

Eviti Imaging: Occult Primary

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For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at <http://www.cms.gov> for additional information.

For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Occult Imaging

Discussion

This imaging guideline provides a standardized framework for the use of diagnostic and surveillance imaging in the management of common adult malignancies, specifically occult primary. The goal is to ensure timely, evidence-based imaging that supports accurate staging, treatment planning, response assessment, and post-treatment surveillance.

Guiding Principles

- Follow evidence-based practices from major guidelines (e.g., NCCN, ESMO, ACR Appropriateness Criteria)
- Ensure imaging aligns with the clinical context and stage of disease
- Minimization of unnecessary radiation exposure
- Promote timely and cost-effective imaging utilization
- Incorporate multidisciplinary collaboration in imaging decisions

Imaging Guidelines

This guideline applies to the following patients:

1. At least 18 years of age with confirmed or suspected diagnoses of occult primary; AND
2. All phases of oncologic care, including one of the following:
 - a) Initial staging
 - b) Treatment response evaluation
 - c) Post-treatment surveillance
 - d) Detection of recurrence or progression; AND
3. All imaging modalities used in oncology care, including but not limited to the following:
 - a) Computed tomography (CT) (neck, chest, abdomen, pelvis, neck, or site-specific)
 - b) Magnetic resonance imaging (MRI) (including site-specific protocols such as pelvis MRI, brain MRI, liver MRI)
 - c) Fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT)
 - d) PET/MRI
 - e) Somatostatin receptor PET/CT (SSTR-PET/CT)
 - f) Nuclear medicine (e.g., bone scan, PSMA PET)
 - g) Single photon emission computed tomography/CT (SPECT/CT) (e.g., octreotide SPECT/CT for neuroendocrine tumors)

Notes:

1. The concurrent utilization of multiple advanced imaging modalities—such as PET/CT and MRI—is not routinely warranted and should be considered only when each modality is expected to provide distinct and clinically relevant information that will directly impact patient management. The selection of the most appropriate imaging study should be individualized, taking into account tumor type, clinical presentation, prior imaging, and other patient-specific factors. Imaging requests will be evaluated on a case-by-case basis to ensure clinical necessity, appropriateness, and the potential to influence therapeutic decision-making.

- When PET imaging is clinically indicated, the appropriate radiotracer should be selected based on tumor type and clinical scenario.

Occult Primary Tumor (Cancers of Unknown Primary) Imaging

Cancer of unknown primary (CUP) refers to a biopsy-proven malignancy where no primary site is identified after standard clinical evaluation and imaging.

The imaging goal is to localize a potential primary, define disease extent, and guide biopsy or treatment decisions.

Imaging is tailored to clinical presentation, histology (e.g., adenocarcinoma, squamous, neuroendocrine), and pattern of metastasis.

Occult Primary Recommendations			
Clinical Scenario	Recommended Modality	Frequency/Timing	Purpose/Notes
Initial Staging	CT chest/abdomen/pelvis	Once at diagnosis	Foundation study - defines disease extent, detects potential primary (e.g., lung, pancreas, kidney, GI tract)
	PET/CT	As clinically indicated	Identifies metabolically active lesions; may reveal occult primary in ~25–40% of cases; especially useful in cervical, head/neck, or squamous cancers of unknown primary (CUP), when clinically indicated due to inconclusive or inadequate findings on conventional imaging
	MRI (site-specific, e.g., brain, breast, pelvis)	As clinically indicated by symptoms or histology	Brain MRI if neurologic symptoms or neuroendocrine histology Breast MRI in women with axillary adenocarcinoma

			and negative mammogram Pelvic MRI if gynecologic origin suspected
	Mammogram ± breast ultrasound (females)	Once at diagnosis	To exclude occult breast primary
	Head and neck evaluation MRI or CT neck ± nasopharyngoscopy	Once at diagnosis, if squamous CUP in cervical nodes	Mandatory in head/neck-dominant nodal metastasis; guides selective mucosal biopsy or tonsillectomy
Initial Staging - Site-Specific Staging After Probable Primary Suggested	Tailored imaging (per suspected site)	Once at diagnosis	If PET/CT or histology suggests site (e.g., lung, pancreas, colon), proceed with site-specific staging protocol
Treatment Monitoring - Systemic or Locoregional	CT or PET/CT (same baseline modality)	Every 2–3 months initially, then 3–6 months depending on response	Assesses treatment response and new lesions; maintain consistency with baseline modality; NCCN does not provide definitive imaging interval guidance
Surveillance - Post-Treatment No Active Disease	CT chest/abdomen/pelvis PET/CT, when clinically indicated due to inconclusive or inadequate findings on conventional imaging	Every 6–12 months up to 5 years	Continued surveillance may be individualized; many cancers of unknown primary (CUP) eventually declare a primary within 1–2 years
Suspected Recurrence	CT chest/abdomen/pelvis PET/CT, when clinically indicated due to inconclusive or inadequate findings on conventional imaging	As clinically indicated	

Notes:

1. If a primary site is identified, management follows the NCCN guidelines for that specific cancer type
2. Cancer of unknown primary (CUP) work-up should always be integrated with IHC profiling and, when appropriate, molecular tumor origin testing to refine diagnosis.
3. FDG-PET/CT has the highest yield for primary detection, especially in:
 4. Squamous CUP in cervical nodes
 5. Single metastatic sites (e.g., liver, bone, brain)
 6. CUP with favorable histology (neuroendocrine, germ-cell-like)
7. Diagnostic yield is highest when PET/CT is performed before biopsy or soon after, to avoid false negatives from treatment or inflammation.
8. MRI should be used selectively when anatomic detail may influence treatment (brain, pelvis, breast).
9. Repeat imaging may be indicated after empiric therapy to identify a subsequently evident primary.¹

Revision and Review History

No.	Description	Date
1	Original Effective Date:	1/1/2026
2	Policy Annual Review Dates:	
3	Department Owner:	Medical Affairs
4	NH Advisory Committee Approval Dates:	
5	Revision Changes:	

References

- ¹ National Comprehensive Cancer Network Guidelines: Occult Primary. https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf. Accessed December 17, 2025.