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Metastatic Tumors of Unknown Primary (Muos) Definition, Frequency and General Considerations

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ABSTRACT

Metastatic tumors of unknown primary (MUOs) present a diagnostic challenge due to the absence of an identifiable primary tumor site. The diagnostic approach for MUOs involves a comprehensive evaluation that includes clinical assessment, imaging studies, laboratory tests, and tissue sampling. Various imaging modalities, such as CT, MRI, PET scans, and ultrasound, are used to assess the extent of metastasis and identify potential primary tumor sites. Treatment options for MUOs include systemic therapies like chemotherapy, targeted therapy, immunotherapy, and hormone therapy, along with supportive care measures. Prognosis varies widely and is influenced by factors such as the extent of metastasis, tumor characteristics, treatment response, and patient factors [1].

Artificial intelligence (AI) has the potential to aid in diagnosis and management through image analysis, predictive modeling, pathology analysis, and risk assessment. The integration of AI requires careful validation and collaboration between healthcare professionals and AI experts. A multidisciplinary approach is crucial for optimal management of MUOs, and ongoing research aims to enhance diagnostic methods, treatment strategies, and prognostic models.

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Introduction

Metastatic tumors of unknown primary (MUOs) refer to cancerous tumors that have spread to other parts of the body without a clear identifiable origin in the primary site. These tumors are often detected when secondary tumors are found but the primary tumor remains undetected despite thorough investigation. Here are some general considerations:

Definition: MUOs are characterized by the presence of metastatic cancer cells in different organs or tissues without a known primary tumor site. It's challenging to determine the primary source due to the absence of obvious symptoms or detectable lesions.

Frequency: MUOs account for approximately 3-5% of all cancer diagnoses. The frequency may vary depending on factors like the diagnostic criteria, available medical technology, and patient population.

Diagnostic challenges: Identifying the primary tumor site in MUOs can be complex and require extensive diagnostic tests. These tests may include imaging scans, biopsies, molecular profiling, and immunohistochemistry, among others. Despite advancements in diagnostic techniques, determining the primary tumor remains elusive in some cases.

Treatment considerations: Treatment for MUOs involves managing the metastatic disease rather than targeting the primary tumor. Therapeutic approaches include systemic treatments such as chemotherapy, targeted therapy, and immunotherapy. The choice of treatment depends on factors such as the site of metastasis, tumor characteristics, and the patient's overall health.

Prognosis: The prognosis for MUOs varies depending on various factors, including the extent of metastasis, the response to treatment, and the individual patient's characteristics. Generally, the prognosis tends to be less favorable compared to cases with identifiable primary tumors, as the absence of knowledge about the primary site complicates treatment decisions [2,3].

Algorithm

While the diagnostic process for metastatic tumors of unknown primary (MUOs) can be complex and may vary depending on specific circumstances, here's a general diagnostic algorithm that healthcare professionals may follow:

Comprehensive history and physical examination: The initial step involves taking a detailed medical history and conducting a thorough physical examination to gather information about symptoms, risk factors, and potential clues to the primary tumor site.

Imaging studies: Imaging techniques such as computed tomography (CT) scans, magnetic resonance imaging (MRI), positron emission tomography (PET) scans, and sometimes bone scans are utilized to identify the locations and extent of metastatic lesions.

Histopathological examination: Biopsies or fine-needle aspirations are performed on accessible metastatic lesions to obtain tissue samples. These samples are then analyzed by pathologists to determine the type of cancer cells and their characteristics.

Immunohistochemistry (IHC): Immunohistochemical staining techniques are employed to identify specific proteins or markers expressed by the tumor cells. This helps narrow down the potential primary tumor sites by comparing the immunoprofile of the metastatic tumor with known primary tumors.

Molecular profiling: Molecular testing, such as next-generation sequencing or gene expression profiling, may be conducted on the tumor tissue to identify specific genetic mutations or gene expression patterns. This information can provide further insights into the origin of the tumor.

Specialized investigations: In certain cases, specialized investigations like endoscopy, bronchoscopy, or mammography may be performed to explore potential primary tumor sites based on the patient's symptoms or initial findings.

Multidisciplinary discussion: A multidisciplinary team, which may include medical oncologists, pathologists, radiologists, and other specialists, reviews all available data to discuss and interpret the findings. They collectively contribute to formulating the most appropriate diagnostic and treatment plan [4].

Value of personal, family history and current illness. Signs and symptoms

Personal, family history, and current illness information are valuable components in the diagnostic process for metastatic tumors of unknown primary (MUOs). They provide important insights that can help guide investigations and narrow down potential primary tumor sites. Here's why they are significant:

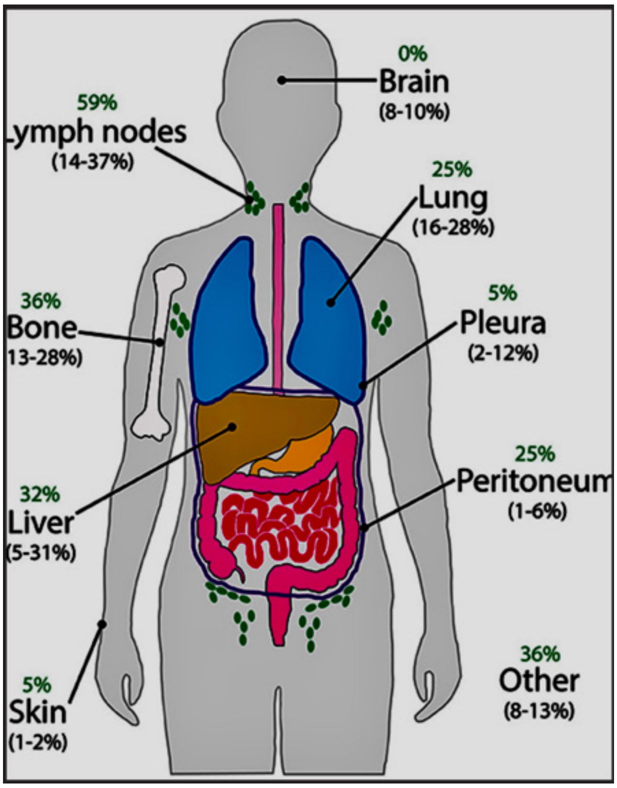
Personal history: A thorough understanding of a patient's personal medical history is crucial. It helps identify any past diagnoses, surgeries, or treatments that may be relevant to the current condition. Previous exposure to carcinogens, occupational hazards, or radiation therapy can also provide clues to potential primary tumor sites. Additionally, information about previous symptoms or health issues that might have been overlooked can be valuable in uncovering a hidden primary tumor.

Family history: Family history plays a role in assessing the genetic predisposition to certain cancers. The presence of specific cancer types or patterns of cancer occurrence in close relatives may indicate a hereditary component. This information helps determine if genetic testing or additional screening measures are necessary, which can aid in identifying the primary tumor site.

Current illness: Detailed information about the current illness, including the nature and duration of symptoms, can provide important clues. Symptoms may vary depending on the location and extent of metastasis. For example, bone pain, cough, or shortness of breath may suggest involvement of the skeletal system, lungs, or other organs. Neurological symptoms, jaundice, or gastrointestinal issues may indicate involvement of the central nervous system, liver, or digestive system, respectively. These symptom patterns help direct further investigations and imaging studies.

Signs and symptoms: Specific signs and symptoms associated with MUOs can vary widely depending on the organs involved and the extent of metastasis. Some common signs and symptoms may include unexplained weight loss, fatigue, pain or discomfort in various areas, enlarged lymph nodes, abnormal laboratory findings, or the presence of distinct physical exam findings. These manifestations are important clinical indicators that guide diagnostic tests and imaging studies.

Incidence by organ (Figure 1)



Role of the laboratory, value of tumor markers, genetic and molecular studies. Pathological Anatomy and immunohatochemistry studies (5)

Biopsy plays a crucial role in the diagnostic evaluation of metastatic tumors of unknown primary (MUOs). It involves obtaining a sample of tissue or cells from a suspicious lesion to examine them under a microscope and perform additional tests. Different types of biopsies can be employed depending on the location, accessibility, and characteristics of the lesion. Here's an overview of common biopsy techniques:

Fine needle aspiration (FNA): FNA involves using a thin needle to extract a small sample of cells or fluid from a suspicious lesion. It is often used when the lesion is easily accessible, such as superficial nodules or masses. FNA provides cellular material for cytological analysis and can yield valuable information about the type of cells present in the lesion.

Core needle biopsy: Core needle biopsy involves using a larger needle to obtain a small cylinder-shaped tissue sample. It is typically performed under imaging guidance, such as ultrasound or CT, to target deeper lesions. Core biopsies provide larger tissue samples, allowing for more accurate histopathological evaluation and additional ancillary studies, including immunohistochemistry and molecular profiling.

Surgical biopsy: Surgical biopsy involves removing a larger portion of tissue through a surgical procedure. It may be necessary

when the lesion is not amenable to FNA or core biopsy, or when a larger tissue sample is needed for comprehensive analysis. Surgical biopsies provide adequate tissue for extensive histopathological examination, including evaluation of tissue architecture, invasion patterns, and potential ancillary studies.
Liquid Biopsy:

Tumor Heterogeneity: MUOs often exhibit significant tumor heterogeneity, making it challenging to identify the primary tumor site. Liquid biopsy provides a non-invasive method to analyze circulating tumor DNA (ctDNA) or other tumor-derived components in the blood, which can help identify genetic alterations or biomarkers associated with the tumor. This can provide insights into the molecular landscape of the tumor and aid in identifying potential treatment targets.

Monitoring Disease Dynamics: Liquid biopsy allows for serial monitoring of the tumor's genetic profile and can provide real-time information on tumor dynamics and treatment response. It can help assess treatment efficacy, detect minimal residual disease, and identify emerging resistance mechanisms. This information can guide treatment modifications and improve patient management over time.

The choice of biopsy technique depends on several factors, including the location and accessibility of the lesion, the expertise of the healthcare team, and the specific goals of the diagnostic evaluation. In some cases, multiple biopsy techniques may be utilized to obtain complementary information or to sample different lesions [6].

Role of the biopsy. Puncture, cytology, surgical biopsy, fine needle aspiration

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Liquid biopsy complement each other in MUOs. Liquid biopsy, on the other hand, provides a non-invasive approach for monitoring disease dynamics, detecting changes in the tumor's genetic profile, and identifying potential resistance mechanisms [7].

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Conventional radiology, contrast studies, magnetic resonance imaging, computed tomography, pet scan

The choice of imaging modality for evaluating metastatic tumors of unknown primary (MUOs) depends on several factors, including the clinical scenario, suspected sites of metastasis, and available resources. Each imaging technique has its strengths and limitations. Here's a brief overview of commonly used imaging modalities:

Conventional radiology: Conventional radiography (X-rays) can be useful in detecting certain bone lesions or assessing lung pathology. It is a relatively simple and cost-effective imaging tool, but it may have limited sensitivity for detecting small or subtle lesions.

Contrast studies: Contrast studies, such as barium studies for the gastrointestinal tract or intravenous contrast-enhanced studies, can provide detailed images of specific anatomical regions. They are particularly useful for evaluating the gastrointestinal system, urinary tract, or blood vessels.

Magnetic Resonance Imaging (MRI): MRI uses a strong magnetic field and radio waves to produce high-resolution images of soft tissues. It is especially valuable for evaluating the brain, spinal cord, pelvis, and soft tissues. MRI provides excellent soft tissue contrast and can detect small lesions. Additionally, functional MRI techniques like diffusion-weighted imaging (DWI) can help identify areas of increased cellular activity.

Computed Tomography (CT): CT scans use X-rays and computer processing to create cross-sectional images of the body. CT is widely used in MUO evaluations due to its ability to provide detailed information about various organs and detect both small and large lesions. It is particularly valuable for assessing the chest, abdomen, and pelvis.

Positron Emission Tomography (PET) Scan: PET scans involve injecting a radioactive tracer that highlights areas of increased metabolic activity. By combining PET with CT (PET/CT), physicians can correlate metabolic information with anatomical images, allowing for more accurate localization of lesions. PET/CT is valuable in identifying areas of increased glucose uptake, which can indicate the presence of active tumor cells [8].

In Positron Emission Tomography (PET) scans, radioactive substances known as radiotracers or radiopharmaceuticals are used to visualize metabolic activity in the body. The most commonly used radiotracer in PET imaging is fluorodeoxyglucose (FDG). FDG is a radioactive form of glucose that contains a positron-emitting isotope of fluorine (F-18).

The choice of FDG as the radiotracer is due to its ability to reflect the increased glucose uptake and metabolism in actively metabolizing cells, including cancer cells. Cancer cells often exhibit increased glucose metabolism compared to surrounding normal cells. By injecting FDG into the body, it is taken up by cells, including cancer cells, and emits positrons as it undergoes decay. The emitted positrons interact with electrons in the tissue, resulting in the emission of two opposing gamma rays. These gamma rays are detected by the PET scanner, allowing for the reconstruction of images that highlight areas of increased glucose uptake.

FDG-PET scans are valuable in detecting and localizing areas of increased metabolic activity, helping identify sites of possible cancerous lesions, including primary tumors and metastases. The images obtained from FDG-PET scans provide functional information, complementing the anatomical details provided by other imaging modalities like CT or MRI.

It's worth noting that besides FDG, other radiotracers specific to certain types of cancers or metabolic processes can also be used in PET imaging, depending on the clinical indication. These specialized radiotracers can target specific molecular markers or receptors associated with particular cancers, providing more specific and tailored information for diagnosis and treatment planning.

The choice of the best imaging modality for MUOs depends on factors such as the suspected sites of metastasis, the need for functional information, and the availability of specific imaging techniques. In many cases, a combination of imaging modalities may be utilized to provide a comprehensive evaluation.

Examples of radiotracers other than fluorodeoxyglucose (FDG) used in Positron Emission Tomography (PET) imaging, along with their indications:

Choline-based tracers: Radiotracers labeled with carbon-11 (11C) or fluorine-18 (18F) can target choline metabolism and are particularly useful in prostate cancer imaging. These tracers, such as [11C]choline or [18F]choline, exploit the increased uptake of choline in prostate cancer cells. They help in detecting and staging prostate cancer, evaluating disease recurrence, and monitoring treatment response.

Sodium Fluoride (NaF): NaF PET scans are used for assessing bone metastases and bone remodeling. The radioactive fluoride ions are taken up by actively remodeling bone, making it useful in detecting areas of increased bone turnover, such as bone metastases or bone lesions associated with primary bone tumors.

Ga-68 Dotatate or Dotatoc: These radiotracers, which contain gallium-68, target somatostatin receptors that are overexpressed in neuroendocrine tumors (NETs). Ga-68 Dotatate or Ga-68 Dotatoc PET scans are valuable for the detection, localization, and staging of NETs, including gastrointestinal, pancreatic, and lung NETs.

F-18 Fluorothymidine (FLT): FLT is a radiotracer that reflects cellular proliferation. It measures the activity of thymidine kinase, an enzyme involved in DNA synthesis. FLT-PET scans are used to evaluate tumor cell proliferation and assess treatment response in various cancers, including lung, breast, and brain tumors.

F-18 Fluoroethyl-L-tyrosine (FET): FET is an amino acid analog that targets increased amino acid transport in brain tumors. FET-PET scans are employed to evaluate brain tumors, distinguish between tumor tissue and non-specific abnormalities, and aid in treatment planning.

In the context of prostate cancer, the use of radiotracers in PET imaging can provide valuable information for diagnosis, staging, treatment planning, and monitoring. Here are some examples of radiotracers commonly used for prostate cancer imaging:

[11C]Choline: [11C] choline PET scans are employed to detect and evaluate prostate cancer, particularly in cases of biochemical recurrence (rising prostate-specific antigen levels after primary treatment). Choline is taken up by cells undergoing membrane synthesis, and prostate cancer cells often exhibit increased choline metabolism. [11C] choline PET scans can help localize recurrent disease and guide salvage treatment decisions.

[18F]Choline: Similar to [11C]choline, [18F]choline is a radiotracer used for PET imaging of prostate cancer. [18F] choline has the advantage of longer half-life compared to [11C] choline, enabling its broader availability. It is also utilized for primary staging, restaging, and monitoring treatment response in prostate cancer.

Prostate-Specific Membrane Antigen (PSMA) Ligands: PSMA is a protein highly expressed on the surface of prostate cancer cells. Radiolabeled PSMA ligands, such as [68Ga]PSMA-11 or [18F] DCFPyL, target PSMA receptors and are used for PET imaging of prostate cancer. PSMA PET scans are sensitive in detecting primary prostate cancer, lymph node involvement, and distant metastases. They play a significant role in staging, restaging, and guiding treatment decisions, including the selection of targeted therapies.

[18F]Sodium Fluoride (NaF): NaF PET scans can be utilized to evaluate bone metastases in prostate cancer. Prostate cancer frequently metastasizes to the bones, and NaF PET imaging can aid in detecting and characterizing bone lesions associated with prostate cáncer [9,10].

Artificial intelligence (AI)

Has the potential to play a significant role in various aspects of prostate cancer diagnosis, treatment, and management. Here are a few areas where AI can contribute to the field:

Image analysis and interpretation: AI algorithms can be trained to analyze medical images, such as MRI or PET scans, and assist in the detection and characterization of prostate cancer lesions. These algorithms can help radiologists and clinicians by providing automated image segmentation, identifying suspicious areas, and quantifying tumor characteristics.

Radiomics and predictive modeling: Radiomics is the extraction and analysis of a large number of quantitative features from medical images. AI techniques can be applied to radiomic data to develop predictive models for prostate cancer diagnosis, staging, and treatment response. These models can help in risk stratification, treatment planning, and clinical decision-making.

Pathology analysis: AI algorithms can be employed to analyze histopathological images and assist pathologists in the evaluation of prostate cancer specimens. They can aid in automated tumor grading, identification of specific tissue patterns, and detection of biomarkers associated with aggressive disease or treatment response.

Risk assessment and personalized treatment: AI models can integrate various clinical, imaging, genomic, and pathological data to assess the risk of prostate cancer progression, recurrence, or treatment response. These models can assist in personalized treatment planning and monitoring, considering individual patient characteristics and disease parameters.

Prognostic and predictive modeling: AI algorithms can analyze large datasets containing clinical, genetic, and imaging information to identify patterns and develop prognostic or predictive models for prostate cancer outcomes. This can aid in estimating the likelihood of disease progression, identifying patients who may benefit from specific treatments, and guiding personalized patient management.

It's important to note that the availability of specific radiotracers may vary across different medical centers or regions. The selection of a particular radiotracer depends on the suspected pathology, the specific clinical question, and the availability of the radiotracer at the imaging facility [11].

Clinical aspects of patients with MUOs. Signs and symptoms
Patients with metastatic tumors of unknown primary (MUOs) can present with a wide range of signs and symptoms depending on the organs involved and the extent of metastasis. Here are some common clinical aspects and signs and symptoms observed in patients with MUOs:

Metastatic Lesions: MUOs typically manifest as metastatic lesions in different organs or tissues. These can include bone, liver, lung, lymph nodes, brain, adrenal glands, or other sites. The presence of multiple metastatic lesions in different locations without an identifiable primary tumor is a hallmark feature of MUOs.

Constitutional Symptoms: Many patients with MUOs may experience constitutional symptoms that are not specific to any particular organ involvement. These symptoms may include unexplained weight loss, fatigue, generalized weakness, loss of appetite, night sweats, or an overall decline in physical well-being.

Organ-Specific Symptoms: Symptoms can also arise from the involvement of specific organs. The presentation may vary depending on the affected organ. For example:
- Bone metastasis: Bone pain, fractures, or spinal cord compression can occur, leading to localized pain or neurological symptoms.
- Liver metastasis: Jaundice, abdominal pain, hepatomegaly (enlarged liver), or abnormal liver function tests may be observed.
- Lung metastasis: Persistent cough, shortness of breath, chest pain, or hemoptysis (coughing up blood) can occur.
- Brain metastasis: Neurological symptoms such as headaches, seizures, changes in vision, weakness, or altered mental status may be present.
- Adrenal gland metastasis: Hormonal imbalances, such as Cushing's syndrome or hyperaldosteronism, may result in specific clinical features.

Lymphadenopathy: Enlarged lymph nodes, either localized or generalized, may be detected during physical examination or imaging studies. These lymph nodes may be the primary site of metastasis or a secondary spread from an undetected primary tumor [12].

Treatments
It's important to note that the presentation of MUOs can be highly variable and may mimic the symptoms of primary tumors originating in specific organs. The absence of a clear primary tumor site and the presence of metastatic lesions without typical primary tumor-associated symptoms make MUOs challenging to diagnose.

The treatment approach for metastatic tumors of unknown primary (MUOs) aims to manage the metastatic disease and alleviate symptoms, as identifying the primary tumor site may be challenging. The treatment options typically include systemic therapies and supportive care measures. Here are some common treatment modalities used for MUOs:

1. Systemic Therapies:
- **Chemotherapy:** Chemotherapy drugs may be used to target and kill cancer cells throughout the body. Combination chemotherapy regimens or individual drugs may be prescribed based on the histological characteristics of the metastatic tumor and patient-specific factors.
- **Targeted Therapy:** Depending on the molecular profile of the tumor, targeted therapies that specifically target certain genetic mutations or altered signaling pathways may be considered. These therapies aim to inhibit the growth and spread of cancer cells.
- **Immunotherapy:** Immune checkpoint inhibitors, such as programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1) inhibitors, may be utilized to boost the immune system's ability to recognize and attack cancer cells.
- **Hormonal Therapy:** In cases where hormone receptors are present on the tumor cells, hormone therapy may be employed. Hormonal agents, such as anti-androgens or estrogen receptor modulators, can help suppress the growth of hormone-sensitive tumors.

2. Supportive Care:
- **Pain Management:** Adequate pain control measures, including medications and non-pharmacological approaches, are crucial to improve quality of life and alleviate any cancer-related pain or discomfort.
- **Palliative Care:** Palliative care focuses on providing comprehensive support to manage symptoms, optimize quality of life, and address the physical, emotional, and psychosocial needs of patients with advanced cancer. It is an essential component of care for MUO patients.
- **Rehabilitation and Symptom Management:** Rehabilitation therapies, such as physical therapy or occupational therapy, can help improve functional abilities and manage specific symptoms. Symptom management strategies may involve addressing specific organ-related complications or side effects of treatment [13,14].

Treatment approaches
Chemotherapy: Combination chemotherapy regimens are often utilized in MUOs. These regimens may include drugs like platinum-based agents (such as cisplatin or carboplatin) in combination with other chemotherapy drugs, such as taxanes (such as paclitaxel or docetaxel) or gemcitabine. The specific chemotherapy drugs and the regimen used may vary based on factors like patient tolerance, overall health, and potential side effects.

Chemohormone Therapy: Chemohormone therapy combines chemotherapy agents with hormone therapy, especially in cases where the tumor expresses hormone receptors. For example, in hormone receptor-positive breast cancer with metastasis of unknown primary, a combination of chemotherapy drugs (such as taxanes) with hormone therapy (such as aromatase inhibitors or selective estrogen receptor modulators) may be considered.

Immunotherapy Chemotherapy: Immunotherapy agents, particularly immune checkpoint inhibitors, have shown promise in the treatment of various cancers, including some MUOs. The use of immunotherapy in MUOs is generally guided by specific biomarkers, such as the expression of programmed death-ligand 1 (PD-L1) or microsatellite instability-high (MSI-H) status. Immunotherapy drugs, either alone or in combination with chemotherapy agents, can be considered for eligible patients.

The selection of the most appropriate treatment scheme requires careful consideration of the individual patient's characteristics, tumor biology, available evidence, and expert recommendations. It's important to consult with healthcare professionals who specialize in the treatment of MUOs, such as medical oncologists or oncology multidisciplinary teams, to determine the optimal treatment approach based on the specific situation.

Additionally, clinical trials and ongoing research efforts are continually exploring new treatment options and combinations for MUOs. Participation in clinical trials, when available, may provide access to novel therapies and contribute to advancing the understanding and management of MUOs [15]. (Figure 2 and 3)

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SELECTED SYSTEMIC THERAPY REGIMENS FOR OCCULT PRIMARIES
ADENOCARCINOMA

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Paclitaxel and carboplatin[1,2] • Gemcitabine and cisplatin[3] • CapeOX[4] • mFOLFOX6[4,5] • FOLFIRI[6-10]	• Docetaxel and carboplatin[11] • Gemcitabine and docetaxel[12] • Docetaxel and cisplatin[13] • Irinotecan and carboplatin[14] • Capecitabine[a,15,16] • Fluorouracil[a,17-20]	• Paclitaxel, carboplatin, and etoposide[b,21] • Irinotecan and gemcitabine[c,22] • FOLFIRINOX[b,d,23] • mFOLFIRINOX[b,d,24,25] • Pembrolizumab[e,26,27] (only in tumors that are dMMR/MSI-H[28] or have TMB-H [≥10 mut/Mb])[29] • Dostarlimab-gxly[e,f,30] (only in tumors that are dMMR/MSI-H) • Selpercatinib (only in *RET* gene fusion-positive tumors)[g,31]

Figure 2

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SELECTED SYSTEMIC THERAPY REGIMENS AND DOSING SCHEDULES FOR OCCULT PRIMARIES
SQUAMOUS CELL

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Paclitaxel and carboplatin[1,2] • mFOLFOX6[4,5]	• Gemcitabine and cisplatin[3] • Capecitabine[a,15,16] • Fluorouracil[a,17-20] • Paclitaxel and cisplatin[32] • Docetaxel and carboplatin[33] • Docetaxel and cisplatin[13,34] • Cisplatin and fluorouracil[a,35-37]	• Docetaxel, cisplatin, and fluorouracil[b,38] • Pembrolizumab[e,26,27](only in tumors that are dMMR/MSI-H[28] or have TMB-H [≥10 mut/Mb])[29] • Selpercatinib (category 2B) (only in *RET* gene fusion-positive tumors)[g,31]

Figure 3

Diagnosis plan for a solitary pulmonary nodule

When a solitary pulmonary nodule (SPN) is detected, a diagnostic plan is developed to evaluate its nature and determine the appropriate course of action. The plan may vary depending on several factors, including the nodule characteristics, patient risk factors, and clinical context. Here's an outline of a typical diagnostic plan for an SPN:

1. Clinical Assessment:

- **Medical History:** A comprehensive medical history is obtained, including information about the patient's smoking history, occupational exposures, previous lung diseases, and any relevant symptoms.
- **Physical Examination:** A thorough physical examination is performed to assess lung function, identify any associated symptoms, and detect signs of potential metastatic disease.

2. Imaging Studies:
- **Chest X-ray:** A chest X-ray is often the initial imaging test that reveals the presence of the SPN. It provides an initial assessment of the nodule's size, location, and characteristics.
- **Computed Tomography (CT) Scan:** A CT scan of the chest is typically performed to provide detailed information about the SPN. It helps assess the nodule's size, shape, density, location, and presence of specific features that may indicate malignancy.

3. Further Evaluation of SPN:
- **Positron Emission Tomography (PET) Scan:** A PET scan may be considered to evaluate the metabolic activity of the SPN. It helps distinguish between benign and malignant nodules by detecting areas of increased glucose uptake.
- **Contrast-Enhanced CT Scan:** In some cases, a contrast-enhanced CT scan may be recommended to further characterize the nodule and assess its vascularity and enhancement patterns.
- **Follow-up Imaging:** Serial imaging with interval CT scans may be recommended to monitor the stability or growth of the nodule over time. This approach helps differentiate between benign and potentially malignant nodules.

4. Tissue Sampling:
- **Biopsy:** If the SPN appears suspicious or there is a high index of suspicion for malignancy, a tissue biopsy may be performed to obtain a sample for histopathological analysis. Biopsy methods can include percutaneous needle biopsy (either fine-needle aspiration or core biopsy), bronchoscopy, or surgical biopsy, depending on the nodule's location, size, and accessibility.
- **Molecular Testing:** Molecular testing of the biopsy sample, such as genetic mutations or gene expression analysis, may be performed to provide additional information about the nodule's characteristics and guide treatment decisions.

The diagnostic plan for an SPN should be individualized based on the patient's specific circumstances, including risk factors, imaging findings, and the presence of any concerning features. It is crucial to involve a multidisciplinary team of radiologists, pulmonologists, and thoracic surgeons to optimize the diagnostic approach and ensure accurate assessment of the nodule [16]. (Figure 4)

Figure 4

Diagnostic plan for cervical lymphadenopathy

When evaluating cervical lymphadenopathy (enlarged lymph nodes in the neck), a diagnostic plan is developed to determine the underlying cause. The plan may vary depending on factors such as the characteristics of the lymph nodes, associated symptoms, and the patient's medical history. Here's an outline of a typical diagnostic plan for cervical lymphadenopathy:

Clinical Assessment:
- **Medical History:** A thorough medical history is obtained, including information about recent infections, exposure to pathogens, systemic symptoms, risk factors for malignancy, and any other relevant medical conditions.
- **Physical Examination:** A comprehensive physical examination is performed, focusing on the neck region to assess the size, number, consistency, and tenderness of the enlarged lymph nodes. Examination of other body regions may be necessary to identify additional lymphadenopathy.

2. Imaging Studies:
- **Ultrasound:** An ultrasound of the neck is commonly used as an initial imaging modality to evaluate the lymph nodes. It provides information about the size, shape, location, and internal characteristics of the nodes, helping to guide further diagnostic steps.
- **Computed Tomography (CT) Scan:** In some cases, a CT scan of the neck and chest may be recommended to assess the extent of lymphadenopathy, identify any associated masses or abnormal structures, and evaluate distant lymph node groups or other potential primary tumor sites.

3. Laboratory Tests:
- **Blood Tests:** Blood tests, such as complete blood count (CBC), inflammatory markers (e.g., C-reactive protein), and infectious serologies (e.g., Epstein-Barr virus, cytomegalovirus), may be performed to assess for signs of infection, inflammation, or hematological disorders.
- **Fine-Needle Aspiration (FNA) Biopsy:** If the lymph nodes appear suspicious or persistent, an FNA biopsy may be performed. A thin needle is used to extract a sample of cells from the lymph node, which is then examined under a microscope to determine the underlying cause.

4. Further Evaluation:
- **Tissue Biopsy:** If FNA results are inconclusive or suggestive of malignancy, a surgical biopsy or excisional biopsy may be recommended. This involves the removal of an entire lymph node or a portion of it for detailed pathological analysis.
- **Infectious Workup:** Depending on clinical suspicion, additional infectious workup may be performed, including serological tests, cultures, or specific molecular tests to identify infectious pathogens.
- **Specialized Imaging:** In certain cases, specialized imaging techniques such as positron emission tomography (PET) scans may be utilized to evaluate for possible metastatic spread or identify potential primary tumor sites [17]. Figure 5

Figure 5

Diagnosis plan for a single and multiple liver injury
When evaluating liver injury, whether it involves a single lesion or multiple liver lesions, a diagnostic plan is developed to determine the underlying cause and extent of the injury. The plan may vary depending on various factors, such as the patient's clinical presentation, medical history, and imaging findings. Here's an outline of a typical diagnostic plan for liver injury:

1.Clinical Assessment:
- **Medical History:** A comprehensive medical history is obtained, including information about prior liver disease, alcohol consumption, medication use, exposure to hepatotoxic substances, and any associated symptoms or risk factors.
- **Physical Examination:** A thorough physical examination is conducted to assess signs of liver dysfunction, such as jaundice, hepatomegaly (enlarged liver), or tenderness in the abdominal region.

2. Laboratory Tests:
- **Liver Function Tests:** Blood tests, including liver function tests (e.g., alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin, alkaline phosphatase), are performed to assess liver enzyme levels and evaluate liver function.
- **Viral Hepatitis Markers:** Testing for hepatitis B and C viral markers, such as hepatitis B surface antigen (HBsAg) and hepatitis C antibody (anti-HCV), may be conducted to exclude viral causes of liver injury.
- **Autoimmune Markers:** Autoimmune markers, such as antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), or liver-specific antibodies (e.g., anti-mitochondrial antibodies), may be tested in suspected autoimmune liver diseases.

3. Imaging Studies:
- **Ultrasound:** Ultrasonography is often the initial imaging modality used to evaluate liver injury. It can assess liver size, identify focal lesions, evaluate bile ducts, and detect signs of chronic liver disease.
- **Computed Tomography (CT) Scan or Magnetic Resonance Imaging (MRI):** If further characterization of liver lesions is required, a CT scan or MRI may be performed. These imaging techniques can provide detailed information about the size, location, number, and characteristics of liver lesions, aiding in the diagnosis and evaluation of liver injury.

4. Further Evaluation:
- Liver Biopsy: In some cases, a liver biopsy may be performed to obtain a tissue sample for histopathological examination. This helps determine the cause and severity of liver injury and guide appropriate treatment decisions.
- Serological Tests: Additional serological tests may be conducted to evaluate for specific liver diseases, such as testing for autoimmune markers, metabolic disorders, or genetic conditions.
- Viral Load Testing: In cases suspected of viral hepatitis, quantitative viral load testing may be performed to assess viral replication levels and guide treatment decisions [18] Figure 6

Figure 6

Diagnostic plan for multiple bone metastases
When evaluating multiple bone metastases, a diagnostic plan is developed to determine the primary tumor source, assess the extent of metastatic spread, and guide treatment decisions. The plan may vary depending on the patient's clinical presentation, medical history, and imaging findings. Here's an outline of a typical diagnostic plan for multiple bone metastases:

1. Clinical Assessment:
- **Medical History:** A comprehensive medical history is obtained, including information about previous cancer diagnoses, prior treatments, and any associated symptoms or risk factors.
- **Physical Examination:** A thorough physical examination is conducted, with particular attention to the skeletal system to assess for bony tenderness, deformities, or other signs suggestive of bone metastases.

2. Imaging Studies:
- **Skeletal Imaging:** Whole-body bone scans using radiopharmaceuticals, such as technetium-99m (Tc-99m) methylene diphosphonate (MDP), can provide an overall assessment of skeletal involvement. These scans can detect multiple bone metastases throughout the body.
- **Computed Tomography (CT) Scan or Magnetic Resonance Imaging (MRI):** CT or MRI scans may be performed to obtain detailed images of specific areas, such as the spine, pelvis, or other regions with suspected bone metastases. These imaging modalities can help evaluate the extent and characteristics of bone lesions.

3. Laboratory Tests:
- **Tumor Marker Evaluation:** Blood tests for tumor markers associated with certain cancers, such as prostate-specific antigen (PSA) for prostate cancer or carcinoembryonic

antigen (CEA) for colorectal cancer, may be conducted to provide clues about the primary tumor source.
- **Biopsy:** If the primary tumor source is unknown, a biopsy of a bone lesion may be recommended. This involves obtaining a tissue sample from a bone metastasis to determine the histological type and origin of the cancer.

4. Further Evaluation:
- **Additional Imaging:** Depending on the clinical scenario and findings from initial imaging studies, additional imaging modalities, such as positron emission tomography (PET) scans or specific organ-directed imaging (e.g., chest CT, abdominal ultrasound), may be utilized to identify the primary tumor source or evaluate other possible metastatic sites.
- **Molecular Profiling:** Molecular profiling of the tumor tissue or liquid biopsies, such as next-generation sequencing (NGS) or circulating tumor DNA (ctDNA) analysis, may be considered to identify specific genetic alterations or mutations that can guide targeted treatment options [19,20]. Figure 7

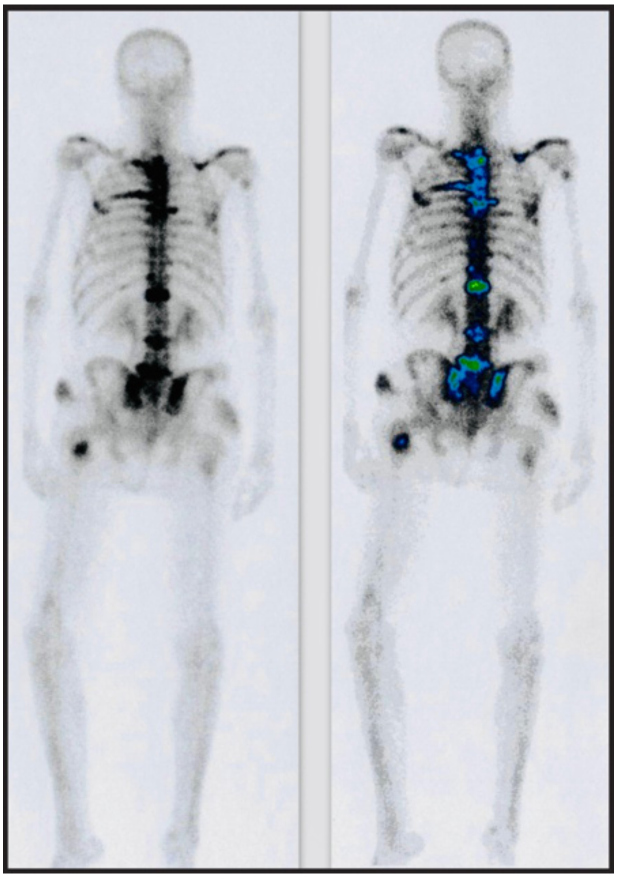

Figure 7

Prognosis
The prognosis for patients with metastatic tumors of unknown primary (MUOs) can vary widely depending on several factors. It is important to note that MUOs encompass a heterogeneous group of cancers, and prognosis is influenced by variables such as the extent of metastasis, tumor biology, response to treatment, and individual patient characteristics. Here are some general considerations regarding prognosis:

Site and extent of metastasis: The number and locations of metastatic lesions can impact prognosis. Extensive metastatic spread to multiple organs may indicate a more advanced stage of disease, potentially affecting treatment options and overall prognosis.

Tumor characteristics: The histological features and molecular profile of the tumor can provide valuable information about its aggressiveness and potential response to specific treatments. Some histological subtypes may have more favorable or unfavorable prognoses.

Response to treatment: The response of MUOs to treatment, such as chemotherapy, targeted therapy, or immunotherapy, can significantly influence prognosis. A positive response, with a reduction in tumor burden or disease stabilization, may improve overall outcomes.

Patient factors: Individual patient characteristics, such as age, overall health status, and presence of comorbidities, can impact prognosis. Patients with better general health and functional status often have improved tolerance to treatments and overall outcomes.

Supportive care: The availability and utilization of comprehensive supportive care, including pain management, palliative care, and psychosocial support, can contribute to improving the patient's quality of life and potentially impacting prognosis.

It is important to note that MUOs generally have a less favorable prognosis compared to cancers with identifiable primary tumors, as the absence of knowledge about the primary site adds complexity to treatment decisions. However, it is difficult to provide specific prognostic estimates due to the heterogeneity of MUOs and the lack of standardized prognostic models [21].

Conclusions
Metastatic tumors of unknown primary (MUOs) present a diagnostic challenge due to the absence of an identifiable primary tumor site. The diagnostic approach for MUOs involves a comprehensive evaluation that includes clinical assessment, imaging studies, laboratory tests, and tissue sampling. The goal is to determine the primary tumor source and guide appropriate treatment decisions. Various imaging modalities, such as CT, MRI, PET scans, and ultrasound, play a crucial role in assessing the extent of metastasis and identifying potential primary tumor sites.

The treatment of MUOs typically involves systemic therapies, such as chemotherapy, targeted therapy, immunotherapy, and hormone therapy, depending on the histological features of the tumor and patient-specific factors. Supportive care measures are also essential to address symptoms, manage pain, and optimize quality of life. The prognosis for MUOs varies widely and depends on factors such as the extent of metastasis, tumor characteristics, response to treatment, and patient factors [22].

Artificial intelligence (AI) has the potential to contribute significantly to the diagnosis and management of MUOs. AI algorithms can assist in image analysis, predictive modeling, pathology analysis, and risk assessment, aiding in accurate diagnosis and personalized treatment planning. However, the integration of AI into clinical practice requires careful validation, adherence to ethical standards, and collaboration between healthcare professionals and AI experts.

Ultimately, the management of MUOs necessitates a multidisciplinary approach, involving various specialists, to provide comprehensive care, address patient needs, and optimize outcomes [23]. Ongoing research and clinical trials continue to advance our understanding of MUOs, providing opportunities for improved diagnostic methods, treatment strategies, and prognostic models.

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