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SPECIAL ARTICLE

Cancer of unknown primary: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

A. Krämer[1,2], T. Bochtler[1,2,3], C. Pauli[4,5], G. Baciarello[6], S. Delorme[7], K. Hemminki[8,9], L. Mileshkin[10], H. Moch[4,5], K. Oien[11], T. Olivier[12,13], A. Patrikidou[14], H. Wasan[15], G. Zarkavelis[16], G. Pentheroudakis[17] & K. Fizazi[14], on behalf of the ESMO Guidelines Committee*

[1]Clinical Cooperation Unit Molecular Haematology/Oncology, German Cancer Research Center (DKFZ) Heidelberg; [2]Department of Internal Medicine V, University of Heidelberg, Heidelberg; [3]Department of Medical Oncology, National Center for Tumor Diseases (NCT), University of Heidelberg, Heidelberg, Germany; [4]Department of Pathology and Molecular Pathology, University Hospital Zurich (USZ), Zurich; [5]Medical Faculty, University of Zurich (UZH), Zurich, Switzerland; [6]Medical Oncology Department, Azienda Ospedaliera San Camillo Forlanini, Rome, Italy; [7]Division of Radiology, German Cancer Research Center (DKFZ), Heidelberg; [8]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [9]Faculty of Medicine and Biomedical Center, Charles University, Pilsen, Czech Republic; [10]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia; [11]Institute of Cancer Sciences, University of Glasgow, Glasgow, UK; [12]Department of Oncology, Geneva University Hospital, Geneva, Switzerland; [13]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, USA; [14]Department of Cancer Medicine, Institute Gustave Roussy, University of Paris Saclay, Villejuif, France; [15]Department of Cancer Medicine, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK; [16]Department of Medical Oncology, University of Ioannina, Ioannina, Greece; [17]European Society for Medical Oncology, Lugano, Switzerland

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INCIDENCE AND EPIDEMIOLOGY

Definition

Cancer of unknown primary (CUP) is defined as a carcinoma or undifferentiated neoplasm for which a standardised diagnostic work-up fails to identify the primary tumour responsible for metastatic seeding.

Incidence

CUP accounts for <5% of cancers but, because of its high mortality rate, its relative contribution to cancer deaths is higher.[1] The incidence of CUP has been declining, probably due to improving success in localising primary tumours.[2] The incidence increases with age and is higher in men compared with women. Adenocarcinoma is the most common histology. Approximately 50% of CUP cases can be categorised as well-differentiated to moderately differentiated adenocarcinomas, ~30% as poorly differentiated adenocarcinomas or undifferentiated carcinomas, ~15% as squamous-cell carcinomas and ~5% as undifferentiated neoplasms.[2,3] Sarcomas, melanomas, germ cell tumours, neuroendocrine tumours and haematological malignancies whose exact site of origin is not established are not included in the CUP definition. Many patients present with metastases in multiple organs, such as the liver (most common), respiratory system, lymph nodes, abdominal cavity, bone and brain.[1] The decrease in CUP incidence has been noted for most metastatic locations and histologies.[1]

Subsequent primary cancers after CUP

CUP diagnostics include a meticulous search for the hidden primary cancer, which explains why no new primaries are diagnosed soon after a CUP diagnosis.[4] The majority of patients with CUP will not have a primary lesion identified during the course of the disease. However, some survivors of CUP may develop (i) initially hidden primary tumours responsible for their metastatic disease or (ii) second primary cancers. Elevated risks for the development of several types of second primaries have been reported,[5] with the highest risks observed for cancers of the small intestine, male genital organs and aerodigestive tract. Significant risks have also been observed for the development of non-Hodgkin's lymphoma and squamous-cell skin cancer, which are known hallmarks of dysregulated immunity, suggesting a contribution of suppressed immune function as a feature of CUP.

Risk factors

Smokers are at risk of developing CUP and this risk correlates with the level of tobacco exposure: from 1.8-fold for smokers

**Correspondence to:* ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, 6900 Lugano, Switzerland
E-mail: clinicalguidelines@esmo.org (ESMO Guidelines Committee).

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of 1-15 cigarettes/day up to 3.5-fold for 16-25 cigarettes/day and 4.1-fold for >25 cigarettes/day.[6] The likelihood of being a smoker was higher in patients with CUP and respiratory system metastases (4.9-fold) than in those with CUP and liver metastases (2.0-fold).[7] Type 2 diabetes (1.8-fold)[8] and autoimmune disorders are also associated with an increased risk of CUP; the relative risks were 3.5 for polymyositis/dermatomyositis, 1.8 for primary biliary cirrhosis and 1.7 for Addison disease.[9] Familial predisposition to CUP is another established risk factor.[10] High body mass index, waist circumference, low socioeconomic status and black ethnic background may be additional risk factors.[6,11]

Survival

The probability of survival after a diagnosis of CUP has remained at ~20% at 1 year and has not improved much over time.[1,2] Around half of the observed deaths occur within the first 3 months following diagnosis, i.e. median survival is ~3 months. Survival is worse for adenocarcinoma and undifferentiated carcinoma compared with squamous-cell carcinoma (1-year survival of <20% and 36%, respectively).[12] Increasing age is associated with a survival disadvantage. Patients with CUP manifestations restricted to lymph nodes have a better prognosis than those with extranodal disease.[1,12]

In a comparison of survival outcomes for patients with CUP versus those with metastatic cancer of known primary and matched location of metastases, in general, patients with CUP had a poorer survival, with the exception of those with brain and respiratory system metastases.[13]

CUP DIAGNOSIS

Histology and immunohistochemistry

Histology and immunohistochemistry (IHC) on good quality tissue specimens are required. A morphological pattern-based approach is first applied to differentiate between epithelial, round, spindle-shaped and anaplastic cancers to identify the pattern of tissue organisation regarding entity and tissue of origin.

For undifferentiated neoplasms or cells of unclear lineage, an initial IHC screening is carried out,[14] typically comprising a broad-spectrum keratin to identify an epithelial phenotype (e.g. AE1/AE3, OSCAR), cluster of differentiation 45 (CD45) for haematolymphoid origin (be aware of downregulation of CD45 expression in immature B-cell neoplasms) and SOX10 and/or S100 for melanoma. In case of a triple-negative screen, a mesenchymal origin must be considered. There is no single screening marker for sarcoma (see Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.11.013).

After lineage classification, a stepwise approach, using additional marker assessments navigated by the clinical work-up results, must be undertaken (see Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.11.013). For carcinomas, cytokeratin (CK)7 and CK20 staining patterns may provide an indication of primary localisation (see Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.11.013). For male patients, metastatic prostate cancer must be ruled out using prostate-specific membrane antigen (PSMA) and/or NKX3.1 as markers. For female patients, GATA3 should be used to screen for breast cancer and SOX10 for triple-negative breast cancer.

Lung cancer. Only ~60% of poorly differentiated and metastatic lung adenocarcinomas stain positive for thyroid transcription factor 1 (TTF1).[15] In the setting of CK7 positivity and TTF1 negativity but suspicion of a lung primary, SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4 (SMARCA4) staining should be considered as many TTF1-negative lung adenocarcinomas show loss of SMARCA4 nuclear staining.[16] Napsin A can be useful in a panel together with TTF1 in the diagnostic work-up of lung adenocarcinoma but it has limited value when TTF1 is negative (see Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.11.013).

Gastrointestinal carcinomas. For analysis of biopsies including an adenocarcinoma in the liver, the initial IHC panel should include CK7, CK20, caudal type homeobox 2 (CDX2) and TTF1 (plus GATA3 and/or SOX10 in women) to screen for metastatic tumours of breast, lung, gastrointestinal (GI) and/or pancreaticobiliary origin (see Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.11.013). At least 80% of colorectal cancers (CRCs) show the classic CK7-negative, CK20-positive, CDX2-positive immunophenotype, with CK20 and CDX2 staining usually being diffuse and strong. Occasional upper GI and rare pancreaticobiliary adenocarcinomas also demonstrate a colorectal immunophenotype. In this setting, special AT-rich sequence-binding protein 2 (SATB2) positivity is fairly specific for tumours of lower GI origin.[17] The differential diagnosis of intrahepatic cholangiocarcinomas (CCAs) by IHC remains difficult due to the lack of specific markers. Immunohistochemical loss of *BRCA1*-associated protein 1 (BAP1) or AT-rich interactive domain-containing protein 1A (ARID1A) can support the diagnosis but the final decision can only be made in conjunction with clinical and radiological findings.[18]

Neuroendocrine tumours. In order to identify neuroendocrine tumours, a synaptophysin and/or INSM1 staining must be carried out in tumours with a solid, trabecular, gyriform or regular glandular growth pattern, uniform nuclei and coarsely stippled ('salt and pepper') chromatin. Likewise, synaptophysin and/or INSM1 staining should also be carried out in high-grade tumours that resemble small-cell carcinomas or large-cell neuroendocrine tumours of the lung. Positivity for CDX2 and ISLET 1 may hint towards primary locations of neuroendocrine tumours in the GI tract and pancreas, respectively (see Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.11.013).

Mesothelioma. Specific caveats in the CUP work-up exist for mesotheliomas, which are typically positive for keratins and

therefore might be misclassified as carcinomas. Mesothelioma should be considered in biopsies originating from the pleura, pericardium and peritoneum. Immunostaining with calretinin should be carried out in these cases and, upon positivity, should be complemented with Wilms tumour 1 (WT1), CK5/6, D2-40 and BAP1 (loss) (see Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.11.013).

Sarcoma. Expression of broad-spectrum epithelial markers by mesenchymal tumours is focal in most cases. However, in cases with an epithelioid morphology, expression of these markers can be diffuse, and strong keratin positivity (e.g. synovial sarcoma, epithelioid sarcoma) often leads to erroneous classification as carcinoma. Keratin positivity might also be seen in small round blue cell sarcomas (e.g. desmoplastic round cell tumour, Ewing's sarcoma).[19] Regardless of broad-spectrum epithelial marker positivity, sarcoma should always be considered in the mediastinum, retroperitoneum and soft tissue, particularly in cases with spindle cell morphology (see Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.11.013).

Haematopoietic malignancies. Broad-spectrum keratins can be expressed by haematolymphoid tumours such as plasma cell neoplasms, anaplastic large-cell and mantle-cell lymphomas.[20] Useful immunohistochemical markers for screening are listed in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.11.013.

Clinical work-up

The minimal mandatory work-up for all patients should comprise the following tests:

- Thorough patient history and physical examination.
- Blood draw with basic blood and biochemical analyses.
- Either computed tomography (CT) with intravenous (i.v.) contrast agent infusion or magnetic resonance imaging (MRI) scans of the neck, thorax, abdomen and pelvis.
- Mammography in females.

Beyond this minimal diagnostic work-up, further tests are indicated according to the clinical and pathological results. This includes the tumour markers α-fetoprotein (AFP) and β-human chorionic gonadotropin (β-hCG) in males with a suspected germ cell tumour; prostate-specific antigen (PSA) in males with a possible prostate cancer; cancer antigen (CA)15-3 and CA125 in females with a suspected gynaecological primary and carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and CA72-4 when a GI primary is suspected and chromogranin A in patients with a possible neuroendocrine malignancy. Despite frequent non-tumour type-specific elevations of CEA, CA19-9, CA15-3 and CA125, these markers may be used to determine the disease course and monitor treatment response. Gastroscopy and colonoscopy are generally recommended whenever a putative GI primary is deemed possible. In contrast, bronchoscopy may be withheld unless IHC or the clinical picture for lung lesions and/or mediastinal lymph nodes implies a lung primary. Diagnostic and staging guidelines for patients with an anticipated CUP diagnosis are summarised in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2022.11.013, and include both the minimal mandatory and additional results-driven tests.

MRI is recommended for suspected head and neck tumours, brain metastases and for suspected pelvic neoplasms. Dedicated protocols are needed for some primary tumours, such as breast or prostate cancers, or for differentiating adenoma from metastasis in case of enlarged adrenal glands.

Whole-body [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG)—positron emission tomography (PET)—CT is optional in the routine CUP diagnostic work-up. Although it is excellent for depicting the true extent of disease and identifying lesions that are otherwise difficult to detect, it is only able to identify a primary in around a third of cases.[21] However, it is generally recommended in the following situations that warrant radical locoregional treatment:

- For patients with single-site/oligometastatic CUP, FDG—PET—CT should be carried out to rule out additional manifestations.[22]
- For patients with cervical lymph node metastases suspicious for head and neck cancer.[23,24]

In these cases, FDG—PET—CT may be carried out early during the diagnostic work-up, ahead of panendoscopy with biopsies and tonsillectomy, to avoid false-positive findings.[23] Furthermore, when clinically suspected, specific tumour entities can be diagnosed if special tracers are used, such as DOTATOC for neuroendocrine tumours or PSMA ligands for prostate cancer.

Differential diagnosis of CUP

With pathological and clinical diagnostic tests complete, the diagnosis of CUP relies on the multidisciplinary team's interpretation of the clinical, pathological and radiographic findings in order to decide whether the tumour manifestations represent a primary cancer or metastases compatible with CUP. The most important diagnostic tool for this purpose is sound clinical reasoning. In the absence of a clearly identifiable primary tumour or an entity-specific genomic alteration (see Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2022.11.013), it must be decided whether one of the visible lesions is likely to represent a primary tumour. Radiological clues in the diagnosis are (i) size and location of lesions and their imaging features, (ii) associated phenomena (see Supplementary Tables S6 and S7, available at https://doi.org/10.1016/j.annonc.2022.11.013), (iii) invasion patterns into adjacent structures and (iv) the distribution of haematogenic and lymphogenic metastases. Specifically, tumours that metastasise along the preformed lymphatic pathways may be surrounded by lymphatic metastases in typical locations, with the closest adjacent lymph node groups usually being the most heavily involved. In the presence of widespread disease, the absence of lymph node

metastases in typical sites may refute the presence of a primary tumour in a suspected location.

In order to standardise the interpretation of findings in ambiguous cases, following established diagnostic algorithms to delineate CUP from cancer entities with a known primary is generally recommended.[18] The respective decision algorithms are based on histology and IHC, metastatic pattern and radiographic criteria, and may be applied, particularly in clinical trials, to ensure the integrity of the study cohorts and to harmonise the eligibility process among different trials for the sake of comparability.

Lung cancer. The differential diagnosis between CUP and non-small-cell lung cancer (NSCLC) poses a recurrent diagnostic dilemma. Since 40% of lung cancers are negative for TTF1, patients presenting with neoplastic pulmonary lesions may either have metastases from an unknown primary tumour to the lung, or one of the lung lesions may be the primary itself, usually an NSCLC, with extrapulmonary as well as pulmonary metastases. The respective decision algorithms are based on pathological and radiographic features of the lung mass, hilar and mediastinal lymph node involvement and the pattern of distant metastases (see Figures 1 and 2). Radiographic features to support the discrimination are shown in Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2022.11.013.

CCA. The presence of intrahepatic lesions and histological proof of adenocarcinoma constitute a recurrent problem in discriminating between primary CCA (with or without additional intrahepatic metastases) and hepatic metastases due to an unknown extrahepatic primary tumour (with or

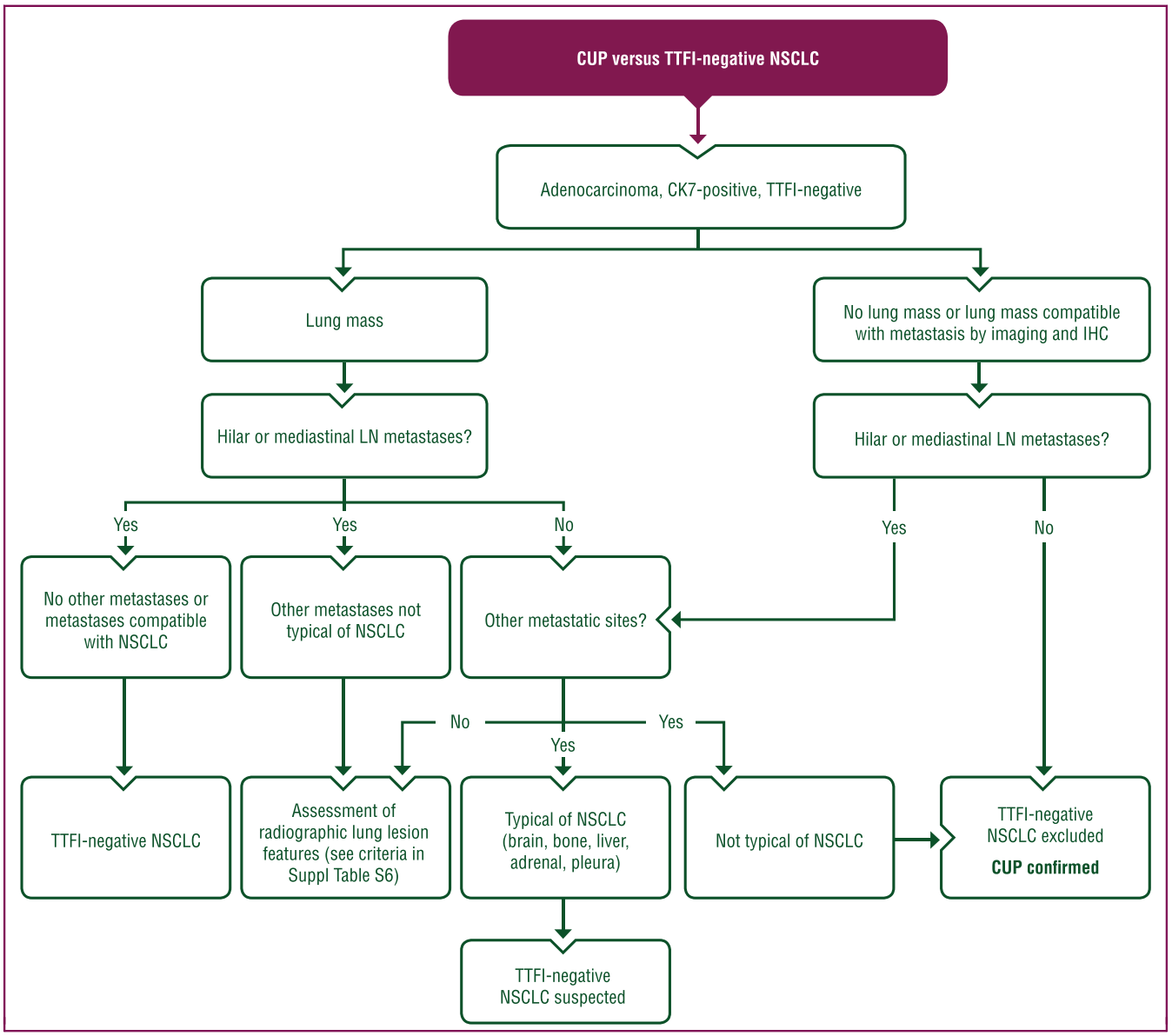

Figure 1. Differential diagnostic algorithm to discriminate between CUP and TTF1-negative NSCLC.
Brain, bone, liver, adrenal glands and pleura are the most common sites of metastatic disease in NSCLC.
Purple: general categories or stratification; white: other aspects of management.
CK, cytokeratin; CUP, cancer of unknown primary; IHC, immunohistochemistry; LN, lymph node; NSCLC, non-small-cell lung cancer; TTF1, thyroid transcription factor 1.

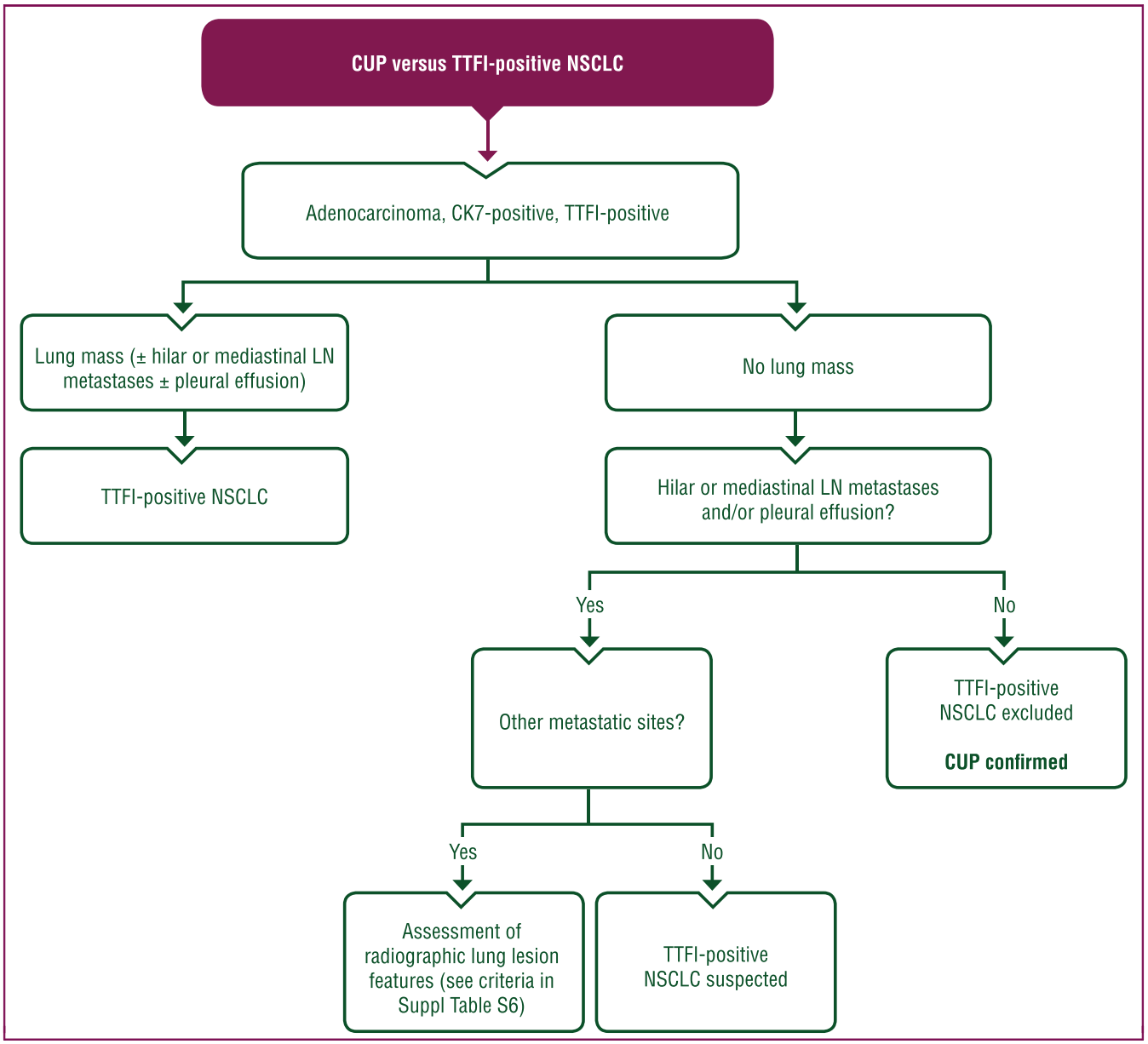

Figure 2. Differential diagnostic algorithm to discriminate between CUP and TTF1-positive NSCLC.
Purple: general categories or stratification; white: other aspects of management.
CK, cytokeratin; CUP, cancer of unknown primary; LN, lymph node; NSCLC, non-small-cell lung cancer; TTF1, thyroid transcription factor 1.

without additional extrahepatic metastases).[25,26] The decision algorithm to differentiate CUP with liver metastases from intrahepatic CCA relies on (I)HC, radiological morphology, size and number of hepatic lesions and the overall metastatic pattern (see Figure 3). Radiologically, the criteria shown in Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2022.11.013, suggest intrahepatic CCA.

Other cancer types. Further algorithms have been established for the differential diagnosis between CUP and ovarian, renal, salivary gland and breast primaries (see Figures 4-7).

For the detection of salivary gland carcinoma, additional studies may be needed. Ultrasound may be sufficient, with contrast-enhanced MRI of the neck as a reliable alternative method. CT is less suitable due to its lower soft-tissue contrast. Although a negative imaging result is sufficient to rule out a primary salivary gland tumour, a positive finding may be more difficult to interpret due to the possibility of lymph nodes located inside the gland that may be involved by metastatic spread. In unclear cases, targeted biopsies of the lesion may be carried out.

Differential diagnosis to relapse of prior malignancy

About 25% of patients with presumed CUP have had a prior malignancy.[27] In these cases, a relapse of the prior malignancy should always be considered. In dubious cases, comparative sequencing of tissue from the prior malignancy and presumed CUP is recommended to identify any clonal

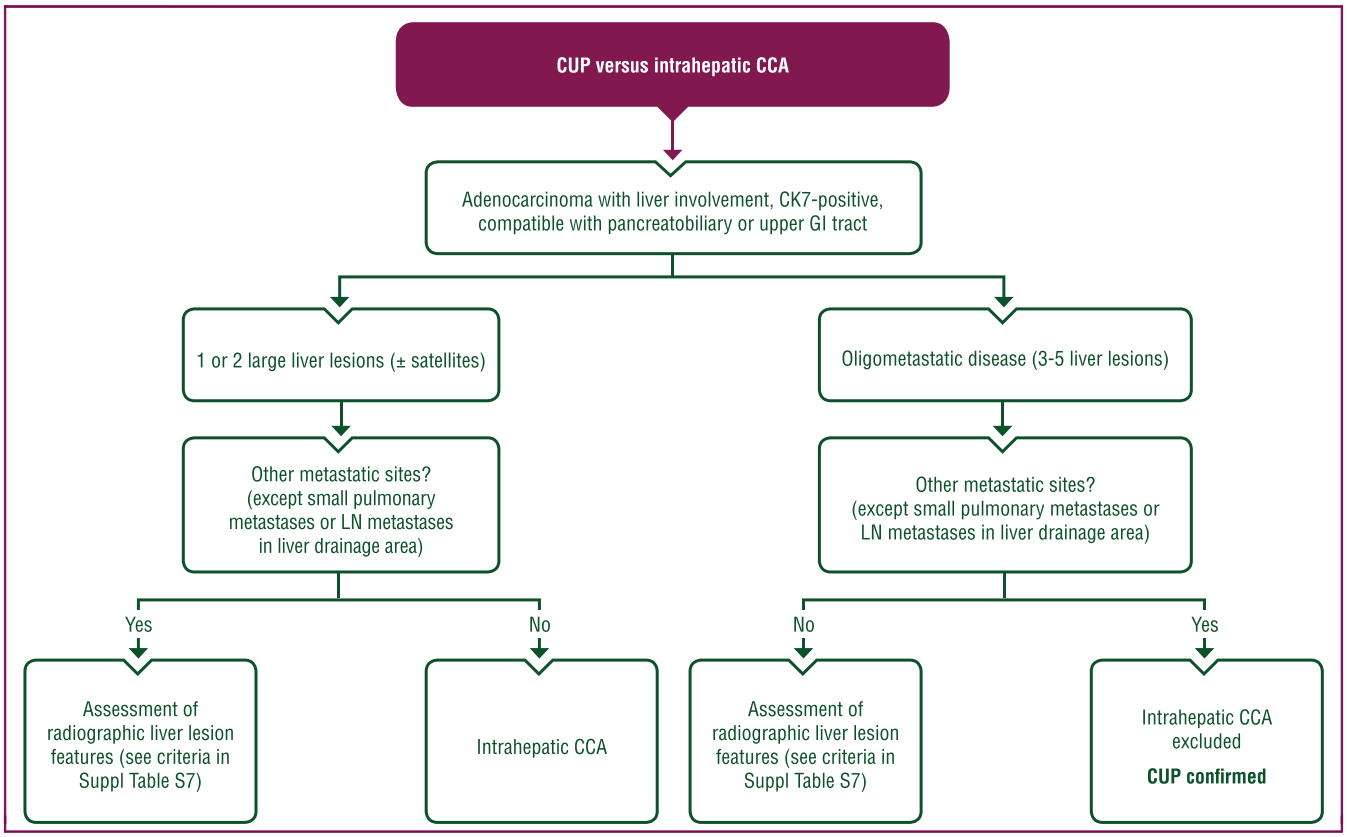

Figure 3. Differential diagnostic algorithm to discriminate between CUP and intrahepatic CCA.
Purple: general categories or stratification; white: other aspects of management.
CCA, cholangiocarcinoma; CK, cytokeratin; CUP, cancer of unknown primary; GI, gastrointestinal; LN, lymph node.

relationships and therefore corroborate or refute a new CUP diagnosis.[27]

Next-generation sequencing

Given the potential treatment options with targeted therapies or immune checkpoint inhibitors (ICIs), panel next-generation sequencing (NGS) may be carried out routinely in CUP using a pan-cancer panel covering relevant molecular targets across different entities. However, randomised trial data to assess the clinical utility of NGS-based approaches in CUP are pending.[28] In individual cases, the molecular profile might also clarify or provide clues regarding the putative primary, e.g. when anaplastic lymphoma kinase (*ALK*), ROS proto-oncogene 1 (*ROS1*; in NSCLC), transmembrane serine protease 2 (*TMPRSS2*; in prostate cancer) or nuclear protein in testis (NUT) midline carcinoma family member 1 (*NUTM1*; in NUT carcinoma) rearrangements are detected or when genomic signatures point towards ultraviolet light or tobacco exposure. A list of genomic aberrations supporting the diagnosis of specific primary tumour entities that can be used in conjunction with the differential diagnostic algorithms depicted in Figures 1-7 is provided in Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2022.11.013. In addition, analysis of the microsatellite instability (MSI) status may be routinely carried out. Testing for tumour mutational burden (TMB) and programmed death-ligand 1 (PD-L1) expression should be considered at least at progression.

Recommendations

Histology, IHC and molecular biology

- Histology and IHC on good quality tissue specimens are required [III, A].
- After lineage classification, a stepwise approach using further IHC markers, navigated by the clinical work-up results, is recommended [III, A].
- NGS may be carried out routinely in CUP [IV, B].
- The clinical utility of gene expression profiling to help elucidate the likely primary is not currently supported by high-level evidence. Consequently, it is not generally recommended outside of clinical research [II, D].

Clinical work-up

- The minimal clinical work-up should consist of a thorough patient history, physical examination, basic blood analyses, CT or MRI imaging of neck, thorax, abdomen and pelvis for all patients, with additional mammography in females [IV, A].
- Further tests may be indicated according to the clinical and pathological picture [V, B].
- FDG—PET—CT imaging is generally recommended for single-site/oligometastatic cases that warrant ablative locoregional treatment as well as for patients with head and neck CUP [IV, B].

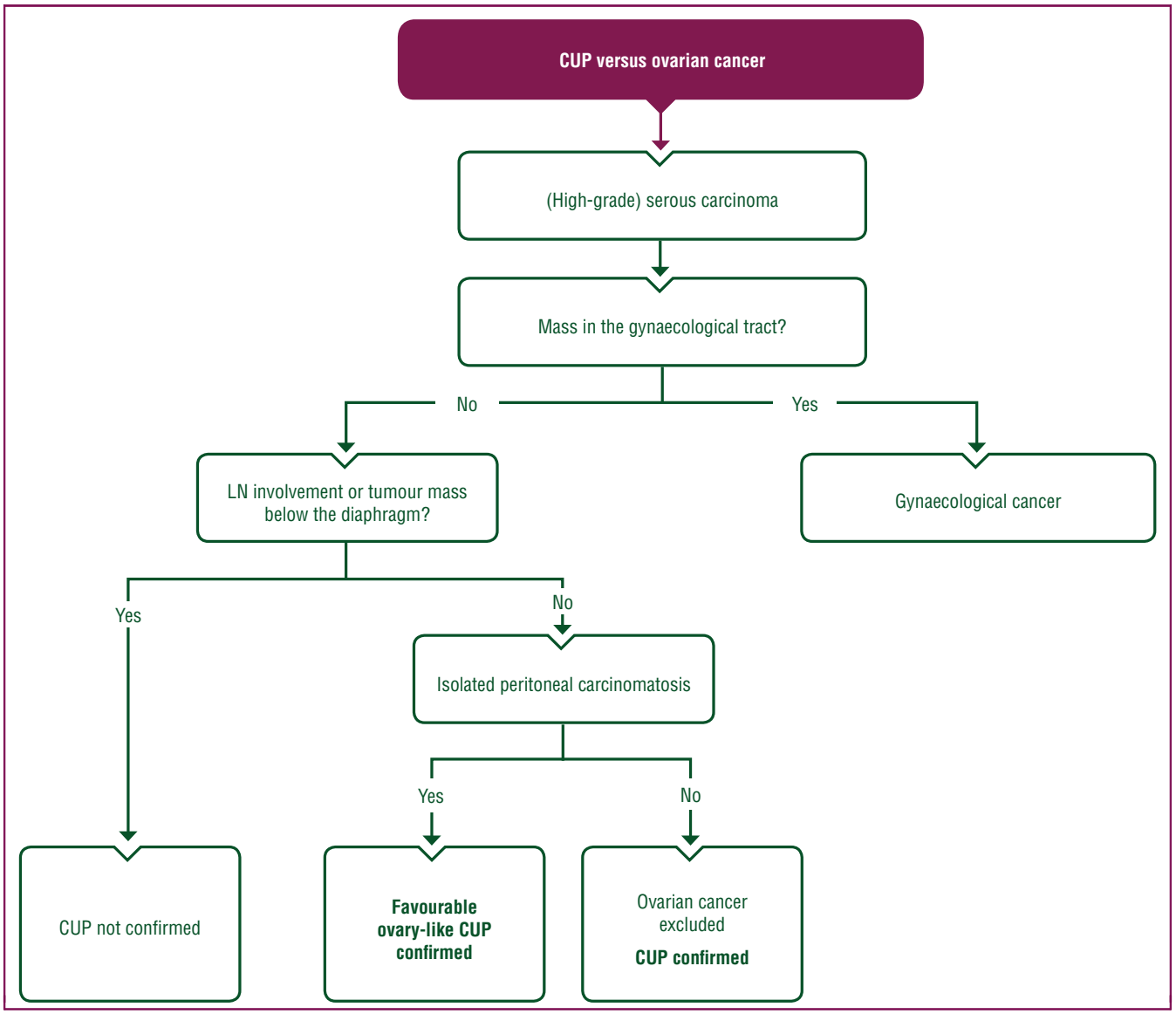

Figure 4. Differential diagnostic algorithm to discriminate between CUP and ovarian cancer.
Purple: general categories or stratification; white: other aspects of management.
CUP, cancer of unknown primary; LN, lymph node.

- FDG—PET—CT imaging is optional in all other cases [III, C].

Differential diagnosis

- Diagnostic algorithms to delineate CUP from specific cancer entities with known primaries can be used [V, B].
- In patients with a prior malignancy, a relapse of this cancer should always be considered [IV, A].
- In individual cases, mutational profiles can provide clues regarding the putative primary [IV, B].

RISK ASSESSMENT

Clinical parameters

Several independent clinical risk factors in CUP have been identified consistently across different studies; first and foremost among them is poor Eastern Cooperative Oncology Group (ECOG) performance status (PS), which reached the highest statistical significance in multivariate risk factor analyses.[29-33] Other independent adverse prognostic factors include male sex,[32,33] unfavourable CUP subtype,[32,34] a higher number of metastatically involved organs,[32,33] the presence of liver metastases[30,35] or visceral metastases[31] and adenocarcinoma histology.[33] Significant independent adverse laboratory parameters comprise elevated alkaline phosphatase (ALP), elevated lactate dehydrogenase (LDH),[30,35] low serum albumin and lymphopenia[30] or elevated neutrophil versus lymphocyte ratio (NLR) as a reflection of the inflammatory state.[31,33] Based on these adverse prognostic factors, numerous clinical risk scores have been proposed.[30,31,33,35] For risk assessment of unfavourable CUP, the authors recommend an easy-to-use two-factor score that combines ECOG PS, as the most robust clinical risk factor, with LDH at first diagnosis (good prognostic group: ECOG PS 0 or 1 and normal LDH; poor prognostic group: ECOG PS >1 or elevated LDH).[35]

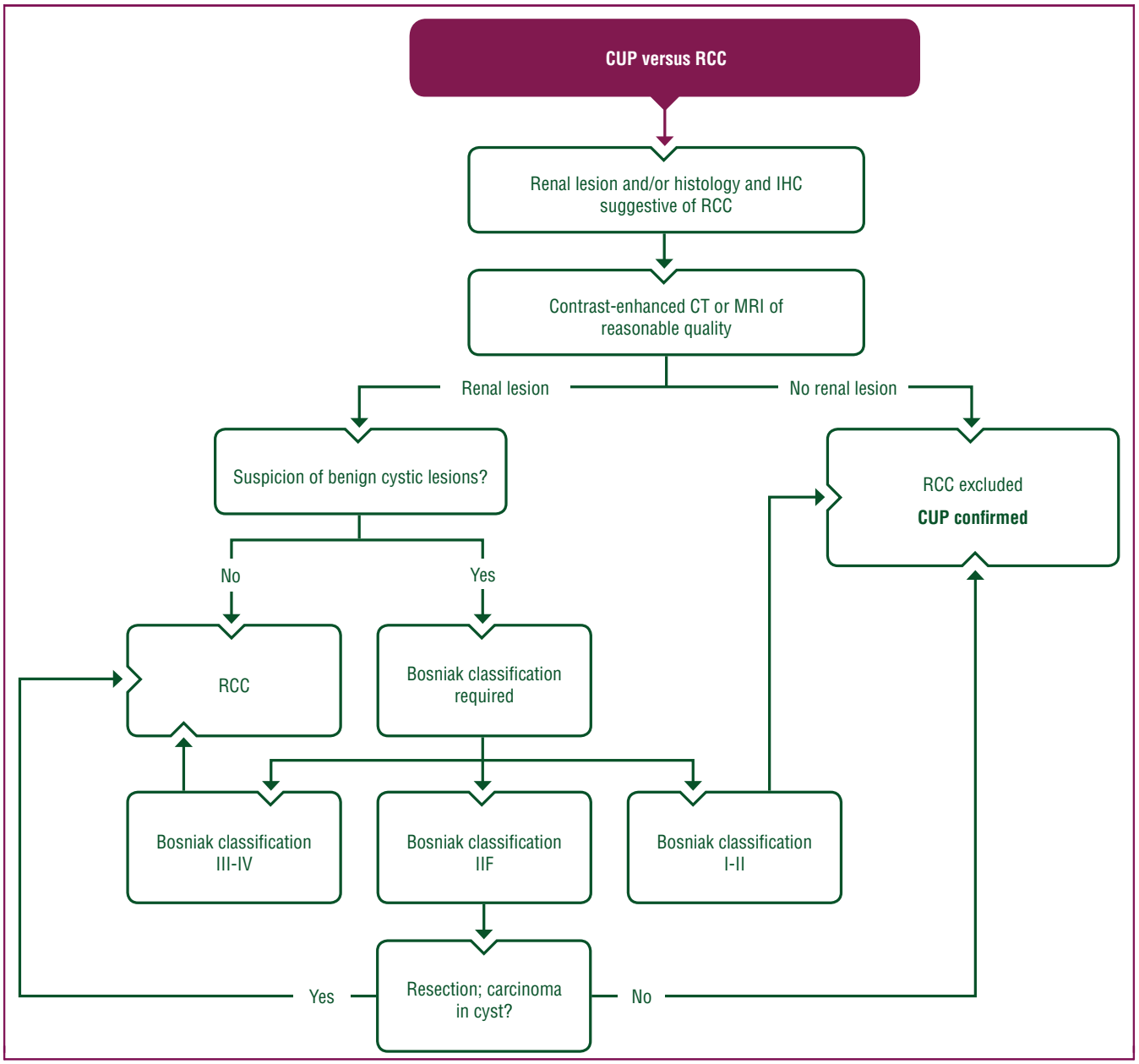

Figure 5. Differential diagnostic algorithm to discriminate between CUP and RCC.
Purple: general categories or stratification; white: other aspects of management.
CT, computed tomography; CUP, cancer of unknown primary; IHC, immunohistochemistry; MRI, magnetic resonance imaging; RCC, renal-cell carcinoma.

Molecular prognostic and predictive markers

Kirsten rat sarcoma virus *(KRAS)* or neuroblastoma RAS viral oncogene homologue (*NRAS*) activation and cyclin-dependent kinase inhibitor 2A (*CDKN2A*) deletion have been shown to confer an independent adverse prognosis by multivariate analysis.[32] Chromosomal copy number losses and deleterious tumour suppressor protein p53 (*TP53*) mutations or deletions of chromosome 17p are associated with poor prognosis in single-site/oligometastatic CUP amenable to localised therapy.[36,37] Neurotrophic tyrosine receptor kinase (*NTRK*) rearrangements predict response to NTRK inhibitors irrespective of the tissue of origin, therefore including CUP.[38,39] Similarly, high TMB and MSI have been established as predictive markers for response to ICI treatment in a tissue-agnostic manner.[40-43] In CUP, higher levels of PD-L1 expression and higher TMB are also associated with better response rates and longer survival in previously treated patients who received nivolumab monotherapy.[44] Therefore, beyond panel NGS and MSI status at initial diagnosis, PD-L1 and TMB may be determined when ICI treatment is considered.

Recommendations

- In patients with unfavourable CUP, prognosis should be assessed by a risk score combining ECOG PS and serum LDH levels [IV, A].
- Determination of MSI, PD-L1 and TMB status is generally recommended when ICI treatment is considered [III, B].

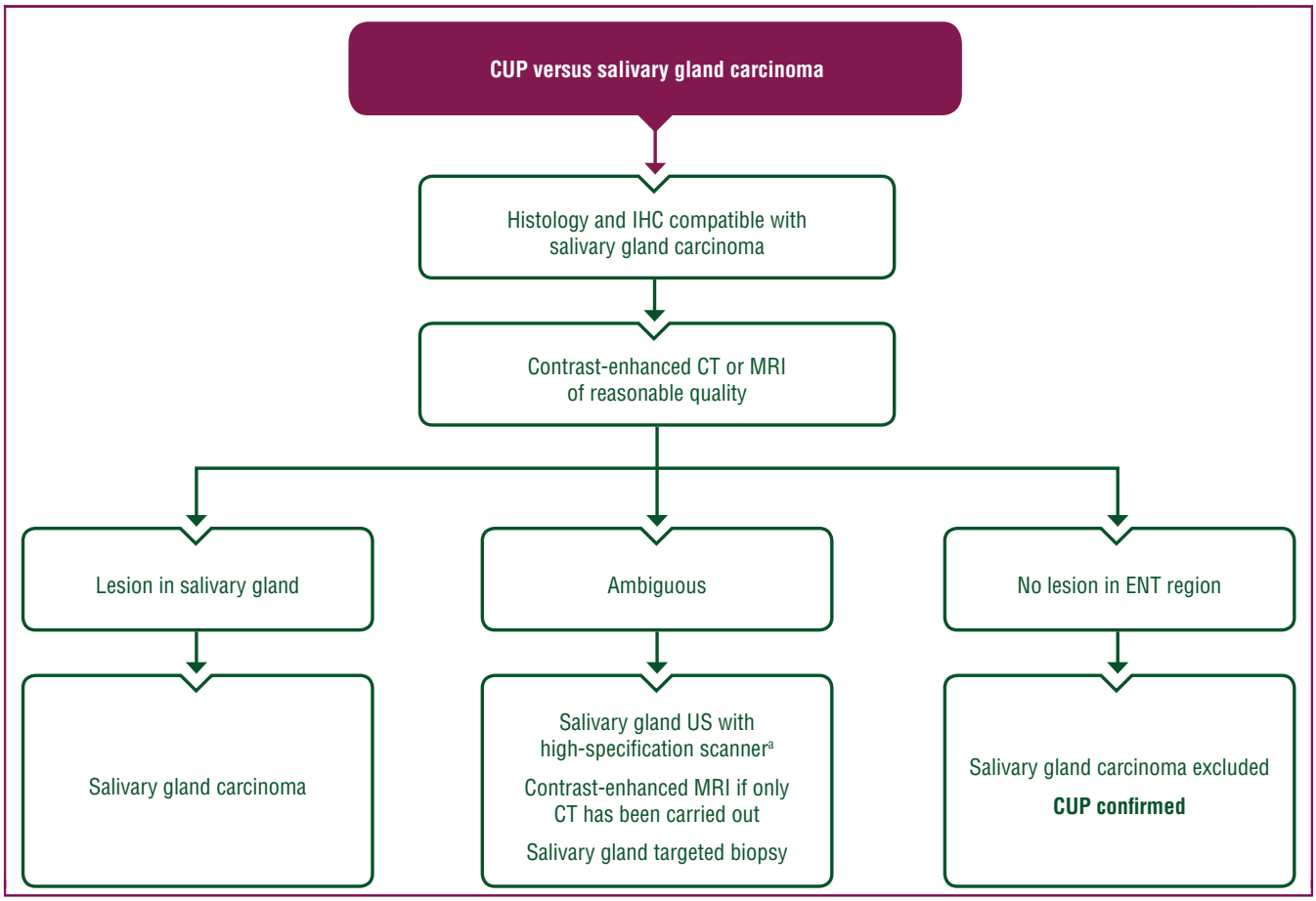

Figure 6. Differential diagnostic algorithm to discriminate between CUP and salivary gland carcinoma.
Purple: general categories or stratification; white: other aspects of management.
2D, two dimensional; CT, computed tomography; CUP, cancer of unknown primary; ENT, ear nose and throat; FPS, frames per second; IHC, immunohistochemistry; MRI, magnetic resonance imaging; US, ultrasound.
[a]High specification includes: broad band linear array transducer with a frequency range of 5-20 MHz suitable for vascular superficial, superficial small parts and elastography applications; electronic phased array colour Doppler system with minimum 50 000 digital processing channels and ≥256 grey shades for sharp contrast resolution; frame rate of ≥500 FPS; gain control for an additional level of flexibility to image quality control; real-time high-frequency 2D imaging for higher resolution and low-frequency Doppler for higher sensitivity; tissue harmonic imaging in power Doppler imaging mode for improved sensitivity and specificity in differentiating blood from tissue.

CLASSIFICATION AND MANAGEMENT OF CUP

Classification and management of favourable CUP

Besides single-site and oligometastatic CUP, favourable CUP is defined by obvious analogies to certain cancers with a known primary. It is generally recommended that these patients receive site-specific treatment tailored to the presumed primary site as this is associated with a more favourable prognosis compared with the vast majority of patients with CUP who are collectively grouped as 'unfavourable'.[45] Around 20% of patients belong to one of the favourable CUP subtypes. The following favourable subtypes should be recognised (see also Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2022.11.013):

- Single metastatic deposit or oligometastatic disease amenable to local ablative treatment (single-site or oligometastatic CUP)
- Women with isolated axillary lymph node metastases (breast-like CUP)
- Women with peritoneal carcinomatosis of a serous papillary adenocarcinoma (ovary-like CUP)
- Squamous-cell carcinoma involving non-supraclavicular cervical lymph nodes (head and neck-like CUP)
- Men with blastic bone metastases and/or IHC or serum PSA expression (prostate-like CUP)
- Adenocarcinoma with colorectal IHC (CK7-negative, CK20-positive, CDX2-positive) or molecular profile (colon-like CUP)
- Carcinoma with renal-cell histological and immunohistochemical profile (renal-like CUP)

The formerly recognised favourable neuroendocrine carcinoma subtypes[45] are not considered in the current guideline. This is because in neuroendocrine malignancies, an elusive primary is a common finding. Neuroendocrine carcinomas should therefore be classified according to the increasingly sophisticated and therapy-relevant subclassification of neuroendocrine malignancies, irrespective of the presence of an obvious primary tumour.

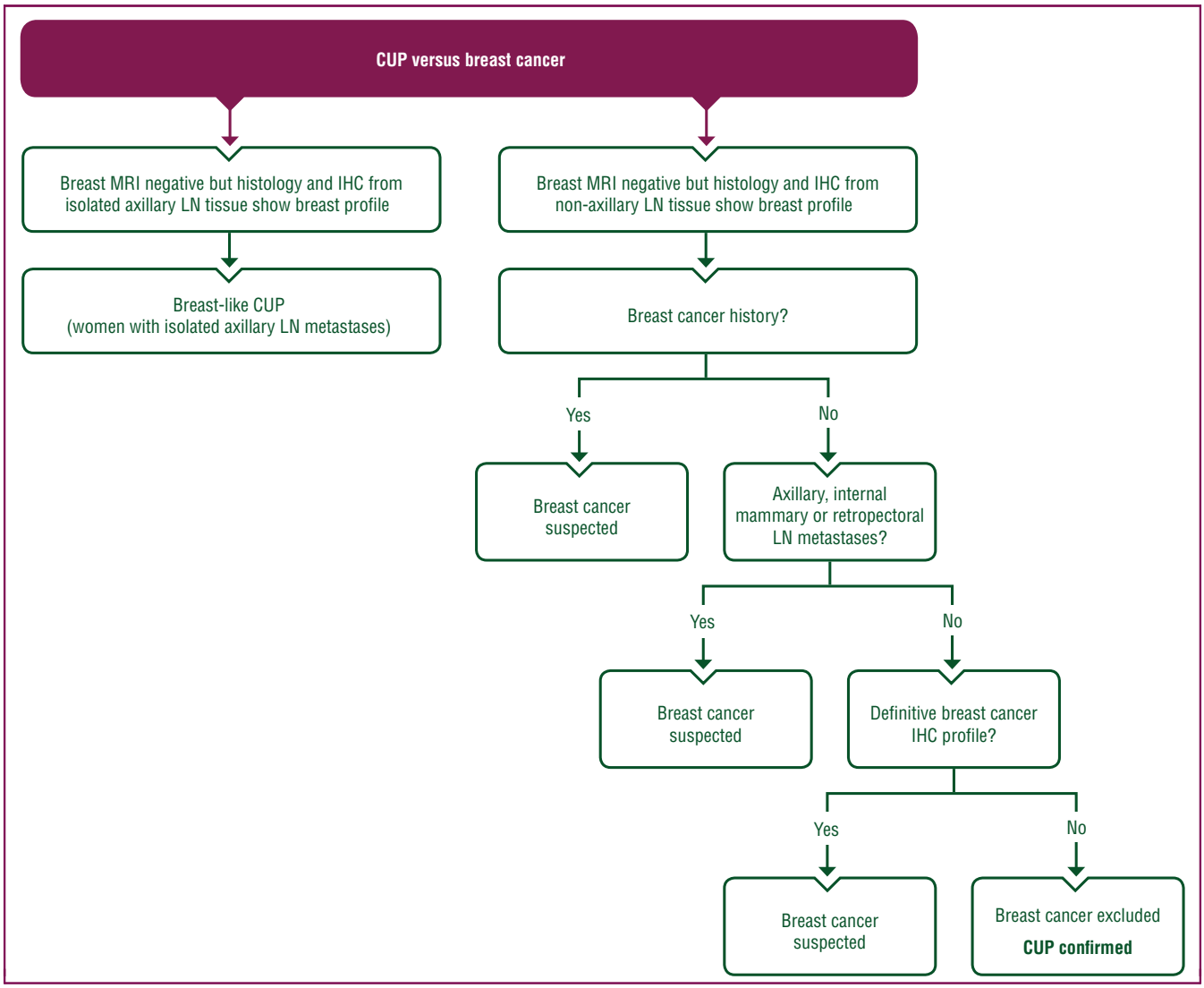

Figure 7. Differential diagnostic algorithm to discriminate between CUP and breast cancer.
Purple: general categories or stratification; white: other aspects of management.
CUP, cancer of unknown primary; IHC, immunohistochemistry; LN, lymph node; MRI, magnetic resonance imaging.

The former favourable subtype known as 'poorly differentiated carcinoma with midline distribution', which was already absent from the 2015 European Society for Medical Oncology (ESMO) CUP guideline, should not be used anymore. Historically, many of these patients actually had extragonadal germ cell tumours. Also, some of these young patients may have an underdiagnosed and aggressive NUT midline carcinoma. Thus, full consideration should be given to these differential diagnoses in male patients with young age and midline metastatic distribution with or without elevated β-hCG and/or AFP.

Likewise, 'squamous-cell carcinoma with inguinal lymph nodes' has not been acknowledged as a distinct favourable subtype since it belongs to the subgroup of single-site and/or oligometastatic CUP, whose therapeutic principles equally apply.

Single metastatic deposit or oligometastatic disease amenable to local ablative treatment (single-site and/or oligometastatic CUP). In the 2015 ESMO guideline, 'CUP with a single metastatic deposit' was already recognised as a distinct favourable CUP subtype.[45] However, patients with oligometastatic disease exceeding the 'single metastatic deposit' definition, who are still potentially amenable to ablative surgery and/or radiotherapy (RT), also seem to benefit from this treatment strategy.[36] The authors have therefore redefined localised CUP by substitution of 'single metastatic deposit' with 'single metastatic deposit or oligometastatic disease amenable to local ablative treatment' as a distinct favourable CUP subtype. In view of the need for standardisation and despite the scarcity of data in CUP, the authors suggest the following oligometastasis definition analogous to other cancer entities:[22,46]

- Local ablative treatment of all lesions by surgery and/or radiotherapy is deemed feasible.
- Oligometastatic state has been confirmed by imaging including PET—CT and brain MRI.
- Number of metastases does not exceed five.
- No involvement of a diffuse organ such as malignant pleural, pericardial, peritoneal or leptomeningeal carcinomatosis.

Local treatment strategies have proven beneficial, with long-term survival observed in a few distinct clinical scenarios.[34] Accordingly, localised treatment is generally recommended as the standard of care in the following situations: single brain metastases,[47,48] squamous-cell carcinoma involving cervical lymph nodes (excluding supraclavicular nodes)[49] as well as inguinal and iliac lymph nodes.[50]

Furthermore, beyond these well-defined scenarios, the use of local surgery and/or RT has opened up the prospect of long-term remission or even cure.[36] Therefore, in single-site or oligometastatic disease, localised treatment is generally recommended when technically feasible and after a careful benefit—risk assessment, irrespective of histology and organs involved by metastases. Limited data suggest that patients with two or more metastases might also benefit from local ablative treatment.[36] The acceptable upper limit regarding the number of metastases, metastatically involved organs and metastasis size is elusive but should not exceed the definition of oligometastatic disease described previously. In order to comply with this definition, it is suggested that local ablative treatment is preceded by a search for additional metastatic sites, which should include the use of PET—CT and brain MRI.[22] There is insufficient evidence to provide recommendations regarding the treatment modality (surgery versus RT) or the administration of (neo)adjuvant chemotherapy (ChT) or immunotherapy. Local recurrences and newly arising metastases at other sites are observed at a similar frequency following local ablative treatment. Local recurrences are frequently amenable to further local ablative treatment.[36]

Women with isolated axillary lymph node metastases (breast-like CUP). This favourable subtype is defined as isolated axillary lymph node metastases in females, an (immuno)histology pattern compatible with breast cancer and the absence of an ipsilateral mammary carcinoma. In several retrospective analyses, breast MRI has been shown to identify the primary in around two-thirds of patients with negative clinical examination and negative mammography,[51] and is therefore mandatory before reaching the diagnosis of breast-like CUP. The lymph node metastasis specimen should be tested for estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) status.[52]

Patients with breast-like CUP should be managed under the presumption of an occult breast primary and thus receive treatment according to primary breast cancer protocols.[53] There is broad consensus regarding axillary lymph node dissection. Additional ipsilateral breast-targeting treatment with either mastectomy or RT has been shown to reduce the risk of recurrence and improve survival and is therefore recommended. However, there is no definitive consensus regarding whether surgery or RT should be the preferred local treatment. Breast RT after axillary lymph node dissection appears to be at least equivalent to mastectomy with respect to locoregional recurrence and recurrence-free survival, implying that patients could be spared surgery.[54-57] When RT is chosen, there is also no consensus as to whether the supraclavicular or internal mammary regional lymph nodes should be included in the radiation field.[55,57] Systemic therapy should be given analogous to the equivalent nodal-positive breast cancer. Given the rapid evolution of systemic therapy in breast cancer, the authors recommend that systemic therapy use in patients with breast-like CUP should be aligned with the current treatment standards for breast cancer.

Women with peritoneal carcinomatosis of a serous papillary adenocarcinoma (ovary-like CUP). This favourable subtype is defined as (isolated) peritoneal carcinomatosis in females with serous or undifferentiated adenocarcinoma histology; the absence of an ovary, fallopian tube or uterine primary cancer[58] and possibly identical to primary peritoneal serous carcinoma.[59] IHC serum and genetic analysis frequently reveals elevated CA125 and *BRCA1/2* mutations consistent with the profile of ovarian cancer.[60] Thus, analogous to ovarian cancer, germline and somatic *BRCA1/2* mutation testing should be carried out.[61] Treatment may be similar to that for stage III/IV ovarian cancer, including surgical debulking for cytoreduction[62] followed by carboplatin—paclitaxel ChT (the addition of bevacizumab is optional)[61] and poly (ADP-ribose) polymerase (PARP) inhibitor maintenance therapy in responding patients.[63]

Squamous-cell carcinoma involving non-supraclavicular cervical lymph nodes (head and neck-like CUP). This favourable subtype is defined as squamous-cell carcinoma in non-supraclavicular cervical lymph nodes without a detectable mucosal primary. Attempts to identify the primary tumour should include flexible endoscopy, contrast-enhanced CT and/or—preferably—MRI of the head and neck as well as FDG—PET. In cases where the primary has remained elusive after these examinations, panendoscopy with biopsies of the naso-, hypo- and oropharynx, as well as bilateral tonsillectomy, should be carried out. Carcinoma tissue should be tested for p16 expression and, in case of positivity, for human papillomavirus (HPV) status.[64] The Epstein—Barr virus (EBV) status should also be determined, and PD-L1 expression may be analysed in patients with relapsed disease or distant metastases.[64] Based on expert consensus, treatment recommendations for head and neck-like CUP have already been described and should be considered as the therapeutic standard.[24,64] Broadly, primary surgery by neck dissection and/or RT ± ChT are recommended as first-line treatment in non-distant metastatic

disease. Patients with small-volume neck disease should receive either surgery or RT ± ChT, whereas both options should be combined in large-volume disease.

Men with blastic bone metastases and/or IHC or serum PSA expression (prostate-like CUP). Blastic bone metastases in the pelvis and lower spine and/or high serum concentrations or IHC expression levels of PSA in males are quite similar to findings in metastatic prostate cancer. It is therefore suggested to align the diagnostic procedures and therapy for prostate-like CUP to metastatic prostate cancer guidelines.[65]

Adenocarcinoma with colorectal IHC (CK7-negative, CK20-positive, CDX2-positive) or molecular profile (colon-like CUP). Colon-like CUP is defined as adenocarcinoma histology compatible with a GI primary, predominant intra-abdominal metastases, a CK7-negative, CK20-positive, CDX2-positive IHC signature characteristic of CRC and negative colonoscopy.[66,67] Gene expression-based colon-like prediction appears to be less strict than IHC criteria.[67] Retrospective data suggest that patients with colon-like CUP treated with site-specific CRC ChT regimens [i.e. 5-fluorouracil—leucovorin—oxaliplatin (FOLFOX) or 5-fluorouracil—leucovorin—irinotecan (FOLFIRI)] achieve response and survival rates similar to those observed in patients with metastatic CRC.[66,67] However, these data are from small patient numbers and additional prospective validation is necessary to substantiate these findings. Nevertheless, treatment analogous to metastatic CRC is generally recommended in colon-like CUP. Accordingly, in patients with microsatellite-stable (MSS) tumours, 5-fluorouracil (5-FU)-based regimens (i.e. FOLFOX or FOLFIRI) may be administered, which can be combined with bevacizumab or, alternatively, an anti-epidermal growth factor receptor (EGFR) antibody in patients with unmutated *KRAS* or *NRAS*. Patients receiving 5-FU should be tested for the lack of dihydropyrimidine dehydrogenase (DPD) before starting treatment.[68] In patients with MSI-high (MSI-H) tumours, ICIs should be used.[69] As CK20 expression is reduced or absent in MSI-H CRCs,[70] the diagnosis of colon-like CUP may also be considered in patients with CK20-negative, MSI-H CUP otherwise fitting colon-like criteria.

Carcinoma with renal-cell histological and immunohistochemical profile (renal-like CUP). The diagnostic algorithm shown in Figure 5 outlines the differential diagnosis between kidney cancer and CUP in patients with renal lesions. However, a small subset of patients appear to display a histological and immunohistochemical profile truly compatible with renal-cell carcinoma in the absence of any renal lesion, with documented responses to renal-specific treatment supporting the accuracy of the presumption of a renal primary.[71,72] In view of the far-reaching therapeutic consequences of applying only tyrosine kinase inhibitor (TKI)- and ICI-based treatments, this subgroup may constitute a novel and distinct favourable CUP subset. Its definition relies on a histology and IHC profile strictly aligned with kidney cancer, such as clear cell or papillary histology (which appears overrepresented) with comprehensive immunostaining for the renal markers PAX8, PAX2, racemase and CD10. Optionally, treatment according to the rapidly evolving kidney cancer protocols may be justifiable,[71,72] with ICIs offering a broader coverage across the malignancy spectrum in particularly ambiguous cases.

Management of unfavourable CUP

ChT. Patients with unfavourable CUP are defined as those who do not belong to any of the aforementioned favourable subgroups and constitute ∼80% of all patients with CUP. According to data from small clinical studies, they have a dismal prognosis despite treatment with a variety of combination ChTs.[29] Platinum-based doublet ChT is generally recommended as the standard of care, although no randomised trials have been conducted to demonstrate superiority over best supportive care.[73] Modest survival benefit and symptom palliation with preservation of quality of life are currently the only realistic aims of therapy for these patients, although rare cases of cure have been reported.[74] Consequently, low-toxicity patient-convenient ChT regimens should be administered to reasonably fit, poor-risk patients (see Supplementary Table S9, available at https://doi.org/10.1016/j.annonc.2022.11.013).

Clinical trials conducted to-date (mostly randomised phase II trials) have evaluated regimens comprising platinum salts, taxanes, gemcitabine, vinca alkaloids or irinotecan, with no evidence of statistically significant superior efficacy demonstrated for any of the protocols.[73,75-79] Generally, platinum-based doublets combined with either a taxane or gemcitabine are widely accepted as the gold standard. Better outcomes were reported with cisplatin—gemcitabine compared with cisplatin alone, although this was not assessed in a large and adequately powered randomised phase III trial.[76] Cisplatin—gemcitabine has also shown a superior efficacy—toxicity ratio compared with cisplatin—irinotecan in a randomised phase II trial.[77] Carboplatin—paclitaxel has demonstrated meaningful activity in CUP as well,[79] although superiority over gemcitabine—vinorelbine did not reach statistical significance with respect to survival or remission in a randomised phase II trial.[78] A prospective, randomised phase III trial of 198 patients comparing gemcitabine—irinotecan with paclitaxel—carboplatin—etoposide reported significantly less toxicity and equal survival rates with the two-drug regimen.[73] As such, doublet ChT regimens are generally recommended as the standard of care, whereas triplet ChT regimens are considered to confer excessive toxicity and are not recommended.

There are no available data regarding the efficacy of different ChT regimes for unfavourable squamous-cell versus adeno-CUP. When extrapolating from other common squamous-cell carcinoma entities, including cervical, head and neck, non-small-cell lung and oesophageal cancer, platinum-based doublet ChT is generally recommended for unfavourable CUP independent of histology.

Although only a few non-ChT drugs have been tested in patients with unfavourable CUP, neither belinostat nor cetuximab have improved on the results demonstrated with carboplatin—paclitaxel in randomised trials and are therefore not recommended.[80,81]

No clinical trial data are available for second-line ChT. Switching between established CUP ChT protocols in progressing patients appears reasonable. Molecular targeted therapy and ICIs may be considered as alternatives. The combination of bevacizumab—erlotinib has shown activity in CUP, with a substantial rate of disease stabilisation also seen in ChT-pre-treated patients, but only 10% of patients reached a partial response.[82]

Site-directed therapy by molecular tissue of origin prediction. Several clinical studies in CUP have used RNA expression- or DNA methylation-based molecular techniques to predict the putative primary, a strategy termed 'tissue of origin' prediction, with subsequent administration of 'site-specific' therapy according to the predicted primary. Despite a promising pilot study,[83] two randomised trials failed to demonstrate superiority of gene expression profiling-based 'site-specific' therapy over standard empiric ChT with either carboplatin—paclitaxel or cisplatin—gemcitabine, respectively.[84,85] Consequentially, no recommendation for the use of gene expression profiling-based 'site-directed' therapy can currently be provided.

Molecular targeted therapy. The mutational profile of unfavourable CUP has been assessed in numerous panel NGS studies to identify targets for molecular therapies.[32,86-90] Beyond *TP53* as the most abundant mutation present in around half of patients, these studies have consistently shown a very heterogeneous mutational landscape with a diverse set of potentially actionable genetic alterations. Discussion of NGS findings in a molecular tumour board is therefore advised. The use of molecular targeted therapies is strongly recommended when the respective compound has received cancer type-agnostic approval, as is currently the case for larotrectinib and entrectinib in *NTRK* fusion-positive cancers.[38,39] Likewise, *BRAF V600E* and RET proto-oncogene (*RET)* can be considered as cancer type-agnostic targets in patients with relapsed or refractory CUP.[91-93] Targeted therapies are also strongly recommended in patients with tumours harbouring a genetic alteration suggestive of a putative primary in which molecular guided therapies are licensed and are the standard of care (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2022.11.013). For example, this currently applies to *EGFR*-mutant as well as *ALK* and *ROS1* fusion-positive tumours, which strongly imply NSCLC as the primary and for which TKIs represent the treatment of choice.[46]

Beyond these recommendations, molecular targeted therapy may be considered in patients harbouring molecular alterations for which approved compounds are available in other cancer entities. Here, ranking of molecular guided therapy depends on the evidence from known primary cancer entities and the respective putative primary. Accordingly, first-line targeted therapy with a BRAF inhibitor appears justified for *BRAF V600E* mutations when lung is the putative primary. Further compounds licensed in non-CUP entities are available for various genetic targets, although evidence in CUP is limited to anecdotal cases.[32,88] Examples include fibroblast growth factor receptor (*FGFR*) fusions, actionable v-erb-b2 avian erythroblastic leukaemia viral oncogene homologue 2 (*ERBB2*) alterations (activating mutations or amplifications), deleterious mutations of *BRCA1/2* or DNA damage repair genes including RAD51 recombinase (*RAD51*) and partner and localiser of *BRCA2* (*PALB2*), activating *KRAS G12C* and phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) mutations as well as MET proto-oncogene, receptor tyrosine kinase (*MET*) amplification. The spectrum of molecular targets is likely to grow in the future.

ICIs. ICI treatment has not yet been established in the general CUP population, although an overall response rate of 22% has been reported in patients with unfavourable CUP who have relapsed or are refractory to first-line ChT.[44] ICIs may be considered for the indications described below.

MSI-H or mismatch repair-deficient CUP. The responsiveness of MSI-H or mismatch repair-deficient (dMMR) tumours to ICIs has been shown across different cancer entities.[41,94-96] Accordingly, pembrolizumab has been granted tumour-agnostic approval from the Food and Drug Administration (FDA) for the second-line treatment of MSI-H or dMMR cancers,[97] which also includes CUP. Accordingly, ICI treatment might be considered as the second-line therapy at the latest for this group.

Based on the superior progression-free survival (PFS) of pembrolizumab over standard-of-care ChT in MSI-H or dMMR CRC,[98] pembrolizumab has been approved by the European Medicines Agency (EMA) and FDA as the first-line treatment in this setting.[67] As it is suggested that treatment of colon-like CUP follows CRC treatment guidelines, pembrolizumab may be used as the first-line treatment in MSI-H or dMMR colon-like CUP.

TMB-high CUP. High TMB represents an established predictor for response to ICI treatment across different cancer entities.[96,99] Accordingly, pembrolizumab is FDA approved for the second-line treatment of TMB-high (TMB-H) cancers [defined as $\geq$10 mutations per megabase (mut/Mb)]. Likewise, nivolumab was more effective in CUP with a high TMB (defined as $\geq$7.75 mut/Mb).[44] Thus, ICI treatment may be considered as the second-line therapy at the latest in TMB-H CUP.

PD-L1-high CUP. High PD-L1 expression has been associated with improved outcomes following ICI treatment across some, but not all, cancer entities.[96,100,101] Similar to other tumour entities, patients with PD-L1-positive CUP tended to achieve a better PFS and overall survival, although this did not reach statistical significance.[44] Accordingly, ICI treatment may be considered as an option in relapsed or refractory unfavourable CUP with high-level PD-L1 expression and no alternative treatment options. It is, however, still unclear

whether the cancer cell-based tumour proportion score (TPS) or the cancer plus cancer environment-based combined positive score (CPS) should be used, and whether cut-offs used should be at 1%, 10% or 50%.

Additional scenarios highly suggestive of a primary cancer in which ICI treatment is established. ICIs may be considered as an option when clinicopathological features imply analogy to a known primary cancer where immunotherapy is an established treatment option, as is the case with NSCLC, head and neck squamous-cell, urothelial or gastroesophageal carcinomas, among others. So far, no data are available to evaluate the benefit—risk profile for the addition of an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody, such as ipilimumab, to anti-PD-(L)1 antibodies.

Peritonectomy

Isolated peritoneal carcinomatosis is, in principle, amenable to cytoreductive surgery ± hyperthermic intraperitoneal ChT (HIPEC) as local therapy. Recommendations in CUP mostly rely on cross-entity analogies[102] and are hampered by the uncertainty of a potentially undetected primary persisting after local peritoneal treatment.

A randomised study conducted in patients with colon cancer and peritoneal carcinomatosis treated with cytoreductive surgery showed a lack of therapeutic benefit and excessive toxicity with the addition of HIPEC.[103] However, outcomes with cytoreductive surgery alone were considered encouraging. Likewise, cytoreductive surgery is standard in ovarian cancer, with some data pointing to a possible beneficial effect for the addition of HIPEC in this entity both in the first-line[104] and relapsed settings.[105] In patients with (i) ovary-like CUP and (ii) mucin-producing or signet ring adenocarcinoma suggesting colon-like CUP and isolated peritoneal carcinomatosis, small retrospective analyses on a total of 40 patients and a few additional case reports suggest prolonged survival times after cytoreductive surgery with peritonectomy.[106-108] Accordingly, for patients with ovary- or colon-like CUP and isolated peritoneal carcinomatosis, assessment for peritonectomy might be an option, whereas additional HIPEC is not recommended as there are no data available for this procedure in CUP. Also, peritonectomy is not recommended in unfavourable CUP.

In view of the associated morbidity and mortality risks, candidates for cytoreductive surgery should be carefully and strictly selected in experienced referral centres based on a good PS, a low burden of peritoneal involvement [as assessed by the peritoneal cancer index (PCI)] and the exclusion of any additional, extraperitoneal metastases.[102,105] The principles of completeness of cytoreduction as the decisive step should be meticulously adhered to, as done in other cancer entities.

Recommendations

Classification and management of favourable CUP

- The formerly recognised favourable CUP subtypes with neuroendocrine differentiation are no longer viewed as CUP subtypes and should be treated according to guidelines for neuroendocrine malignancies [IV, B].
- The formerly recognised favourable CUP subtype termed 'poorly differentiated carcinoma with midline distribution' is no longer viewed as a CUP subtype. Historically, many of these patients actually had extragonadal germ cell tumours [IV, B]. Also, some of these young patients may have an underdiagnosed and aggressive NUT midline carcinoma [IV, B].
- The former favourable subtype of 'localised CUP' has been redefined to also include oligometastatic disease amenable to local ablative treatment [IV, B].
- In patients with single-site or oligometastatic CUP, localised treatment with ablative surgery and/or RT is suggested [IV, B].
- Before localised treatment, patients with single-site or oligometastatic CUP should receive PET—CT and brain MRI [IV, B].
- In general, patients with one of the six favourable CUP subtypes defined by analogy to cancers with a known primary should be treated with site-specific therapy [III, B].
- Breast MRI should be carried out and demonstrate negative results before reaching the diagnosis of breast-like CUP [IV, A].
- In addition to systemic therapy, breast treatment with RT (or alternatively surgery) is recommended in breast-like CUP [IV, A].
- Renal-like CUP may constitute a novel favourable CUP subset that benefits from TKI and ICI treatments [V, C].

Management of unfavourable CUP

- For patients with newly diagnosed unfavourable CUP and adequate PS, platinum-based doublet ChT is generally recommended as the standard of care [III, B].
- There is currently no high-level evidence that gene expression profiling-directed therapy leads to an improvement in patient outcomes. Consequently, such strategies are not recommended outside of clinical trials [II, D].
- For patients with ovary-like and colon-like CUP and isolated peritoneal carcinomatosis, assessment for peritonectomy without HIPEC might be an option [IV, C].
- In view of the ongoing poor prognosis and lack of high-level clinical evidence in patients with CUP, inclusion in clinical trials is encouraged [V, A].

Molecular targeted treatment

- In patients with *NTRK* fusion-positive CUP, treatment with an NTRK inhibitor is recommended [III, A].
- In *EGFR*-mutant as well as *ALK* and *ROS1* fusion-positive CUP, treatment with the respective TKI is recommended [II, A].
- For patients with *BRAF V600E* mutations, treatment with a BRAF inhibitor from second-line onwards may be an option; BRAF inhibitors may be considered for first-line treatment when lung is the putative primary [III, C].
- Limited evidence suggests that compounds targeting additional genetic alterations licensed in non-CUP

entities may be an option for patients with CUP harbouring these genetic alterations [III, C].
- If no clinical trials are available in the second-line setting, molecular targeted treatments and ICIs may be considered as alternative options [V, C].

Immunotherapy

- Patients with MSI-H or dMMR unfavourable CUP may receive ICI treatment in the second-line setting [III, B].
- Patients with MSI-H or dMMR colon-like CUP may receive ICI treatment in the first-line setting [III, B].
- Patients with TMB-H unfavourable CUP may be considered for ICI treatment in the second-line setting [III, B].
- For patients with PD-L1-high unfavourable CUP, second-line ICI treatment may be an option [III, C].

FOLLOW-UP AND LONG-TERM SURVIVORSHIP

In patients with unfavourable CUP who are receiving treatment, and after treatment discontinuation, restaging and follow-up by CT or MRI should be carried out at 3-month intervals provided that the patient is deemed fit for further therapy.

Long-term survivors exist among patients with single-site or oligometastatic CUP who have received ablative surgery/RT and those with other favourable CUP subtypes such as women with isolated axillary nodal metastases.[34] Long-term survival for up to 50 months has also been documented among patients with unfavourable CUP, although this is rare.[34]

For patients with single-site or oligometastatic CUP who have received local ablative treatment, no consensus guidelines for routine follow-up have been established. Since early diagnosis of local relapse might enable additional local ablative treatment,[35] follow-up with CT or MRI should be carried out at 3-6 month intervals during the first 2 years, followed by 6-12 month intervals in years 3-5.

In view of the elevated risk for secondary malignancies, long-term CUP survivors may adhere to cancer screening guidelines recommended for the general population, which includes screening for colon, breast, prostate and skin cancer. If family history and/or molecular work-up have raised the suspicion of a germline cancer-predisposing mutation, genetic counselling and testing should be offered. If confirmed, a germline cancer-predisposing mutation should warrant additional screening.

Recommendation

- Follow-up by CT or MRI may be carried out at 3-month intervals, provided that the patient is deemed fit for further therapy [IV, B].

METHODOLOGY

This Clinical Practice Guideline (CPG) was developed in accordance with the ESMO standard operating procedures for CPG development (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S10, available at https://doi.org/10.1016/j.annonc.2022.11.013.[109,110] Statements without grading were considered justified standard clinical practice by the authors. Future updates to this CPG will be published on esmo.org as a Living GL version or an eUpdate, to be made available at: https://www.esmo.org/guidelines/guidelines-by-topic/cancers-of-unknown-primary-site.

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