Hello, I am Maura Polansky at the University of Texas MD Anderson Cancer Center. I am a Physician Assistant in the Department of Gastrointestinal Medical Oncology and the Program Director for Physician Assistant Education.

Today, I will be covering the diagnosis and staging of solid tumors. Our objectives today are to discuss solid tumors, how they are diagnosed and staged, how we access the primary site of disease, and how we determine the primary site of disease when it is not apparent at the time of presentation.

Patients present with malignancy in various different clinical scenarios. At times, they are diagnosed simply based on a screening physical exam or screening test. Other times, patients come in with particular physical findings or symptoms that ultimately lead to the diagnosis of cancer. And occasionally cancer is found as an incidental finding when a test is performed for another reason, such as a patient who may come in after a motor vehicle accident and have a CAT scan. The clinical presentation may be related to the primary site of disease but, when metastatic disease is present, sometimes this is what leads to the initial evaluation.

The initial diagnosis of cancer is made based on pathology. In almost all situations a biopsy is required in order to confirm malignancy. There are very rare situations in which a patient has a very defined clinical presentation, risk factors, laboratory studies, or imaging studies supporting the diagnosis, and pathology is not required, such as in hepatocellular carcinoma. These are certainly the exception and not the rule. Otherwise, biopsy is really required. Tissue sampling can be obtained, and should be obtained, fairly early in the evaluation of patients with suspected malignancy. It can be obtained from a variety of different mechanisms that [we] will be discussing. And the most important first determination is whether or not the patient has a malignancy versus a benign process.

Cytology allows for typically a less invasive acquisition of cancer cells by the aspiration of fluids and the evaluation of the cells within the fluid. This is in contrast to a pathologic sampling in which actual tissue is obtained either through a core biopsy, needle biopsy, surgical biopsy, or even an excisional biopsy.

With cytology, the cells within the fluid are evaluated. This fluid can be obtained by aspirating a tumor, such as in fine needle aspiration; the removal and analysis of an abnormal fluid collection, such as pleural fluid or ascitic fluid: review and analysis of normal fluid, such as urine or CSF: or with washings in which saline is instilled into a cavity and aspirated for review, such as with the bladder or the lung.

Pathology sampling can be obtained from radiographic biopsy. In this case, you see a needle that has been set into the chest cavity by means of a CT scan to obtain a sampling of a lung nodule. Other means include endoscopic biopsies, a directed biopsy for a lesion that can be palpable on a physical exam. Random biopsies are sometimes obtained when a patient has known or suspected dysplasia, such as an endoscopic biopsy. And at times a surgical biopsy may be necessary.
With cytology, we are able to find out about the cellular morphology and primarily this can distinguish malignancy versus benign disease. The sampling is limited and, therefore, further subclassification may or may not be possible. When tissue is obtained through a pathologic sampling, we can learn more about the tissue morphology and typically further classification and subclassifications can be made. Determination of the invasiveness of the tumor into surrounding tissue can also be obtained when a pathologic biopsy is obtained.

Light microscopy with H and E staining can typically determine the major different subtypes of malignancy and additional subtypes can be determined with additional staining or certainly suggest a particular subtype.

These are the some of the major classifications of cancer. The patient who has a neoplasm [that] can be subdivided into a carcinoma or one of many other types of tumor such as melanoma or sarcoma. Carcinomas are then subdivided into a number of different additional classifications primarily being adenocarcinoma and squamous cell carcinoma, but several others also exist.

When a patient comes in with a diagnosis of malignancy or has a tumor present, one has to consider whether, in fact, this is the primary site of disease or it could represent a metastasis from another site of disease. The clinician will consider the clinical presentation of the patient, that is, signs, symptoms, risk factors, the location and number of tumors within that site, and the typical pattern of metastatic spread for a particular malignancy. Biopsies are usually obtained from the most accessible site of disease, trying to reduce the risk to the patient while also obtaining a good diagnostic yield. And at times, site is determined based on indications for treatment. That is, if it is suspected that the patient has metastatic disease, then the metastasis may be more appropriate to biopsy because that not only confirms the diagnosis, but helps with the actual staging of the patient.

For patients who come in with metastatic disease, at times the primary site of disease is not apparent at initial presentation. This is called an occult primary. This is to be distinguished from an unknown primary in which the patient has been appropriately and thoroughly evaluated and the primary site can still not be determined. When patients have lymphomas, melanomas, sarcomas, although the primary site of disease may not be determined, the patient has a clear established diagnosis and treatment can be tailored to that diagnosis. However, when a patient has a more broad classification of tumor, such as carcinoma or simply a neoplasm, then it can be much more helpful in guiding therapy if a particular primary site can be determined. And there are known strategies for making the determination about what test should be ordered in this situation.

Again, as we look back at the major subclassifications, when we are talking about occult or unknown primaries, we are typically talking about the various types of carcinoma, most commonly adeno- [or] squamous cell carcinoma, neuroendocrine tumors, and
some of the other tumor types. And occasionally patients simply have a neoplasm and further calcification cannot be obtained because of either limited tissue or the amount of differentiation being so poor.

If a patient is known to have a metastatic lesion that is an adenocarcinoma, the clinician should consider the various different types of primary sites of adenocarcinoma. These include breast, prostate, most sites within the GI tract, ovarian, lung, and endometrial cancer.

Alternatively, if the patient is known to have a squamous cell carcinoma, consideration still of lung cancer, but of head and neck cancers, proximal esophagus, anus, the genitourinary tract should be considered. Although skin cancers are often squamous cell carcinoma, these rarely metastasize and, therefore, would not be a serious consideration.

Neuroendocrine tumors typically occur within the GI tract either the large or small bowel or pancreas or within the lungs. So these would be sites for consideration.

If a patient is simply found to have a poorly differentiated carcinoma and further subclassification cannot be performed, then these various different subtypes have to be considered with all the different primary sites that may be the culprit.

And similarly, on rare occasions, we see a patient who simply has a poorly differentiated neoplasm and virtually all cancer types have to be considered.

Immunohistochemical staining can help in the classification of tumors and can provide some further information about possible primary sites. However, a battery of tests is not recommended. This not only raises the cost, but can provide simply a list of positive staining that really does not help in making the determination of [the] primary site. Instead, when there is consideration of various sites by the clinical presentation, a stain may help to sway the likelihood of it being one cancer versus another. For example, if the patient has a tumor in the liver and it is biopsied, trying to determine whether or not this is an adenocarcinoma versus a hepatocellular carcinoma can be aided by looking at the pattern of staining. Similarly mucinous adenocarcinomas typically occur either in the GI tract or in the ovarian [speaker indented to say ovary], and a pattern of staining is usually quite different for these two sites of disease.

There are a wide variety of immunohistochemical staining, many of them I have listed here, some of the more common ones, such as the cytokeratin staining, PSA, TTF1, ER/PR and so forth.

An example to use the cytokeratin staining might be a patient who has a solitary lung lesion and has had a remote history of colon cancer. This could certainly be metastatic colon cancer or a lung primary. And, as we looked at the pattern of staining for cytokeratin 20 and cytokeratin 7, we typically see a different pattern of staining --- of staining between colon and lung cancer. And, therefore, these two stains are routinely
performed to help sway the clinician in what the appropriate diagnosis is, which can substantially alter the treatment of management.

Keep in mind that pathology can be quite helpful in aiding in the diagnosis of a patient, but has limitations. One is the limitations of sampling. Again, we have talked about the limitations of cytology versus being able to obtain more tissue. The cost that is incurred, the more staining that is performed, and how that can sometimes actually be misleading with almost too much information provided. Stains are neither 100% sensitive or specific, so again, can simply lead to further consideration or further evidence of one disease versus another. And really, looking back at the H and E staining, the clinical scenario is most important in guiding the overall impression of the primary site of disease. And consultation with the pathologist can be quite helpful and this really depends on the experience of the clinician and the pathologist.

If, after a biopsy is obtained, the primary site is still not determined, then reconsideration of the clinical presentation. Is this patient at particularly high risk of certain types of cancers based on family history or other personal history? What about the patient’s presenting signs and symptoms? Do they suggest a possible site of primary disease? Are there any laboratory studies that support one diagnosis or another? And then imaging studies should be performed in a thoughtful manner. That is, we don’t order lots and lots of tests. We order those that we feel will be appropriate given the tissue type and given the clinical scenario. The NCCN Guidelines™ can be quite helpful in guiding this evaluation for those who do not often see cancers of unknown primary. And consideration of consulting with the pathologist to see what additional information he or she may be able to suggest.

I mentioned tumor markers. These are substances found in the blood and at times urine and another normal fluid. It can --- they can be very helpful in screening, such as with PSA for prostate cancer and with alpha-fetoprotein for hepatocellular carcinoma. They have a small, but limited role in making an initial diagnosis of a primary site of disease. They can be very helpful for surveillance for a patient who has already completed treatment and is felt to be in remission. If the tumor marker rises, that may suggest recurrent disease. And they also can be used to monitor a patient on therapy to see if it appears that they are having an early response or the treatment is not effective. As with staining, tumor markers are not completely sensitive or specific. There are many tumor markers, such as CEA, that can be elevated in a wide variety of malignancies. And they can occasionally be affected by other factors, such as hepatic function or whether a patient is a smoker.

There are a variety of different types of tumor markers. Some are hormones, enzymes, proteins or antigens; and a number of them have been listed here. Many of these I am sure you are familiar with.

Tumors can be classified based on attributes of their behavior and, therefore, a staging system has been established to help in further guiding the process of treatment,
estimating prognosis, and are important in clinical research so that we are sure when we are looking at two different treatment arms that these are patients who are similar.

The American Joint Committee on Cancer is the primary staging system used for solid tumors. It includes both pathologic staging and clinical staging. The most commonly used, that of the TNM staging, looking at the tumor, the regional lymph nodes, and metastases.

The tumor can be staged by different characteristics depending on the type of tumor it is. For certain tumors, we look at the size of the tumor, such as in lung, breast, ovarian, or prostate cancer. Tumors over a particular size have a higher T-staging.

This is in contrast to a tumor such as a tumor within the bowel wall. This is an endoscopic ultrasound that shows a tumor that extends throughout the muscularis of the colon and therefore is a T3 lesion. Similarly with bladder cancers and melanomas, the depth of penetration is what determines the T-staging.

Nodal stage is related to regional lymph nodes, the location and the number of nodes within the direct region of the primary tumor. Keep in mind that, if the patient has a lymph node distant from the site of [the] primary, then this would represent metastatic disease.

There are cases where the patient’s nodes can be assessed by physical exam, such as if a patient has a melanoma or breast cancer. Head and neck cancers, for example, will drain into the neck region and can be palpated on exam. Anal cancers have the inguinal region as their --- one of their sites of nodal drainage and, therefore, these areas can be assessed and should be assessed on physical exam of these patients. And with all patients, examination of all the palpable nodal basins, cervical, supraclavicular, axillary and inguinal nodes, should be performed as part of an initial evaluation to determine if there is regional or metastatic nodal involvement.

Additional nodes can be evaluated by CT, MRI, or ultrasound. The size of the nodes and the characteristic of the nodes can be determined by the radiologist to be suggestive of that of nodal involvement. And, if necessary, biopsy or aspiration of that node may be necessary to determine if, in fact, they are involved, and this would be done only if this is going to affect the clinical management of the patient.

Nodes are most commonly identified and diagnosed at the time of surgical resection of the primary site of disease. And this is the most accurate and useful information, although there are times where, in a preoperative setting, one needs to determine if nodal involvement is present.

Metastases can certainly be suspected based on clinical examination or presenting symptoms. If a patient has organomegaly or palpable mass, such as an intra-abdominal mass or soft tissue tumor, this can certainly be suggestive of metastatic disease. Clinical evaluation and determination of what diagnostic tests should be
ordered should be determined based on common sites of metastatic spread for that particular tumor type. And there are consensus guidelines regarding the appropriate evaluation for patients when they have a particular tumor type. Rarely, surgical evaluation is needed for establishing the presence of metastatic disease, but occasionally this is required or this occurs if a patient is going to surgery.

There are number of common imaging studies that are used in the evaluation of cancer patients, CT, MRI, ultrasound, PET scan, and bone scan.

With CT scan, we obtain cross-sectional imaging typically in the range of 3 to 5 mm, sometimes as wide as 10 mm sections. It does require IV contrast and GI contrast is typically used for evaluation of the abdomen or pelvis. And there are sometimes contraindications particularly to IV contrast if the patient has renal impairment.

CT scans are commonly used for evaluation of the lung, the liver, the pancreas, the brain, and lymph nodes, such as the example here with the lesion in the liver seen on CAT scan.

MRI uses radiofrequency signals to produce an image. It does require being in a closed MRI machine. Although there are open MRI machines, these are inferior to closed machines and really play very little role in the management and evaluation of cancer patients. Some patients will require sedation in order to be in a closed MRI machine.

MRIs are particularly useful at looking at CNS tumors and soft tissue masses. They can also be used, however, to image all the other sites that were mentioned with CT scan, such as brain, lung, and liver. And they can be particularly helpful in distinguishing certain types of tumors, different characteristics within the tumor (such as those in the liver). So, additional information can sometimes be performed and obtained beyond that obtained in the CAT scan.

Ultrasound avoids the risk of radiation and contrast. It can be performed percutaneously, endoscopically, or intraoperatively.

It is very helpful in helping to distinguish cystic versus solid tumors, such as in the breast or in the ovary or liver where we often see cystic lesions and can really provide some complementary information beyond that of CT or MRI.

Bone scan is a nuclear medicine study in which a patient is injected with a tracer. It identifies areas of high bone turnover that may be malignancy although other processes can also result in this abnormal signaling. One of the advantages: the entire skeleton is surveyed with a bone scan. So this is a particularly useful test when patients have a malignancy that commonly metastasizes to the bone.

PET scan is another nuclear medicine study that obtains physiologic images detecting positrons emitted after injecting a patient with a tracer. FDG is laced with a positron --- a radiotracer isotope, which emits a positron on decay and it identifies areas of high
metabolic activity in the body that can be malignancy. But other conditions, such as inflammatory or infectious processes can also light up on PET scan.

PET scan is used in staging more routinely for a number of different cancers. It can identify possible sites of disease including lymph node involvement and metastatic disease and it is routinely combined with CAT scan to give more anatomic detail to the site of involvement.

In conclusion, the diagnosis of most cancers requires review of pathologic information obtained from biopsy or aspiration. The determination of a primary site of disease requires consideration of the clinical presentation, pathologic review, and consideration of patterns of metastatic spread. Cancer staging is a very important step in evaluation of patients with malignancy to estimate prognosis; help to guide treatment recommendations; and also in stratifying patients who will be participating in clinical trials. This concludes our presentation today. We hope you find this useful and we will welcome your feedback.