BroadcastMed | mac_multifocal-lung-cancer-blackmon-720p.mp4

SHANDA BLACKMON: Hi, my name is Dr. Shanda Blackmon, and I'm a Thoracic Surgeon at Mayo Clinic. Today, Dr. Zaid Abdelsattar and I are going to present a case for you of multifocal lung cancer, a woman who came in with bilateral ground-glass opacities. We'll talk about how to diagnose these cases, what the differential diagnosis can sometimes be, and importantly, how to stage these patients.

We'll also talk about a specific video of how to do the case technically, and then, focusing on patients who have lung resection, we'll also talk about how to recover these patients. And then we'll talk a little bit about the pathology and go through the review of the literature on multifocal lung cancer. I hope you enjoy this video. We worked very hard to put it together for you.

Video-assisted thoracoscopic left lower lobectomy in the setting of a patient with multiple synchronous lung lesions. We have no relevant disclosures. The case is of a 69-year-old woman who is an active tennis player. Prior to presenting with us with the lesion, she had had an earlier upper lobe lung cancer.

This was discovered incidentally on low-dose screening chest CT scan. She was diagnosed after removal with a pathologic well-differentiated adenocarcinoma, stage IIB, N0, M0. She was treated with a right posterolateral open thoracotomy with a right upper lobectomy in 2013 and received adjuvant therapy with chemotherapy.

The CAT scan of her chest showed multiple subsolid nodules that were identified throughout predominantly the left lung. These were mixed solid and ground-glass opacities. Compared to the recent and prior study done several months prior, the nodules were not definitely changed. However, many had progressed from more remote examinations. For example, a 3-millimeter ground-glass nodule peripherally within the left upper lobe was new from a prior May exam. And a semisolid nodule within the left upper lobe and left lower lobe both appeared to enlarge.

These nodules that were within the lung, part solid and ground glass, raise the suspicions of multifocal lung cancer. She had moderate emphysema with scattered probable parenchymal scarring. She had isolated origin of the left vertebral artery, which was a normal variant, aortic and coronary artery vascular calcifications, and stable sub-centimeter mediastinal and hilar lymph nodes. Her adrenal glands appeared normal.

The PET scan that was performed re-demonstrated sub-centimeter, semisolid, and ground-glass nodules. They did not appear significantly changed from the CT appearance that was done several days separate from the PET scan. None of the nodules demonstrated significantly increased FDG uptake. However, they were likely below the size and solidity of PET detection and remained concerning for low-grade adenocarcinoma.

Typically, lesions that are less than 8 millimeters will not show up on PET scan. And typically, ground-glass opacities will not show activity significant enough on PET scan. She had non-specific, mild right hilar and subcarinal lymph node uptake that could be reactive. She had a focus of moderate FDG uptake in the sigmoid colon without any definite CT correlate.

This uptake could be physiologic. However, the patient would require a colonoscopy to completely clear her. The ground-glass opacity is suspicious for a low-grade adenocarcinoma, could be represented in this scan as well-differentiated adenocarcinoma, specifically in the right upper lobe from her earlier lesion and now the multiple lesions in the left lower lobe.

She is a former smoker with a 25 to 30 pack-year smoking history and quit 25 years ago. She was found to have multiple foci of new suspicious lesions on surveillance scans. And predominantly, these were located in the lower lobes of the lung. These counted a number up to 10. She had no new lung lesions that were suspicious on the right side of the lung and had adequate pulmonary function to tolerate a lobectomy.

Her FEV1 was 98% of predicted. Her DLCO was 87% of predicted. And preoperatively, you would like for these numbers to be greater than 60% for a patient to tolerate a lobectomy. Post-operatively, you'd like for those numbers to be greater than 40%, calculating how much lung you remove.

We discussed her care in the Multidisciplinary Lung Ablation Tumor Board. The left lower lobe predominant lesion and gave an indeterminate probability of invasive adenocarcinoma based on the CANARY analysis, which we will show you. Her PET scan was negative. Her brain MRI was negative. In patients who present with multifocal lung cancer, there is a 6% chance of a positive unexpected brain finding on MRI. The EBUS fine-needle aspiration on 6/14/2017 showed stations 11R, 4R, and 11L, all of which were negative.

The Multidisciplinary Lung Ablation Tumor Board is a compilation of thoracic surgeons radiologists, interventional radiologists, medical oncologists, researchers, pathologists, and radiation oncologists. All of these people come together to serve the patient and determine what reasonable intervention is best for the patient. We work in an multidisciplinary fashion to discuss these cases so that patients get what we can offer in the best way.

The CANARY analysis was developed to determine the predicted probability of a lung cancer or a presence of adenocarcinoma. This is a computerized learning algorithm that uses all of the factors associated with the lesion-- the solid component, the size, the change over time-- that go into predicting the characteristics of the nodule being a lung cancer or an adenocarcinoma.

The nodule number 1, which you can see in the histogram, has predominantly an indeterminate lesion, as is the second one, which was a good probability, with less red hues. Those lesions that have warm tones are more likely to be adenocarcinoma. And those lesions that are predominantly comprised of a histogram of cool tones are less likely to be adenocarcinoma.

You can see the location of the two different lesions, which is slightly subtly different. The strategy for resection can sometimes include factors like surgery, VATS surgery versus open, segmentectomy versus wedge versus lobectomy, stereotactic body radiation, brachytherapy, or ablation. The equipment that we use for the lung resection includes a mix of a VATS set and staplers.

The VATS slide that we use includes showing the port positions on the left side for a left-sided approach, with a utility port ranging from 2 to 4 centimeters just lateral to the nipple and the anterior axillary line, a camera port, which is typically 1 centimeter in the posterior axillary line, and then an optional additional port that is typically located just posterior and inferior to the utility port.

The Mayo Clinic VATS pan available by multiple different companies will show you the instrumentation that we use. This typical pan involves all the different instruments that you will see during this equipment setup and during this case. We also like to use an energy device at times. Some type of a bipolar or harmonic device is useful in these cases, especially to limit blood loss during the lymph node dissection.

The VATS left lower lobe begins with encircling, stapling, and dividing the inferior pulmonary vein on the left side. We then begin to encircle, staple, and divide the left lower lobe bronchial branches. We take the left lower lobe bronchus with an encircled stapler, and then that exposes the pulmonary artery. The pulmonary artery can then be taken as the entire basilar branches with the superior segmental branch all as one staple division, or with the superior division taken separately.

In the video, you will see, typically, the configuration of a patient who had left lower lobectomy. This is the particular patient that we discussed. The video begins with taking down the inferior pulmonary ligament. The inferior pulmonary ligament and the posterior aspect of the pleura can be taken with an electrocautery device. By bending the electrocautery device slightly at the tip, your increased range of motion is enhanced.

The aorta is in the center of the screen. The head of the patient is at the top of the screen. And the foot of the patient is at the bottom of the screen, along with the diaphragm. The pericardium is seen to the left. The inferior pulmonary ligament is being taken down. Any lymph nodes that are seen in this area are taken as a specimen.

A peanut device is passed through the anterior inferior port. The camera is in the posterior inferior port. And the peanut device is used to spread the tissue along the edge of the vein to show us the delineation of the superior segmental vein and the basilar vein. We can use the peanut device to completely encircle the inferior pulmonary vein on the left side. And once that pathway is well cleared, a stapler can be used to pass along the same way.

It is important to note that the peanut device is a very soft, blunt-tip instrument. One should avoid using sharp instruments when passing behind structures, especially when you cannot see where they're passing, and using tactical visual cues to notice when tension is being placed on a vessel. The stapler is a gray load stapler that encircles, staples, and divides the inferior pulmonary vein. That is the tightest staple line which is particularly useful on a structure as thin as the pulmonary vein.

The inferior pulmonary ligament has now completely been divided along with the inferior pulmonary vein. And subsequently, we are taking lymph nodes that are on the posterior aspect of the left lower lobe bronchus. A node grasper is particularly useful for this portion of the procedure. And going into the subcarinal space, taking the station 7 lymph nodes, which will be located slightly to the right, and then, to the left, those station 11 peribronchial lymph nodes will enhance your exposure of the bronchus.

Using the slightly bent tip cautery device will allow you to encircle, staple, and divide the bronchus as it is dissected free. However, sometimes it will be important to take lymph nodes as you encounter them. A Russian clamp can easily be used in this section of the surgery, where it can be used to grasp and firmly hold on to structures with a more broad intent, rather than using something fine like a long DeBakey.

Dual-action instruments are always better than single-action instruments, as they pass through the ports easier. Using the suction to pass around a structure is a safe way to pass, especially when you can see the artery just on the other side of the bronchus. Once we are successfully able to pass the suction device behind the bronchus, we know that our stapler will also be big enough to go around the back of the bronchus.

You should be careful during this section of the passage to make sure that you do not have tension on the lung, to make sure that you are not inadvertently dividing the entire left bronchus on the left main stem, and only taking the left lower lobe, and also to make sure that you have not damaged the pulmonary artery as you pass the stapler around the airway.

Taking additional lymph nodes at this point in the surgery is prudent. It will allow you to have better visualization and to see the passages better. It will also allow you to pass the instruments easier with less obstruction now that the lymph nodes are out of the way. When passing around the left lower lobe pulmonary artery, it's important to make sure that you have not inadvertently taken the lingular artery, as is seen on the left.

It is also important to make sure that you have not inadvertently taken any of the posterior additional branches going to the left upper lobe from the pulmonary artery. You only want to take the basilar pulmonary artery and/or the superior segmental pulmonary artery. In this case, we left the superior segmental pulmonary artery to be taken at a later time. And you will see it when the lung is retracted.

After that has been done, we then turn our attention towards taking the fissure. A small portion of the fissure was dissected to identify the lingular pulmonary artery branch and make sure that we were not inadvertently taking that. A completely stapled fissure means a shorter duration of hospital stay and a better seal of the lung with less post-operative air leak.

It is important to make sure that you are only taking the fissure and that you are not taking any additional portions of the hilum of the left lung. And you can see the pulmonary artery was quite close in the staple line.

Completing the fissure with an additional [INAUDIBLE] stapler will allow you to complete the fissure. It is important to start with a 45 stapler, as a 60 stapler may not be able to go into the port and take the front portion of the fissure with enough clearance. However, once you get towards the back of the lung, taking a 45-degree and changing it to a 60-degree will allow you to have a longer, more cost-effective staple line. And you should have adequate clearance.

Taking the posterior aspect of the fissure at this point, it's important to stay along the edge. To save money, you can sometimes try to remove the lung through the protected port. If the lung is too big and you're spilling blood into the chest, that is not good. So in some cases, we place the long into an Endo Catch bag. The port protector does cost money. And if you're taking a small portion of the lung, you can often take it inside the port. Delivering the smallest portion of the lung allows you to easily do that.

Here, you can see there is a bronchial artery that started bleeding after we completed our station 7 lymph node dissection. Applying a small sponge to the area is always a nice way to start to get hemostatic control. As you could see, this is a tiny little vessel. And just applying some electrocautery to the vessel and/or a clip will easily control the bleeding bronchial artery.

I would caution you to avoid placing clips onto small bronchial arteries prior to performing your staple lines because when you create the staple lines, it is possible for the clip to get caught.

In this portion of the movie, we're dissecting the AP window lymph node. And the AP window lymph node can easily be taken inside this area. You want to make sure that you're not damaging the phrenic nerve, which is just to the left side. And you want to make sure that you're not damaging the recurrent laryngeal nerve, which is wrapping and located very close to the AP window. By using a broad specimen grasper, you can hold on to the lymph node without having it fracture as you remove it.

After the pathologic specimen was examined, we found that stations 5, 7, 9L 10L, 11L, and multiple other intrapulmonary peribronchial lymph nodes were all negative for tumor. We took a total of 22 lymph nodes during this lobectomy. Forming 10 nodules ranging in size from 0.4 to 1 centimeter in size, the margin was negative for tumor.

The patient did well after surgery and was discharged on post-operative day number 3. She was noted to have a small infiltrate in the left area at the base of the lung. There is no infiltrate in the left lower lobe because the left lower lobe of the lung had been removed. She took Tylenol only for pain.

Some pearls and tips for this case include that you can take the left lower lobe sequentially from the bottom up approach only if it is safe. Make sure the superior segmental branch of the pulmonary artery has been taken as well as the bronchus.

Thank you for your attention. Now that we have completed the discussion of the case, we will discuss the criteria for the definition of second lung cancers. Martini and Melamed described the original criteria for defining synchronous versus primary multiple primary lung cancers.

The tumors are physically distinct and separate, and histologic type is different. If it's the same, it should be in a different segment, lobe, or lung if the origin is from carcinoma in situ, if there is no carcinoma in the common lymphatics, and if there is no extra pulmonary metastasis at the time of diagnosis.

With regard to metachronous multiple primary lung cancers, the histology should be different. And if the histology is identical, there should be a free interval between the cancers of two years, or the origin from carcinoma in situ, or the second cancer is in a different lobe or lung, but no carcinoma in the common lymphatics and no extra pulmonary metastasis in and at the time of diagnosis.

A modification of the Martini and Melamed criteria was published by [INAUDIBLE]. And that included either different histological conditions or in the case where you had same histological conditions with more than two of the following-- anatomically distinct, associated premalignant lesion, no systemic metastases, no mediastinal spread, and different DNA ploidy.

Shen and others published in the *Chest* edition in 2007 further delineated the criteria for second lung cancers. If they had the same histology but were anatomically separated, the cancers could be in different lobes, there should be no nodal disease in the N2 station or N3, and no systemic metastases.

If the lesions were the same histology but temporarily separated, they felt that a four-year interval between the cancers was reasonable and no systemic metastases from either cancer. If the lesions were of different histology, they felt that that would be sufficient, or if they had different molecular genetic characteristics, or they were arising separately from foci of carcinoma in situ.

There have been multiple different publications and more than 17 studies of patients with metachronous tumors, including more than 940 patients, 170 pneumonectomies, and a projected five-year survival for patients who present with metachronous primary lung cancer is projected to be between 23% and 70%.

One particular study published from here at Mayo Clinic include the discussion of metachronous primary lung cancers treated with surgery. They looked at 80 consecutive patients over 13 years. And of the 44 metachronous cancers, the first pulmonary resection was majorily resected as a lobectomy. The second pulmonary resection was less often lobectomy and more often a wedge resection or segmentectomy, although pneumonectomy was performed in seven patients.

For patients with metachronous disease, there were two patients with 30-day operative death. For the first resection, the five-year survival was over 50% for patients with stage I disease. And the 10-year survival was 27%. For the second resection, the five-year survival rate was 40% for stage I disease. And the 10-year survival rate was almost 30%.

The remaining 36 patients had synchronous cancers. And those were resected predominantly as a lobectomy. 22 of the 30-day operative deaths occurred making a 5.6% mortality rate. The five-year survival rate was 15.7%. And the 10-year survival rate was 14%.

The average lifelong rate of developing a new primary lung cancer approximates 1% to 6% per year after surgery for non-small cell lung cancer. The distinction between multiple synchronous or metachronous as being different from metastasis is very important and sometimes can be decided at the time of resection, but more often is better if it's clarified before surgery. The multiple synchronous primary lung cancers are potentially curative if they're detected at an early stage, evidenced by some patients going on to have long-term survival.

With regard to metachronous disease, newly developed molecular and genomic methods are expected to contribute a more solid and clear differentiation. Surgical treatment, whenever feasible, is considered the modality of choice for most of these patients, especially patients with second primary lung cancers, as opposed to those with metastases who are more typically treated with palliative care. Newer ablative techniques can often be tested and may be eventually proven to be equivalent. Currently, these are still being studied.

The type and extent of surgery should focus on parenchymal-sparing approaches, yet adequate cancer surgery. The prognosis of patients with second primary lung cancers largely depends on the time of detection, the stage of disease, the location of the second cancer. Surveillance after surgical resection of the initial tumor is primary, mandatory.

Metachronous disease, presented as a group of patients from Yang and others in the *Annals of Thoracic Surgery* in 2014, looking at patients who had a first lung cancer, there were 143 patients. The majority of them were men. Most of them had less than a 20 pack-year smoking history. The majority of the approach was thoracotomy. And the resection preferred was a lobectomy for these patients.

The perioperative findings of the second intervention included that the patients had a compromised FEV1 in 18% of the time, that the second approach was most of the time a thoracotomy, and that the metachronous tumor was more often on the contralateral side. The extent of the second resection in this series was often again a contralateral lobectomy.

When looking at overall survival for patients who present with a metachronous lung cancer in primary lung cancers and the second metachronous resection, was probably markedly less in the second tumor resection than at the time of the first tumor resection, as expected.

The survival curves are seen. For the first tumor resection on the left, on the slide labeled "A," the second tumor resection on the right, on the graph labeled "B." When looking at factors that affected survival, the stage of the tumor was the number-one driving factor. Those with an earlier stage had a better survival.

When looking at additional factors, tumor size played a role. Tumor size-- with a tumor less than 2 centimeters predicted an improved survival. Patients who had a pack-year smoking history less than 20 also had an improved survival. Patients who had non-multiple station lymph nodes that were positive also had improved survival.

Gender also played a role. Women tend to fare better than men when it came to looking at patients who survive with regard to metachronous lung cancer. Those who did not have N2 disease also had a better survival. And those who did not require a pneumonectomy had improved survival, as would be expected. Those patients requiring a completion pneumonectomy had a markedly decreased survival curve.

When looking at a multivariable analysis for independent risk factors of survival, again, seen with an odds ratio presentation, those with a TNM stage II or higher were twice as likely to have a poor survival. Those with a pack-year smoking history greater than 20 years had an odds ratio of 1.8. And those with a tumor size greater than 2 centimeters had an odds ratio of 1.9. All of these were statistically significant.

When graphing the survival, as according to Taioli and others, including a paper that was conducted by Raja Flores in the *Seminars of Thoracic Surgery,* they looked at patients who were treated with primary lung cancer and a second primary lung cancer.

Those who were treated for a second primary lung cancer fared the best if they had surgical intervention. Those that were treated with radiation, such as stereotactic radiation, fared the second best. And those that didn't get surgery or radiation fared the worst. Of course, some of these patients may not have been treatment candidates and may have been taken down a palliative role.

When looking at the multivariable analysis of determinants of overall survival for the second primary lung cancer, this group also found that surgery for the second lung cancer was predictive of a better survival. Radiation for a second lung cancer also predicted better survival, but was inferior to surgery. Those patients who had an advanced stage had an almost 2.8 times hazard ratio, making a worse survival.

And those who were, according to age, every year increase in increment of age, predicted a worse survival. The time between the first and the second cancer also seemed to be somewhat predictive. When looking at the variables that predicted overall survival for the primary lung cancer, again, surgery, radiation, stage, age, and time between the cancers was predictive.

MD Anderson then performed a study led by David Rice, looking at second primary lung cancers. They analyzed 569 patients who underwent complete resection of pathologic stage I lung cancer. The median follow up was almost six years. And the second primary tumors developed in 88 or 15% of their patients. 56% of these were second primary lung cancers with an incidence of 1.99 per 100 patient years. The median interval from initial surgery was four years.

The second primary lung cancer never developed in patients who had never smoked. And the current smokers had a higher incidence of second primary lung cancer than former smokers. Age, sex, stage, histology, tumor location, and initial surgery had no effect on the second primary lung cancer development.

Despite semiannual follow-up with chest radiographs, 24% of patients had metastatic disease at the time of diagnosis of the second primary lung cancer. Surgical resection was performed in only 63% of these patients because those that presented with metastatic disease often were not referred for surgery. The median survival in the surgical group was four years and in the non-surgical group was only one year. This was statistically significant, as Dr. Flores's study showed. The second primary lung cancer-related mortality for the whole cohort was 3.7%.

Our treatment algorithm for patients who present with synchronous bilateral lung primary disease includes an initial history and physical, an assessment for fitness for surgery, pulmonary function testing, and if the FEV1 and DLCO predict poor outcome, we perform cardiopulmonary exercise testing and/or VQ testing and/or a six-minute walk test.

CAT scan, PET scan, brain MRI, mediastinal staging, less invasive before more invasive, CANARY analysis on occasion, and Multidisciplinary Thoracic Tumor Board discussion. Brain MRI is very important, as many of these patients will have undetected brain metastases. Therefore, we recommend all patients with separate primary lung cancers be considered for brain evaluation.

Our study that has been submitted for publication led by Dr. Leventakos and company included a 14-year period with 146 patients initially thought to have multifocal lung cancer. There was no clinical evidence of lymph node involvement in any of these patients. 32 of these patients had brain imaging performed during the evaluation, 28 having an MRI and 4 having CT. And 78% of these patients presented with synchronous primary lung lesions. Two of these patients had brain mets, and this drastically changed our management.

They concluded that multiple primary lung cancer seems to be increasing, and it may be due to contemporary screening strategies and improvement and survival, which then leads to a concomitantly increased opportunity to develop new primary lung cancers. All of these patients should be adequately staged prior to undergoing any type of treatment modality.

The increasing incidence of adenocarcinoma will lead to the clinical scenario where both lesions will have the same histology. Multifocal adenocarcinoma is a separate clinical entity that requires special consideration. Treatment requires careful coordination and assessment in a multidisciplinary team. This includes a careful review of all the studies available and all of the pathology slides and assessment for surgical fitness by a thoracic surgeon.

Patients with metachronous lung cancer should be approached with a curative intent as long as a select group of patients will be experiencing long-term survival, as seen in many of these studies that I've presented to you.

With regard to multiple primary lung cancer management, stage is the most significant predictor of overall survival after resection. Surgery currently is the best standard available. Standard principles of surgical resection should include anatomic resection, like a segmentectomy, and a parenchymal-sparing approach.

In those patients that are high-risk surgical candidates after cardiopulmonary exercise testing or who are likely to require treatment for additional lesions, one or more potentially multiple lesions could be considered for definitive non-operative local therapy such as stereotactic body radiation or ablative therapy with cryotherapy or microwave therapy.

Patients with resected synchronous primaries-- the decision to give adjuvant platinum-based chemotherapy should be based on the lesion with the highest stage. In patients with either synchronous or metachronous stage II or III lung cancer, adjuvant cisplatin-based chemotherapy should be considered based on the survival benefit observed in patients with a single resected lesion.

Some pearls to take from our presentation-- always give patients the benefit of the doubt. Resect the least amount of lung in the least invasive manner the first time, but with the best cancer resection, to avoid completion pneumonectomy or contralateral recurrence after a pneumonectomy scenario.

In patients with adequate pulmonary reserve, another parenchymal-sparing approach should then be considered if they present with new cancers. Extraordinary measures should be taken only after a Multidisciplinary Thoracic Tumor Board discussion in an experienced center treating such disease.

We'd like to thank you for your attention. And we look forward to having an interesting discussion with you following this presentation. Thank you again for allowing us to present multiple synchronous primary lung cancers and metachronous primary lung cancers to you today.