreas/upper abdomen with MRCP
Colon-like adenocarcinoma (immunohistochemically CK7-, CK20+, CDX2+)	• Colonoscopy, capsule endoscopy/push enteroscopy if indicated
All others	• Targeted examinations based on medical history, findings, histology, and staging

4.2.1.3 Further diagnostics: Stage II

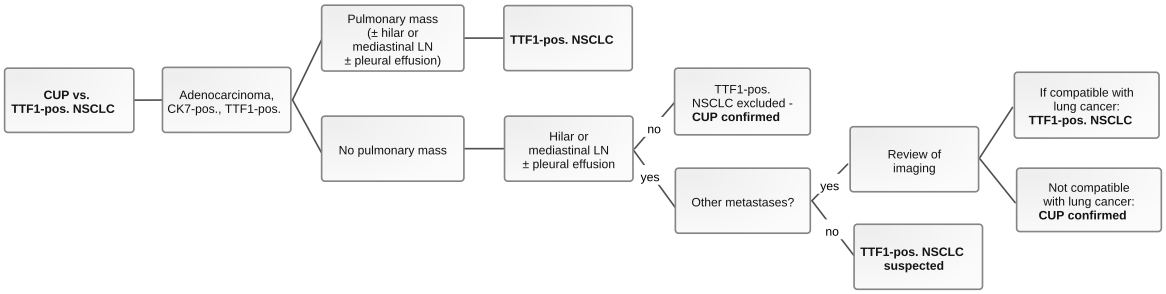
This diagnosis is followed by a second step based on tumor presentation and histology, including immunohistochemistry. The following flow charts (Figures 1-7) are partial results of the CUPISCO study [21], the first large international prospective study with central pathology review and central expert review of each individual patient prior to inclusion in the study [28]. Based on the criteria of immunohistochemistry, local lymph node stations, and distant metastases, these algorithms provide guidance on whether a malignant mass should be interpreted as a primary tumor or a metastasis, thereby facilitating the differential diagnosis between CUP syndrome and defined tumor entities. The result is a much clearer definition of "true" CUP patients. The algorithms have already been incorporated into the current ESMO guidelines [20]. They are of significant practical importance.

Figure 2: CUP vs. TTF1-negative NSCLC



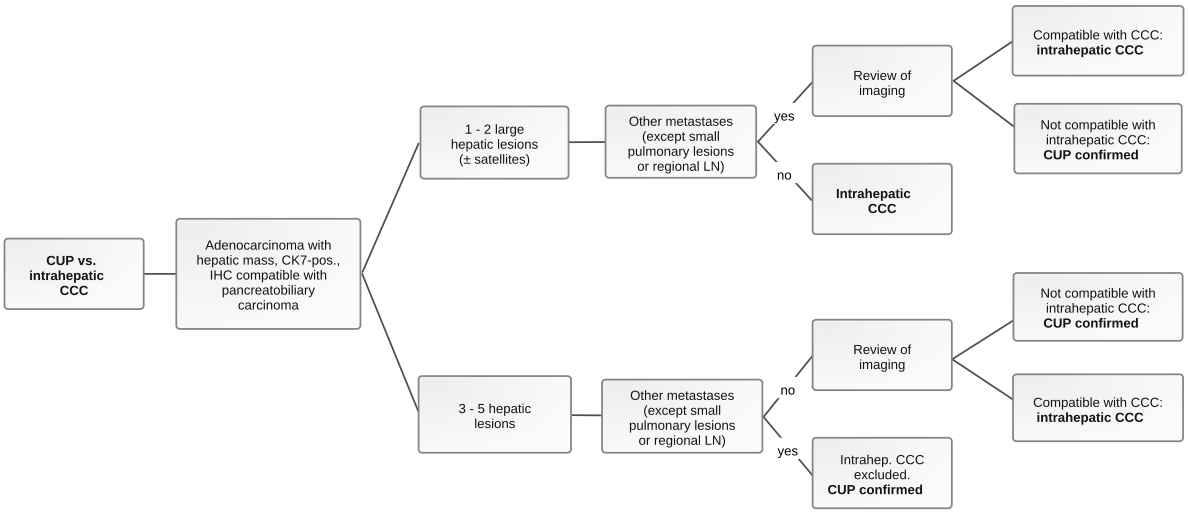
Legend:
CK – cytokeratin, IHC – immunohistochemistry, LK – lymph node, NSCLC – non-small cell lung cancer, TTF – thyroid transcription factor
NSCLC pattern: metastases in the brain, bone, liver, adrenal gland, pleura

Figure 3: CUP vs. TTF1-positive NSCLC



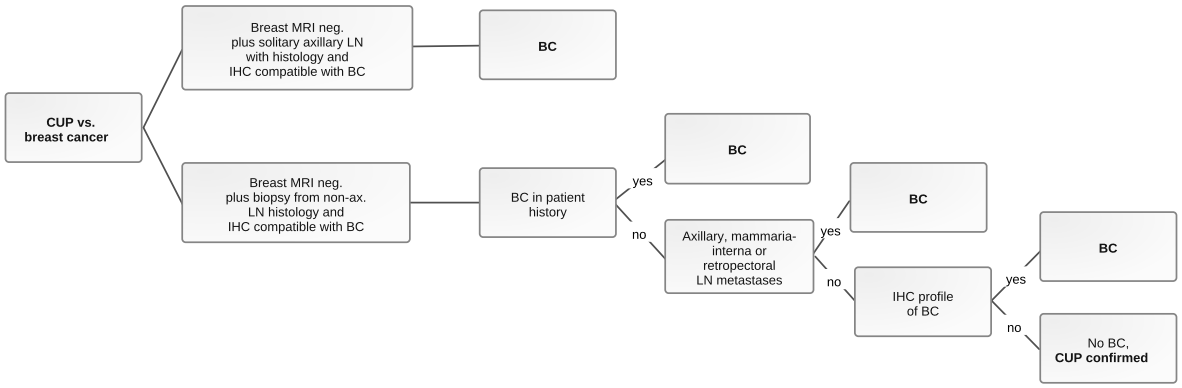
Legend:
CK – cytokeratin, LN – lymph node, NSCLC – non-small cell lung cancer, TTF – thyroid transcription factor

Figure 4: CUP vs. intrahepatic cholangiocellular carcinoma



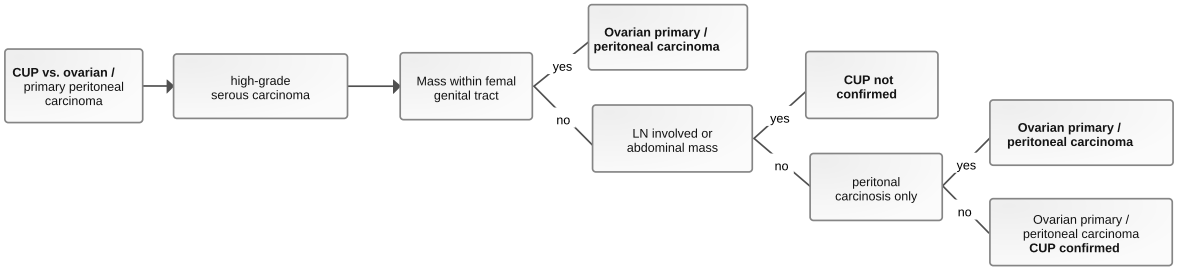
Legend:
CCC – cholangiocellular carcinoma, CK – cytokeratin, IHC – immunohistochemistry, LN – lymph node

Figure 5: CUP vs. breast cancer



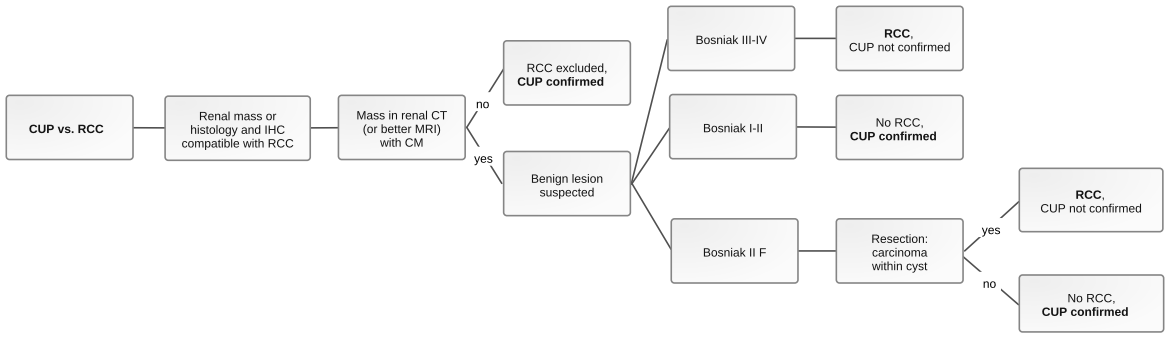
Legend:
ax – axillary, IHC – immunohistochemistry, LN – lymph node, MRI – magnetic resonance imaging, BC – breast cancer

Figure 6: CUP vs. ovarian/primary peritoneal carcinoma



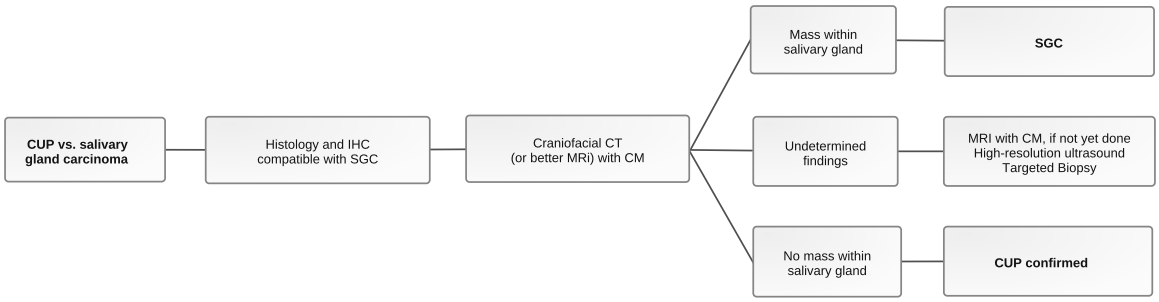
Legend:
LN – lymph node

Figure 7: CUP vs. RCC (renal cell carcinoma)



Legend:
CT – computed tomography, IHC – immunohistochemistry, CM – contrast medium, MRI – magnetic resonance imaging, RCC – renal cell carcinoma

Figure 8: CUP vs. salivary gland carcinoma



Legend:
SGC – salivary gland carcinoma, CT – computed tomography, IHC – immunohistochemistry, CM – contrast medium, MRI – magnetic resonance imaging

4.2.1.4 Psycho-oncological considerations in diagnosis

For the vast majority of patients affected, as well as for many healthcare professionals, a diagnosis of CUP syndrome causes great uncertainty. It seems to them as if the true disease is not being recognized, and as a result, the treatment may be less effective and their prognosis less favorable than if the primary tumor were known. Many patients therefore require special mental support [83, 93]. It is therefore particularly important for those affected to understand that CUP is not an unfortunate case of undiagnosed disease, but rather a distinct malignancy with diagnostic and therapeutic algorithms backed-up by national and international guidelines. Support from self-help groups is particularly valuable in this regard (in German-speaking countries: www.CUP-Forum.de).

4.4 Prognostic factors and survival

In published studies, the median survival time for CUP syndrome is 6-10 months, the 1-year survival rate is 25-40%, and the 5-year survival rate is 5-15% [3]. Registry data show a median survival of approximately 3 months with a 1-year survival rate of 20% [20].

Prognostic factors include general condition, markers of systemic inflammation (C-reactive protein, absolute neutrophil count) [84], serum albumin level, serum lactate dehydrogenase (LDH), comorbidity, number of metastases, and the presence of liver metastases. However, these factors are not predictive, and therefore do not allow for an individual assessment of survival [29].

On the other hand, it is essential to distinguish between the so-called favorable subgroups and the larger proportion of patients with an unfavorable prognosis ("unfavorable subset"). The subgroups with a favorable prognosis are summarized in Table 7. Some tumor manifestations that were attributed to CUP for decades are no longer included because they can be identified with certainty and require specific therapy, see Table 8.

Table 7: Prognostically favorable subgroups in CUP syndrome

Manifestation	Comments
Local (resectable) disease (single-site or oligometastatic CUP)	Solitary metastasis, surgically resectable or oligometastasis amenable to curative radiotherapy, involvement of only one lymph node region
Cervical lymph node metastasis of squamous cell carcinoma or undifferentiated carcinoma (head-and-neck-like CUP)	Approximately 3-5% of all squamous cell and undifferentiated head and neck tumors
Axillary lymph node metastases in women (breast-like CUP)	See Figure 5 See Onkopedia guideline on breast cancer in women (German Version only)
Peritoneal carcinomatosis due to high-grade serous adenocarcinoma in women (ovary-like CUP)	Strictly, these malignancies are no longer classified as CUP syndrome, but rather as primary peritoneal carcinoma Distinguishing them from other forms of peritoneal carcinomatosis can be challenging, so particular accuracy is essential
Colon-typical adenocarcinoma (colon-like CUP)	Immunohistologically CK7-, CK20+, CDX2+
Renal cell carcinoma-typical histology and immunohistochemistry (renal-like CUP)	Histology (clear cell/papillary) **and** immunohistochemistry (positive for PAX8, PAX2, racemase, and CD10), see Onkopedia guideline on renal cell carcinoma

Table 8: Subgroups that are no longer classified as CUP syndrome

Manifestation	Comments
Specific histology	Not classified as CUP e.g., melanoma, sarcoma, Merkel cell carcinoma, hematological neoplasia, etc.
Extragonadal germ cell tumor	No longer counted as CUP syndrome. Can be reliably differentiated by IHC. Discussion with pathologists! Affects men, < 50 years of age, poorly differentiated carcinoma, retroperitoneal/mediastinal/pulmonary, rapid progression, see Onkopedia guideline on male germ cell tumors
Neuroendocrine tumors	No longer classified as CUP syndrome. NET grades I, II, and III: NET-specific therapy according to NET guideline; NEC: see Onkopedia guideline Small cell lung carcinoma; large cell neuroendocrine lung carcinoma
Osteoblastic skeletal metastases with elevated PSA (prostate-like CUP)	No longer classified as CUP syndrome. Can be reliably differentiated by IHC (PSA, PSMA, NKX3.1)

5 Therapy

5.1 Treatment structure

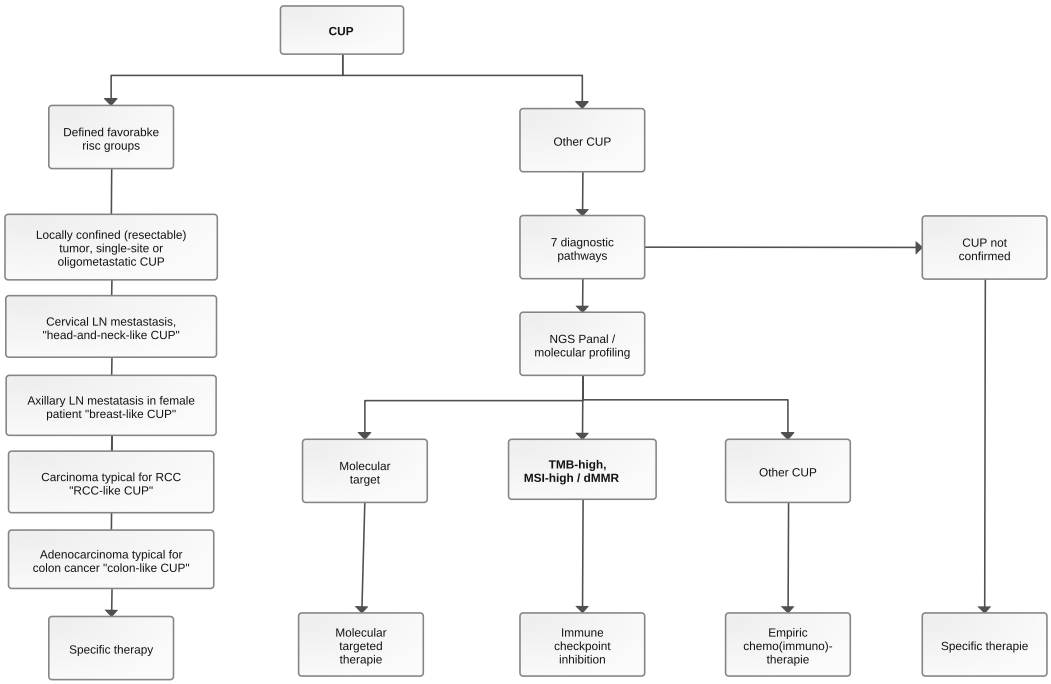
The treatment strategy depends on

- the general condition and treatment preferences of the patient
- the proof of a defined subgroup, see Table 7
- the distribution pattern
- the histology/immunohistology
- the immunogenicity of the tumor
- molecular tumor diagnostics, including testing for driver mutations
- the provisional diagnosis.

Patients with CUP syndrome of a defined subgroup receive an adjusted therapy (see below). However, the majority of patients (approx. 70-85%) do not fall into this category and are classified as "unfavorable manifestations."

The treatment structure is summarized in Figure 9.

Figure 9: Treatment structure for CUP syndrome



Legend:
LN – lymph node, RCC – renal cell carcinoma, NGS – next-generation sequencing, TMB – Tumor Mutational Burden, MSI – Microsatellite Instability, dMMR – deficient MisMatch Repair

5.1.1 Locally confined stages

In cases of solitary metastasis, resectable oligometastasis (e.g., in the liver), or involvement of only one lymph node region, local radical therapy is performed with curative intent [3, 20]. If surgery is not possible in cases of solitary metastasis or oligometastasis, radio(chemo)therapy should be considered.

5.1.1.1 Cervical lymph node metastases, "head & neck-like CUP"

5.1.1.1.1 Levels I, II, III, V, VI (not level IV = supraclavicular)

Frequency and primary tumor

- Approximately 3-5% of all head and neck tumors, 70-90% male patients
- 50% squamous cell carcinoma, 35% undifferentiated carcinoma, immunohistologically almost always classified as squamous cell carcinoma (CK 5/6, p40, p63), rarely lymphoepithelial EBV-associated carcinoma, rarely adenocarcinoma, etc.
- Locoregional primary tumors in 70–80% (head and neck area, occasionally thyroid), approx. 15–25% lung carcinomas
- Tumors with HPV DNA detection or p16 expression originate predominantly from the oropharynx (especially tonsils and base of tongue); the prognosis is better than for HPV-negative tumors, and radiotherapy can be limited to a smaller field (oropharynx). The oropharynx must be explored very carefully; unilateral or bilateral tonsillectomy and, if necessary, mucosectomy of the base of the tongue is advisable [30].
- 5-year survival rate for N1 involvement 61%, N2 involvement 51%, N3 involvement 26%; extracapsular spread (ECE+) 57%, ECE- 82% [26, 31, 32, 33].
- Note: EBV-associated lymphoepithelial carcinomas: rare, primary site in the nasopharynx

Therapy [26, 30, 32, 34, 82]

- For N1 stages without additional risk factors (unilateral): functional neck dissection (FND) with or without subsequent ipsilateral postoperative radiation *or* primary definitive radiotherapy
- For N2 stages without additional risk factors: functional neck dissection (FND) with subsequent (unilateral or bilateral) postoperative radiotherapy *or* primary definitive radiotherapy
- For N3 stages (LK > 6 cm) or additional risk factors (involvement of 2 or more lymph nodes, extranodal spread (ECE+), R1 resection, or safety margin < 5 mm): unilateral or bilateral FND if indicated; combined postoperative bilateral chemoradiotherapy. Alternatively, neoadjuvant radiochemotherapy prior to FND may be useful
- For adenocarcinoma: FND with postoperative radiotherapy, histology-adjusted further therapy if indicated. Cure is rare, but the 2-year survival rate is approximately 50%.

Table 9 gives an overview of the procedure for CUP in the head and neck region after neck dissection; see Onkopedia guideline on head and neck squamous cell carcinomas.

Table 9: Procedure after neck dissection for head and neck CUP [35, 36, 37, 38]

For non-HPV-associated carcinomas	
pN1	Follow-up care or unilateral RT
pN2a	Unilateral RT
pN2b	Unilateral or bilateral RT
pN2c, pN3	Bilateral RT
(Only) for ECE+ or R1	RT + platinum-based chemotherapy
For HPV-associated carcinomas	
pN1	For solitary LK: follow-up care or unilateral RT For 2-4 LK: unilateral RT
pN2	Bilateral RT
(Only) for ECE+ or R1	RT + platinum-based chemotherapy

Legend:
HPV – human papillomavirus, RT – radiotherapy, ECE – extracapsular extension (growth beyond the capsule)

5.1.1.1.2 Level IV (supraclavicular = deep caudojugular cervical lymph nodes)*

**See* [39]

Frequency and primary tumor

- Very rare as a localized form, usually disseminated disease
- Adenocarcinoma 35%, lung carcinoma as primary tumor 50%, breast 30%
- "Virchow's gland": gastric carcinoma, but also germ cell tumor and many others possible

Therapy

- Squamous cell carcinoma, undifferentiated carcinoma, and adenocarcinoma: lymph node dissection, followed by radiation

- Neuroendocrine (small cell) carcinoma: see below, solitary metastasis of a neuroendocrine (small cell) carcinoma

5.1.1.2 Axillary lymph node metastases in women – "breast-like CUP"

These represent a defined special case of CUP syndrome in women. For differentiation between "true" CUP and breast cancer, see Figure 5. As a rule, diagnosis and therapy are the same as for node-positive breast cancer.

Frequency and primary tumor

- In women in >75%, in men occasionally breast cancer as primary tumor (often BRCA-associated in men)
- Otherwise, lung carcinoma is common, occasionally amelanotic melanoma, malignant lymphoma, soft tissue sarcoma (immunohistology!)
- 5-year survival rate 50–88%

Treatment for adenocarcinoma or undifferentiated carcinoma [20, 40, 41, 90, 91]

- Lymph node excision, axillary dissection if indicated (level I + II)
- Mastectomy or quadrant resection is not indicated
- (Neo)adjuvant chemo(immuno)therapy as for node-positive breast cancer, see Onkopedia guideline on breast cancer in women (German Version only)
- Followed by radiotherapy of the ipsilateral breast as after breast-conserving therapy
- Followed by adjuvant systemic therapy as for node-positive breast cancer

Therapy for squamous cell carcinoma

- Axillary dissection
- Followed by radiotherapy including the infra- and supraclavicular lymph node regions

5.1.1.3 Regionally limited thoracic/mediastinal lymph nodes

Frequency and primary tumor

This manifestation is rare; the primary tumor is often identifiable (see Figures 2, 3, and 5). Primary tumors are often pulmonary, however, thymic carcinoma, breast cancer, or a primary mediastinal germ cell tumor should also be considered. In some cases, long-term survival after surgery or combined radiochemotherapy has been reported. Immunohistology often allows for a more precise assignment of the possible primary tumor. Driver mutations should always be explored.

Supplementary diagnostics

PET-CT and bronchoscopy, IBUS (intrabronchial ultrasound) or transesophageal ultrasound if indicated; see Onkopedia guideline on non-small cell lung cancer.

Therapy

- Primary radiochemotherapy as for NSCLC, surgical resection if indicated, including suspicious lung areas; subsequently, if PD-L1 positivity is ≥1%, immune checkpoint blockade as for NSCLC (note: it is advisable to apply for cost coverage in advance)

- If a significant driver mutation is detected: appropriate therapy, e.g., with tyrosine kinase inhibitors (TKI).

5.1.1.4 Solitary inguinal lymph nodes

Frequency and primary tumor

This manifestation is rare and is often attributable to a locoregional primary tumor (vulva, vagina, cervix, penis, urethra, urinary bladder, anus, skin of the lower extremities).

Additional diagnostics

Dermatological examination, gynecological examination, urological examination, proctoscopy, cystoscopy; histology/immunohistology (exploration for amelanotic melanoma or soft tissue sarcoma), HPV status in tumor tissue.

Therapy

- Surgical resection
- followed by radiotherapy including the iliac lymphatic drainage pathways, if indicated, as radiochemotherapy with fluoropyrimidine-based chemotherapy

5.1.1.5 Solitary brain metastasis

Frequency and primary tumor

Registry data show an extremely poor median survival of approximately 2 months for CNS metastases with unknown primary tumor [42]. However, this does not apply to solitary metastases, where the situation is much more favorable and there are patients with long-term survival. The primary tumor can be identified in 60–75% of cases. In most cases, it is lung cancer, less commonly gastric/AEG or breast cancer [92].

Supplementary diagnostics

Cerebral MRI, PET-CT; histological confirmation and immunohistochemistry are mandatory (approximately 13% of foci assessed as metastases prove to be primary brain tumors on histological examination) [92].

Therapy [42, 43, 44]

- Extirpation, if neurosurgically possible, followed by radiotherapy of the resection bed
- Gamma Knife or stereotactic radiotherapy for inoperable lesions <5 cm
- Whole brain radiotherapy only in cases of incomplete resection or numerous foci or after histological findings (in small cell neuroendocrine carcinomas)

5.1.1.6 Solitary lung metastasis

Frequency and primary tumor

The crucial factor is the distinction from primary lung carcinoma, see Figures 2 and 3. Solitary lung metastases as the only tumor manifestation are extremely rare; they are usually multiple.

Therapy

- Atypical resection, frozen section, lobectomy if necessary, systematic lymphadenectomy

- Radiotherapy or adjuvant chemotherapy, if indicated, depending on histology and individual case

5.1.1.7 Solitary bone metastasis

Frequency and primary tumor

Rare, usually multiple. In cases of osteolysis, lung and renal cell carcinoma should be investigated, and in cases of osteoplastic components, breast and prostate carcinoma should be investigated, as well as gastric carcinoma.

Supplementary diagnostics

Histological confirmation! (DD myeloma/plasmacytoma, Paget's disease, primary bone tumors, etc.)

Therapy

- Resection with curative intent
- Followed by radiotherapy if indicated
- In case of unfavorable localization, primary definitive (not palliative!) radiotherapy
- Depending on histology, immune checkpoint blockade or TKI therapy if appropriate [45]

5.1.1.8 Solitary liver metastasis / oligometastasis in the liver

Frequency and primary tumor

Rare, usually multiple [35]. Differentiated neuroendocrine carcinomas (well-differentiated NET) have a favorable prognosis.

Therapy [36]

- Resection; local ablative therapy methods
- Palliative chemotherapy, (only) if locoregional therapy is not feasible, see below (disseminated disease)

5.1.1.9 Solitary metastasis of a malignant melanoma

No longer considered part of CUP syndrome.

Frequency and primary tumor

In several studies, solitary lymph node metastases of malignant melanoma with unknown primary tumor have a better prognosis than those with known primary tumor [46, 47], while in others this is not the case [48]. A recent comparative genomic analysis shows no significant differences between melanomas with unknown versus known primary tumors [49].

Therapy

- Similar to malignant melanoma with known primary tumor

5.1.1.10 Solitary skin or soft tissue metastasis other than melanoma, including Merkel cell carcinoma

Frequency and primary tumor

Rare; lung or breast cancer is the most common primary tumor [50]. Merkel cell carcinoma has attracted particular attention due to specific and promising treatment options available [51, 52]. It can be clearly diagnosed histologically: neuroendocrine carcinoma with evidence of Merkel cell polyomavirus.

Therapy

- Resection, followed by radiotherapy if indicated
- For Merkel cell tumors, immune checkpoint blockade with avelumab or pembrolizumab if curative resection/radiotherapy is not possible

5.1.2 Advanced stages

5.1.2.1 Extragonadal germ cell tumors

No longer classified as CUP syndrome. Can be reliably differentiated from other carcinomas by immunohistochemistry, see Table 1; consultation with pathology is advisable! Caution is advised in men < 50 years of age, poorly differentiated carcinoma, retroperitoneal/mediastinal/pulmonary tumor manifestation, rapid progression.

For the procedure, see the Onkopedia guideline on male germ cell tumors.

5.1.2.2 Neuroendocrine tumors

5.1.2.2.1 Neuroendocrine tumors – NET grade I-III

No longer classified as CUP syndrome.

Frequency and primary tumor

An unknown primary tumor is not uncommon in (liver) metastases of a well-differentiated neuroendocrine carcinoma, occurring in up to 20% of cases. The spontaneous course is usually favorable, with multiple liver metastases occurring frequently and lung or skeletal metastases occurring much less frequently [53]. Specific immunohistochemistry and gene expression diagnostics can almost always be used to distinguish between pancreatic NET and intestinal NET, and thus often to identify the primary tumor [54, 55, 56].

Supplementary diagnostics

68-gallium somatostatin receptor PET-CT; hormonal diagnostics for endocrine-active NET, see ENETs guideline NET [57].

Therapy

- As for metastatic differentiated neuroendocrine tumors, see ENETs guideline [58]
- An exploratory laparotomy often identifies the primary tumor; (only) in cases of potentially completely resectable metastasis should it be performed in a designated center [27].

5.1.2.2.2 Undifferentiated neuroendocrine carcinomas (NEC)

No longer classified as CUP syndrome.

Frequency and primary tumor

Neuroendocrine carcinomas (NEC) can develop in a wide variety of organs. Classic small cell carcinomas must be distinguished from large cell neuroendocrine carcinomas (LCNEC). An unknown primary tumor is a rare, special case. There is a relatively high sensitivity to chemotherapy, but it is slightly lower in extrapulmonary carcinomas than in small cell lung carcinoma. Note: Merkel cell carcinomas are also neuroendocrine carcinomas; they must be identified according to 5.1.1.10.

Treatment

- Similar to small cell lung cancer with platinum-etoposide-based chemotherapy plus atezolizumab, durvalumab, serplulimab, or tislelizumab; possibly plus radiotherapy, see Onkopedia guideline for small cell lung cancer
- For Merkel cell carcinoma: immune checkpoint blockade

5.1.2.3 Women with peritoneal carcinomatosis due to adenocarcinoma

Serous high-grade carcinoma in women is no longer considered part of CUP syndrome, but should be regarded as primary peritoneal carcinoma in women – see Onkopedia Ovarian Carcinoma. However, it is sometimes difficult to distinguish this form of peritoneal carcinomatosis from other primaries. The immunohistological profile (e.g., p53, WT1, PAX8) can be helpful here. This can be of crucial importance for patients affected.

Criteria:

Female gender, peritoneal carcinomatosis, no other metastases ± malignant pleural/pericardial effusion ± retroperitoneal lymph node metastases. Patients with typical histology (serous papillary adenocarcinoma) and immunohistology should no longer be classified as CUP syndrome, but as "primary peritoneal adenocarcinoma." The prognosis is slightly less favorable than for primary ovarian carcinoma [59].

Treatment:

- Similar to ovarian carcinoma with (if indicated) debulking surgery, carboplatin/paclitaxel-based adjuvant or preoperative chemotherapy supplemented with bevacizumab/PARP inhibitor.

If the histology is not consistent with ovarian carcinoma, especially in the case of adenocarcinoma consistent with a pancreaticobiliary or gastric profile ("upper GI"), a "prognosically unfavorable CUP syndrome" is present. In some cases, the primary tumor is found in the appendix [60].

5.1.2.4 Hormone-sensitive carcinoma

5.1.2.4.1 ER (estrogen receptor)-positive carcinoma

Further criteria

A thorough search for breast cancer, endometrial cancer, and ovarian cancer must be conducted.

Criteria for breast cancer are: history of breast cancer (even decades ago), axillary, supraclavicular, or mediastinal lymph node involvement, malignant pleural effusion, (mixed osteolytic-osteoplastic) bone metastasis, immunohistology: hormone receptor, HER2, GATA3, mammaglobin A, or GCDFP-15 expression.

Treatment

As for metastatic breast cancer, see Onkopedia guideline Breast cancer in women (German Version only) or Breast cancer in men (German Version only)

5.1.2.4.2 Prostate-like (Androgen receptor-positive) carcinoma

Criteria for prostate cancer are osteoplastic bone metastasis, elevated serum PSA, immunohistochemical detection of NKX3.1, PSMA, or PSA.

Prostate carcinomas are almost always AR-positive, but salivary gland carcinomas, triple-negative breast carcinomas, and others can also express AR.

Therapy

- As for prostate cancer

5.1.2.5 Colonic-type adenocarcinoma (immunohistologically CK7-, CK20+, CDX2+)

Additional criteria

- Liver metastases and/or peritoneal carcinomatosis.

Therapy

- As for metastatic colon cancer, see Onkopedia guideline on colon carcinoma or Onkopedia guideline on rectal carcinoma

5.1.2.6 Renal cell carcinoma (clear cell or papillary, immunohistologically PAX8+, PAX2+, CD10+/-, racemase+)

Additional criteria

For differential diagnosis, see algorithm in Figure 7. Lung or bone metastases, retroperitoneal lymph node metastases [20].

Therapy

- As for metastatic renal cell carcinoma, see Onkopedia guideline for renal cell carcinoma.

5.1.3 Prognostically unfavorable manifestations

Criteria

Disseminated metastasis, either multiple in one organ (liver, lung, bone, brain, pleural or peritoneal carcinomatosis) or in different organ systems, not belonging to the defined groups. These "unfavorable manifestations" account for 75-85% of CUP syndromes.

5.1.3.1 Adenocarcinoma (ACUP) / undifferentiated carcinoma (UCUP)

The CUPISCO study [21] on adeno- and undifferentiated CUP has substantially changed the treatment algorithm for this group of patients. This prospective study of 636 strictly selected patients shows that personalized therapy based on the molecular tumor profile as recommended by a molecular tumor board significantly improves the outcome in first-line treatment after three cycles of primary chemotherapy. It has thus provided the first evidence that therapy based on the molecular profile and used in the first line can improve the prognosis in CUP. All patients with a possible therapy sequence should therefore undergo both comprehensive molecular characterization via NGS (next generation sequencing) (see Onkopedia guideline on precision oncology) and an examination of immunogenic tumor biology [20].

5.1.3.1.1 Immunogenic tumor biology

This is characterized by microsatellite instability (MSI-H) / defective mismatch repair enzymes (dMMR). These defects lead to a very high somatic mutational burden in a wide variety of primary tumors with very good response rates to therapy with immune checkpoint inhibitors.

Studies looking for other predictors of a possible response to immune checkpoint blockade show that high TMB (tumor mutational burden) is a relevant parameter. The exact PD-L1 cut-off for CUP syndrome has not yet been precisely defined and appears to be between 10 and 16 mutations/megabase [14, 22, 61]. The CUPISCO study, which used a cut-off of 16 mutations/megabase, shows a 2-year PFS of approximately 30% and a 2-year OS of 65% in this patient population after first-line monotherapy with atezolizumab [21].

Small phase II studies with pembrolizumab or nivolumab monotherapy [22, 23] show an objective response rate (ORR) of approximately 20%, a PFS of 4 months, and an OS of 11-14 months in non-stratified patient cohorts. Another phase II study with ipilimumab plus nivolumab as combination therapy shows an ORR of 16% in ≥ second-line therapy. With high TMB, there is a response rate of 60% with a small fraction of long-term survivors; with low TMB, the response rate is only 7.7%. PDL1 status (positive vs. negative), on the other hand, had no prognostic significance in this study [61].

In the CUPISCO study, numerous patients without a proven immunogenic or molecular tumor profile received atezolizumab (see below, chapter 5.1.3.1.1 and chapter 5.1.3.1.3) in addition to chemotherapy, with a small survival benefit without raising the survival plateau. Atezolizumab has not yet been approved for general use as combination immunochemotherapy in patients without an immunogenic or molecular tumor profile.

The significance of PDL1 expression (TPS and CPS) in CUP has not been conclusively clarified. It may provide an important indication for treatment with chemotherapy plus immune checkpoint blockade in patients with the provisional diagnosis of an immunogenic tumor (lung, stomach/esophagus, cholangiocellular carcinoma, urothelial, squamous cell carcinoma, and many others). A cut-off for TPS or CPS has not been determined for CUP. In second-line or further-line therapy, the option of immune checkpoint blockade should be considered on an individual basis in cases of PDL1 expression.

Therapy

- For MSI-H or dMMR, pembrolizumab or atezolizumab
- In cases of high tumor mutational burden (TMB-high, ≥10 mutations/megabase): PD1/PDL1 checkpoint inhibitor +/- CTLA4 inhibitor (off-label)
- In cases of immunogenic tumor biology with PDL1 expression: consider PD1/PDL1 checkpoint inhibitor in the second line of therapy (off-label).

5.1.3.1.2 Therapeutically relevant genetic alterations

Currently, the most exciting approach in treatment is molecularly based therapy based on genetic alterations of so-called "druggable targets" on tumor cells (see Onkopedia guideline on precision oncology). Ideally, NGS (next generation sequencing) is used to create molecular profiles of the tumor cells with the aim of identifying suitable targeted substances (tyrosine kinase inhibitors and monoclonal antibodies). The often complex findings are interpreted by a molecular tumor board (MTB). Based on the MTB's recommendation, an application for cost coverage for the proposed treatment must generally be submitted in Germany, which in turn is often approved.

In the CUPISCO study [21], slightly more than a quarter of all patients showed therapy-relevant genetic alterations. One-fifth had an immunogenic tumor. In the remaining patients, targeted therapy with TKIs or monoclonal antibodies led to both a prolongation of PFS compared to chemotherapy (8.1 months vs. 4.7 months) and a 2-year PFS of 20% vs. 10%. The effect was particularly favorable in cases of BRAF V600 mutations and FGFR2 fusions. The study was not powered for a statistical comparison of these groups.

Overall, genetic alterations are found in more than 85% of CUP cases, with approximately 25-35% showing changes that are amenable to currently approved agents [21, 62, 63]. Therapeutically addressable alterations in PIK3CA, FGFR2, ERBB2, IDH, and BRAF (5-10%) are more common, while alterations in EGFR, MET, KRAS p.G12C, ROS1, NTRK, and ALK are less commonly identified.

Due to the statistically significant advantage in by far the largest and best-selected prospective randomized study ever conducted in CUP, both molecular characterization (NGS panel test or WES – whole exome sequencing) and targeted therapy are required if a treatable genetic alteration is detected [21, 89].

Therapy

- As for known primary tumor with corresponding driver mutation.

5.1.3.1.3 Tumor biology without evidence of immunogenicity and without evidence of therapy-relevant genetic alterations

If there are no options for TKI therapy or immune checkpoint blockade, empirical chemotherapy is indicated.

When selecting chemotherapy, e.g., combination therapy or monotherapy, it is advisable to consider age, comorbidity, LDH, functional status, and treatment preferences, possibly after a geriatric assessment.

First-line therapy

The so-called standard protocol consists of a platinum-based combination therapy ("platinum doublet"). However, a randomized clinical comparison to a best supportive care concept has never been conducted. The addition of an EGFR antibody or a histone deacetylase inhibitor to chemotherapy without biological markers as a selection criterion has not shown a benefit [64, 65].

The CUPISCO study shows a moderate, but statistically significant prolongation of survival in this group by adding an immune checkpoint blockade with atezolizumab to platinum-based combination therapy [21]; however, it is advisable to obtain a cost coverage statement from the health insurance company in Germany for this treatment.

The following chemotherapy options are available and have been empirically proven in more recent studies:

- Carboplatin-paclitaxel-based chemotherapy [66, 67]
- Cisplatin – gemcitabine ("French regimen") (caution: toxicity) [68]

Selecting the therapy most likely to target the primary tumor is tempting, but by definition difficult in CUP. Molecular genetic methods based on methylation patterns, microRNA, or gene expression patterns consistently postulate results with approximately 85% accuracy. The alignment of therapy with the results of genetic profiling was prospectively randomized in three studies. Two of these used a 92-gene test (CancerType ID), and both, like a meta-analysis from 2020, showed no advantage for "personalized" therapy based on the presumed primary tumor over empirical chemotherapy [18, 71, 72]. In a recent Chinese single-center study [86] , targeting the presumed primary tumor determined by a 90-gene panel, resulted in a significantly better outcome than empirical chemotherapy with an HR of 0.68. The most frequently suspected primary sites in this cohort were the stomach/esophagus (15%), lung (13%), ovary (12%), cervix (12%), and breast (10%). However, since this study offered targeted therapy options in addition to the concept of primary tumor prediction in the experimental arm, it remains unclear whether the demonstrated advantage is actually attributable to the treatment concept based on the presumed primary tumor or not. The question of the practical benefits of such tests has not yet been decided.

In many cases, treatment is carried out in practice in line with the primary tumor suspected by the treating physician based on the available information. This approach is not evidence-based. It may be useful in individual cases, but it can also reduce the chances of successful treatment. In general, this approach is directed not to the most therapy-sensitive primary tumor, but the one that is considered most likely. For example, the supposedly broad-spectrum combination of capecitabine and oxaliplatin in first-line CUP is not effective even when criteria for a gstrointestinal primary tumor are present, if the group of colon-typical CUP has been clearly excluded. PFS was only 2.5 months and OS only 7.5 months in a well-documented prospective study with 39% of liver metastases as the presenting site [75].

Details on the standard chemotherapy regimens can be found in the appendix on treatment protocols (German version only).

Second-line therapy

There are no convincing trials on second-line therapy. The few studies available provide information on small numbers of selected patients. If a driver mutation is detected, the corresponding TKI should be given in the second line at the latest. In cases of high tumor mutation burden (TMB-high) or microsatellite instability/mismatch repair deficiency, immune checkpoint blockade is recommended [61], if not already given in the first line. In other cases, an alternative chemotherapy regimen from the options for first-line treatment may be appropriate for patients

in good condition. In the second line, empirical therapy based on the working diagnosis should always be considered.

Unfortunately, the prospects for patients with CUP primarily progressive on first-line chemotherapy are limited with second-line chemotherapy, so the indication should be carefully considered and discussed with the patient. In the CUPISCO study, the outcome of second-line treatment in patients refractory to first-line platinum doublet chemotherapy was extremely poor, with a PFS of only 2 months and an overall survival of 6 months, despite the regular use of immune checkpoint blockade, sometimes combined with chemotherapy [79].

5.1.3.2 Chemotherapy/radiotherapy for squamous cell carcinoma (SqCUP)

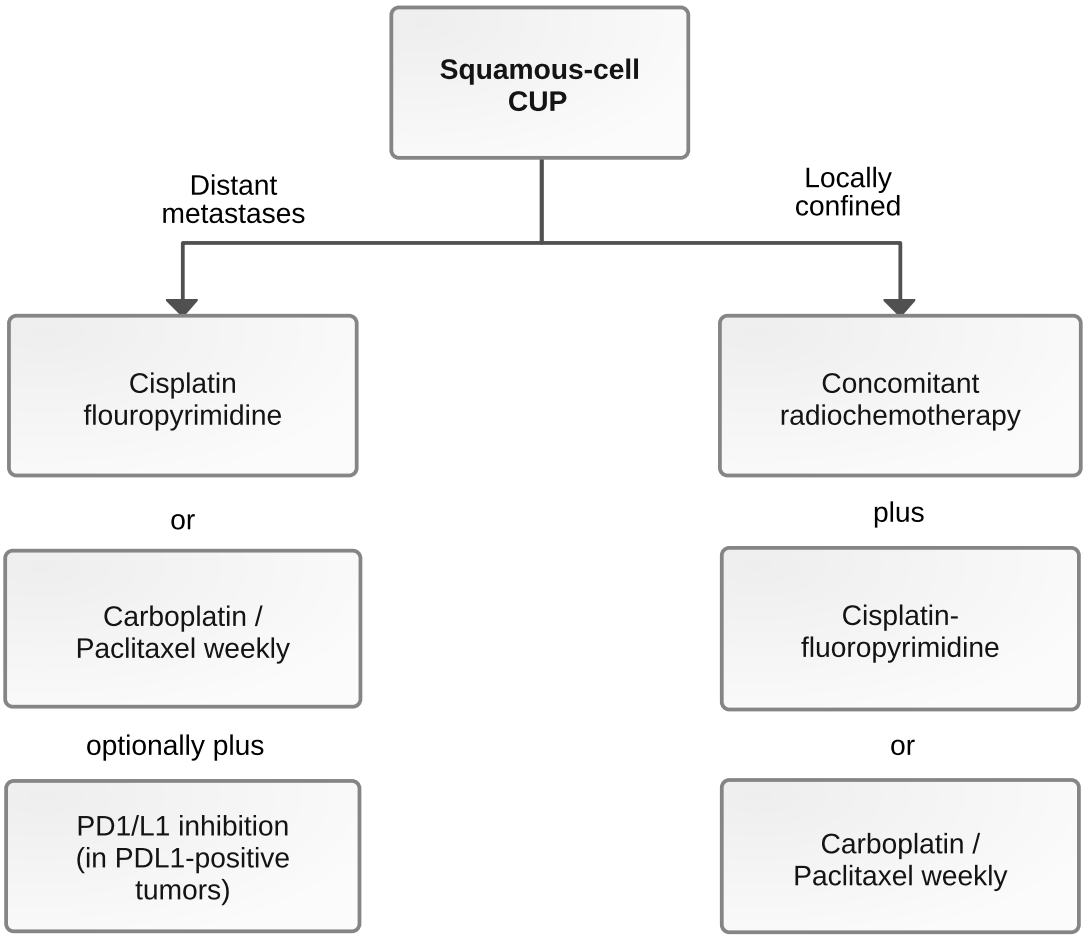
In squamous cell carcinoma, histology does not allow a reliable conclusion to be drawn about the location of the primary tumor. HPV detection in metastases is common in primary gynecological malignancies and anal carcinomas, as well as in head and neck tumors. In case of cervical lymph node metastases, HPV detection makes a primary tumor in the oropharynx highly likely. In numerous studies on CUP syndrome, squamous cell carcinomas were treated the same way as adenocarcinomas and undifferentiated carcinomas, however, it is not possible to assess the outcome of this therapy in cases of squamous cell histology due to its rarity.

Therapy

- Combined radiochemotherapy, e.g., cisplatin/fluoropyrimidine or carboplatin AUC=2 / paclitaxel 50 mg/m^2 weekly, in case of PDL1 expression plus immune checkpoint blockade if indicated
- In second-line therapy, an immune checkpoint inhibitor is useful (if not already given in first-line therapy), especially if there are indications of immunogenic tumor biology
- The administration of an EGFR antibody should be discussed on a case-by-case basis

For the treatment algorithm, see Figure 10.

Figure 10: Treatment algorithm for squamous cell carcinoma



Legend:
Abbreviations: SqCUP – squamous cell CUP, PDL1 – programmed death ligand 1

5.3 Special settings

5.3.1 Bone metastasis

Therapy

- Consistent analgesic therapy, symptomatic radiotherapy if indicated
- Bisphosphonate or denosumab therapy

Spinal metastases with imminent spinal cord compression represent a special situation: **oncological emergency!** The prognosis is poor, especially if visceral metastases are also present and if the patient is immobilized Immediate surgery or radiotherapy can often prevent paraplegia [73].

7 Monitoring and follow-up

7.2 Follow-up

There are no evidence-based guidelines for CUP syndrome. Due to the diversity of the clinical picture, detailed recommendations are not helpful. The following applies in general:

- For curative therapy: structured follow-up
- For palliative therapy: symptom-oriented follow-up

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9 Active studies

None currently in German-speaking countries.

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16 Disclosure of Potential Conflicts of Interest

according to the rules of DGHO, OeGHO, SGH+SSH, SGMO

Author	Employer[1]	Consulting / Expert opinion[2]	Shares / Funds[3]	Patent / Copyright / License[4]	Fees[5]	Funding of scientific research[6]	Other financial relations[7]	Personal relationship with authorized representatives[8]
Bochtler, Tilmann	Nationales Centrum für Tumorerkrankungen (NCT) Heidelberg Universitätsklinikum Heidelberg Im Neuenheimer Feld 460 69120 Heidelberg Klinische Kooperationseinheit Molekulare Hämatologie / Onkologie, Deutsches Krebsforschungszentrum Heidelberg (DKFZ) und Medizinische Klinik V, Im Neuenheimer Feld 280 69120 Heidelberg	**No**	**No**	**No**	**Yes** Arbeit als Studienonkologe für die CU-PISCO Studie, die von Roche gesponsort wird. Im Rahmen dieser Tätigkeit Vergütung der Arbeit als Studienonkologe / Vorträge an den Arbeitgeber (keine persönlichen Honorare)	**No**	**Yes** Arbeit als Studienonkologe für die CU-PISCO Studie, die von Roche gesponsort wird. Im Rahmen dieser Tätigkeit Erstattung von studienbezogenen Reisen.	**No**
Borner, Markus	Selbständig	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Ernst, Thomas	Universitätsklinikum Jena	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Hübner, Gerdt	1. Selbst (eigene Praxis) 2. Ameos Klinika Ostholstein (Teilzeit), Hospitalstr. 22, 23701 Eutin	**Yes** Roche	**No**	**No**	**Yes** Roche	**No**	**No**	**No**
Kraywinkel, Klaus	Robert Koch-Institut, Berlin	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Neben, Kai	Klinikum Mittelbaden Abteilung für Hämatologie, Onkologie und Palliativmedizin Balgerstrasse 50 76532 Baden-Baden	**Yes** Janssen, BMS, MSD, Takeda, Sanofi, Miltenyi, Pfizer, Roche, AstraZeneca, Novartis	**No**	**No**	**No**	**No**	**No**	**No**
Stöger, Herbert	seit 10/2021 an Medizinischer Universität Graz im Ruhestand; laufende internistisch-onkologische Ordination;	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Weiss, Lena	Klinikum der Universität München	**No**	**No**	**No**	**Yes** Servier, Roche	**Yes** Illumina	**Yes** AMGEN	**No**

Legend:

[1] - Current employer, relevant previous employers in the last 3 years (institution/location).

[2] - Activity as a consultant or expert or paid participation in a scientific advisory board of a company in the health care industry (e.g., pharmaceutical industry, medical device industry), a commercially oriented contract research organization, or an insurance company.

[3] - Ownership of business shares, stocks, funds with participation of companies of the health care industry.

[4] - Relates to drugs and medical devices.

[5] - Honoraria for lecturing and training activities or paid authors or co-authorships on behalf of a company in the health care industry, a commercially oriented contracting institute or an insurance company.

[6] - Financial support (third-party funds) for research projects or direct financing of employees of the institution by a company in the health care industry, a commercially oriented contract institute or an insurance company.

[7] - Other financial relationships, e.g., gifts, travel reimbursements, or other payments in excess of 100 euros outside of research projects, if paid by an entity that has an investment in, license to, or other commercial interest in the subject matter of the investigation.

[8] - Personal relationship with an authorized representative(s) of a healthcare company.