NCCN Guidelines® Insights

Occult Primary, Version 3.2014
Featured Updates to the NCCN Guidelines

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Abstract
The NCCN Guidelines for Occult Primary tumors provide recommendations for the evaluation, workup, management, and follow-up of patients with occult primary tumors (cancers of unknown primary). These NCCN Guidelines Insights summarize major discussion points of the 2014 NCCN Occult Primary panel meeting. The panel discussed gene expression profiling (GEP) for the identification of the tissue of origin and concluded that, although GEP has a diagnostic benefit, a clinical benefit has not been demonstrated. The panel recommends against GEP as standard management, although 20% of the panel believes the diagnostic benefit of GEP warrants its routine use. In addition, the panel discussed testing for actionable mutations (eg, ALK) to help guide choice of therapy, but declined to add this recommendation. (J Natl Compr Canc Netw 2014;12:969–974)

Please Note
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Occult Primary, Version 3.2014

**Overview**

Occult primary tumors, or cancers of unknown primary (CUPs), are defined as histologically proven metastatic malignant tumors whose primary site cannot be identified during pretreatment evaluation.\(^1\)\(^2\)

These tumors have a wide variety of clinical presentations, and most patients have a poor prognosis. Patients with occult primary tumors often present with general complaints, such as anorexia and weight loss. Early dissemination, aggressiveness, and unpredictability of metastatic pattern are characteristic of these tumors.\(^3\) Life expectancy is very short, with a median survival of 6 to 9 months.\(^4\)

**Tissue of Origin Identification**

In an attempt to identify the tissue of origin of occult primary tumors, biopsy specimens are often analyzed using immunohistochemistry (IHC).\(^5\)\(^-\)\(^8\)

In addition, gene expression profiling (GEP, or gene signature profiling) is recommended for tissue of origin identification.\(^6\) There may be diagnostic benefit, not necessarily clinical benefit. The use of gene signature profiling is a category 3 recommendation.\(^6\)

NCCN Guidelines Insights

For many patients, the apparent uncertainties surrounding the diagnosis of an unknown primary cancer may result in significant psychosocial distress and increased difficulty in accepting treatment options. Empathetic discussion about the natural history of these types of cancer and their prognosis, and the provision of support and counseling both by the primary oncology team and specialized services may help to alleviate this distress. See NCCN Guidelines for Distress Management.

Routine use of PET/CT is not recommended. PET/CT scans may be warranted in some situations.

Based on clinical findings.

Some recommendations are based on expert consensus and may not be evidence-based.

**NCCN Categories of Evidence and Consensus**

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
filing) or other molecular profiling assays have been developed to attempt to identify the tissue of origin in these patients.\(^9,10\) The hope is that through basing treatment on the suspected tumor type, patient outcomes will be improved.

**Molecular Profiling**

Talantov et al\(^{11}\) developed a GEP assay designed to detect tumors originating from the lung, breast, colon, ovary, pancreas, and prostate through evaluating the expression of 10 specific genes using real-time quantitative reverse-transcription polymerase chain reaction (qRT-PCR). In a blinded study, this assay identified the tissue of origin of metastatic carcinomas for which the primary was known in 204 of 260 tested samples, with an overall accuracy of 78%. Varadhachary et al\(^{12}\) assessed the feasibility of this assay retrospectively in 104 patients with CUPs. A presumed tissue of origin was identified in 61% of patients, and the results were believed to be compatible with clinicopathologic features and response to therapy in most cases.

Similarly, Ma et al\(^{13}\) developed a 92-gene–based qRT-PCR assay to identify the site of origin of metastatic tumors, especially in patients with CUPs. In a retrospective multicenter study, this assay identified primary sites in 75% of patients after the initial diagnosis of CUP.\(^{14}\) A more recent validation study of 149 archival tumor specimens found similar rates (74%–77%) of diagnostic accuracy compared with identified primary tumors, IHC diagnoses, and clinical/histologic findings.\(^{15}\) This test is commercially available.

Using a microarray approach, Monzon et al\(^{16,17}\) developed a 1550-gene test, which had an 88% sensitivity and a 99% specificity for diagnosing uncertain primary tumors in a blinded multicenter validation study.\(^{18}\) This test is also commercially available.

Another microarray GEP assay has been developed that assesses the expression of 495 genes to identify the tissue of origin.\(^{19}\) This assay has also been validated\(^{20}\) but is not currently commercially available in the United States. A recent feasibility study by GEFCAPI (Groupe d’Etude Français des Carcinomes de site Primitif Inconnu) found that use of this test changed clinical management in as many as 50% of cases.\(^{21}\) This group is planning a randomized phase III trial to assess changes in progression-free survival (PFS) between patients with CUP treated empirically and those treated based on results of GEP.

Another form of molecular profiling has recently generated some interest for its potential to identify the tissue of origin of CUPs. This assay is based on the presence of microRNAs (miRNAs), which are noncoding RNAs that regulate gene expression and show high tissue specificity.\(^{22–24}\) Using a panel of 48 miRNAs, blinded sets of samples were identified with an accuracy of 85% to 89%.\(^{22,23}\) When this assay was prospectively studied in patients with occult primary tumors, the tissue of origin diagnosed was consistent with clinical and/or pathologic features of the disease in 62 of 74 patients (84%).\(^{24}\) This assay is commercially available. This research group recently developed a second-generation microarray assessing the levels of 64 miRNAs to identify 42 tumor types.\(^{25}\) The assay was validated on a set of 509 blinded samples and showed a sensitivity of 85%.

Several GEP tests are now commercially available and are being evaluated in prospective clinical studies in an attempt to determine whether the information they provide translates into clinically meaningful benefit for patients.\(^{26}\) In one study, 32 patients whose tumors were classified as being of colorectal origin by 2 GEP assays (the 10-gene assay of Talantov et al\(^{11}\) and the 92-gene assay of Ma et al\(^{13}\)) showed a response to colorectal chemotherapy regimens as expected for patients with stage IV colorectal cancer.\(^{27}\) Results from a prospective, nonrandomized phase II study of 289 patients with CUPs in which treatments were based on the identification of primary sites by the 92-gene assay showed that clinical features and response to treatment were generally consistent with assay results.\(^{26}\) Although the median survival time of 12.5 months in the subset of patients that received GEP-directed treatment was better than that in the predefined historical cohort, the panel believes that similar results might be expected from empiric use of these regimens in a group of patients with unknown primary cancer predominantly below the diaphragm who have good performance status (PS). Thus, the clinical benefit from use of these molecular assays, remains to be determined. A recent review compared 3 commercially available tests.\(^{28}\)

**IHC vs GEP**

In a recent, blinded, multicenter study by Handorf et al,\(^{29}\) the diagnostic accuracy of the 1550-gene GEP assay was compared with that of IHC staining in a set of metastases from known primaries. The results indicated that the accuracies were similar, with 89% accuracy for GEP and 83% accuracy for IHC (\(P=0.013\)). A similarly designed study by Weiss et
al\(^{10}\) compared the 92-gene GEP assay with IHC and found similar results (79% accuracy for GEP vs 69% for IHC; \(P=.019\)). The Handorf study\(^{29}\) also showed that performing additional rounds of IHC testing after a first round generally failed to provide additional diagnostic information. The panel thus recommends that only one round of staining (8–10 stains) be performed when IHC is used.

**Panel Recommendations Regarding Tissue of Origin Identification**

Overall, the panel believes that neither IHC, a diagnostic tool in widespread use, nor GEP should be used indiscriminately. The panel finds it noteworthy that thus far the literature on GEP and IHC in the workup of CUPs has focused far more on establishing a tissue of origin than on establishing whether such identification leads to better outcomes in patients.

Currently, the panel believes that available outcomes data are not sufficient to recommend the routine use of molecular profiling in the workup of occult primary tumors; use of these tests is thus a category 3 recommendation. Therefore, although the panel recognizes the diagnostic benefit of GEP, most members have concerns that a clinical benefit has not been shown. However, some panelists believe the diagnostic benefit of GEP warrants its routine use. Consequently, the panel added a footnote to the 2014 version of the NCCN Guidelines explaining that the use of molecular profiling as standard management is a category 3 recommendation. Overall, the panel does not recommend molecular profiling for identifying tissue of origin as standard management in the diagnostic workup of patients with CUP.

**Testing for Actionable Mutations**

The panel also discussed whether to recommend testing for actionable mutations (eg, EGFR and ALK mutations if lung cancer is suspected), using either individual gene testing or comprehensive profiling, to guide choice of therapy. Identification of certain mutations would allow molecularly targeted agents to be given to patients in attempt to improve outcomes. For example, crizotinib is used in patients with locally advanced or metastatic non–small cell lung cancer positive for the ALK gene rearrangement,\(^{31–33}\) and could therefore be tried in patients with ALK mutations and CUPs of possible lung origin. The panel noted, however, that data in the CUP setting for such an approach are lacking. Furthermore, some panel members reported that they have not seen good results from such an approach in their clinical experience. For these reasons, the panel declined to add a recommendation for actionable mutation testing in the 2014 version of the guidelines.

**Conclusions**

These NCCN Guidelines Insights for Occult Primary tumors highlight the shift in consensus for the recommendation against routine molecular profiling for identifying tissue origin. This year, more panelists support GEP for standard diagnostic workup, because they believe the diagnostic benefit is sufficient to warrant this recommendation. However, most of the panelists still believe that a clinical benefit must be shown before GEP can be recommended as part of standard management (thus a statement was added explaining that the use of GEP is a category 3 recommendation). The panel also believes that, until more robust outcomes and comparative effectiveness data are available, pathologists and oncologists must collaborate on the judicious use of both GEP and IHC on a case-by-case basis, with the best possible individualized patient outcomes in mind.

The panel also discussed testing for actionable mutations, with the intention of administering molecularly targeted therapy, but did not include that recommendation, citing a lack of data showing a clinical benefit with this approach.

**References**


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Posttest Questions

1. True or False: Most of the NCCN Occult Primary panel believes that a clinical benefit must be shown before GEP can be recommended as part of standard management in the diagnostic workup of patients with occult primary tumors.
2. Recent studies comparing the accuracies of IHC and GEP assays found which of the following?
   a. The accuracies of IHC and GEP for the identification of tissue of origin were similar.
   b. Performing additional rounds of IHC testing after a first round generally failed to provide additional diagnostic information.
   c. Both of the above.
   d. None of the above.
3. True or False: Studies have shown that the approach of testing for actionable mutations and then treating with the corresponding molecularly targeted agent leads to improved outcomes in patients with occult primary tumors.