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Should Surgery Have a Role in Managing Very Limited Small Cell Lung Cancer (SCLC)?

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Dr. West:

I'm going to turn now about a controversial topic in small cell lung cancer and that is the issue of whether we should be doing surgery potentially for the minority of patients with small cell lung cancer that appears to be very early stage. That's not the majority of patients with small cell cancer, but the issue comes up from time to time and we'll talk about why we might consider that.

To start with, we'll go over some basic principles about how small cell lung cancer tends to behave and the demographics behind it. What we've actually seen over the last several decades is an ongoing decline in the incidents of small cell lung cancer. When I was medical school we were taught that small cell lung cancer accounts for about 25% of lung cancer and by the time I was in my residency training after medical school, it was about 20%, then 15% and pretty much every time we look those numbers are going down to now 13% or less of lung cancer in the United States. Why that is, is somewhat debatable, but what we typically see is a breakdown in the staging that is 1/3 limited disease and 2/3 extensive. Although there is a staging system that goes from stage I to stage IV in small cell lung cancer, like non-small cell lung cancer, most of the studies and our treatment approaches are based on a breakdown of whether the cancer is limited to the same side of the chest, the main cancer and lymph nodes involves all within what could be treated with one radiation field, radiation port, or whether it is extensive; that is spreading to the other side of the chest, to the liver, to the bones, the brain, adrenal glands, etc.

Most of the time, even limited disease involves the lymph nodes nearby and often in the middle of the chest. Its really only about 5%, if that, proportion who have what some have termed very limited small cell lung cancer that would be stage I or stage II, where there's no nodal involvement in the middle of the chest, the mediastinum.

Importantly, as well most patients are not staged with surgical procedures and the available evidence is that when we have done more detail staging such as surgery, even a limited surgery, we find that a lot of the patients who on scans don't appear to have involvement of nodes actually do. We maybe over-interpreting the proportion of patients who have very limited disease because we're only assessing on our CT scans or PET scans which may under-represent the extent of spread.

Small cell lung cancer tends to spread early on and because of that and the fact that it is so sensitive to chemo and radiation, at least initially, the main treatment approach with curative intent for patients with limited stage small cell lung cancer is a combination of chemotherapy and concomitant chest radiation.

Surgery is certainly something that may be considered and it has been done before, particularly for patients who seem to have this very limited small cell lung cancer; that is with either no nodes involved, or maybe with some N1, that is lymph nodes involved that are within the lung but not in

the middle of the chest between the two lungs, disease. We'll talk more about why we might consider that.

The main support has come from a series of retrospective studies looking back at the experience at a single institution often over a course of several decades. In the studies that have been published on the results for patients who have undergone surgery for early small cell lung cancer, they have largely been encouraging enough for the authors, who are usually lung surgeons, to advocate that we think about this more significantly than in general we do in the cancer community.

You can see from the table in the middle of this slide that these studies are still with small numbers of patients even though they are collecting patients over all of them more than ten years, and in some cases 30 years; but we're talking about a few dozen patients; and when you really restrict to the patients who appear to have stage I small cell lung cancer, you're talking about anywhere from 18 to 48 patients in the largest series, and that is over a course of many, many years.

The results do look pretty favorable, with five-year survival in the range of 27%-42% for the overall resected population. And higher than that in the patients with stage I disease, even in some cases beyond 50%.

A key to point to make is that we're talking about a very, very limited group of patients over many, many years at centers that have been treating many cancer patients. So this is clearly not for the majority of patients, and a key question is whether there is something different about these patients and maybe it has more to do with the cancer than with the treatment that these patients have undergone.

What we can say is that there really are other settings in lung cancer or other thoracic cancers where these kinds of questions have come up asking whether it has more to do with the unique characteristics of the cancer itself than the treatment we pursue for it. For instance, indolent slow-growing bronchioalveolar carcinoma, or BAC, has been associated with a very prolonged survival certainly in patients with very small early stage lung cancers and even in patients with more advanced multifocal cancers. Because of that, people have asked whether the treatments that we use that seem to produce better results than we see in other lung cancers is really because of the great effectiveness of our treatments or just that we're seeing the natural history of a slower process.

We've seen in patients who have limited mesothelioma who may have surgery and do very well the question of whether they're doing well because they have the surgery or because they were unusually fit and had unusually limited mesothelioma or a mesothelioma that responded especially well to chemotherapy before surgery, raising the question of whether it really was the behavior of the cancer and not the issue of the surgery conferring the great benefit.

We know that patients who have preoperative chemo and radiation for, say, a stage IIIA non-small cell lung cancer do better and often far better if they had a very good response prior to surgery. And, the people who had no evidence of any residual cancer at the time of surgery, or at least clearance and sterilization of areas of nodal involvement do much better over a long-term period. We don't know whether it's because the subsequent surgery did a great job or whether the people who responded the best were going to do very well because they had very responsive cancer.

Finally, the issue of patients with a very low tumor burden people, with a so-called precocious metastasis to the brain or the adrenal glands, who sometimes defy all odds of how well a patient can do with so-called metastatic disease, we don't know whether it is because they were treated very aggressively for metastatic disease or because they had the unusual situation of having a very low tumor burden over a long period of time that made them a remarkable case, even regardless of how they were treated.

So, this issue keeps coming up about whether it's really the treatment or is it the value of patient selection?

The new issue that has come up, I should say what has really stimulated the further discussion of this question is an analysis of a large database called SEER, just published in the *Journal of Thoracic Oncology* within the last couple of months looking at the outcomes for a little over 1,500 patients with stage I small cell lung cancer who were treated at a wide range of centers in the United States over a 16-year period.

Of those 1,500 or so patients, 205 underwent a lobectomy surgery and didn't receive postoperative radiation, which is a debatable component of small cell lung cancer treatment in patients who have undergone surgery. It really isolates the potential value of surgery as the local treatment for the cancer that you can see. What the study reported was that the five-year survival for the patients who underwent surgery was about 50%, and that was more than was seen for the five-year survival for people who did not undergo surgery for stage I small cell lung cancer.

There are a few important caveats to add. I mentioned earlier that for the patients who haven't undergone surgery that is really a combination of patients who truly have stage I disease and patients who on scans looked like they have stage I disease, but would have been found, had they gone to surgery, to have more advanced disease. So we almost inevitably see that the surgically staged populations in lung cancers and other settings do better than the people staged without surgery because it's a higher bar to be stage I after surgery than based on scans alone.

Another issue is that the patients who underwent surgery may have been the patients who were unusually fit, younger, may have had the smallest tumor burden, smaller nodes, smaller nodules than the patients who were still stage I but for whatever reason were not offered or did not pursue surgery.

There are other reasons to be cautious about the role of surgery for even very limited small cell lung cancer. One point is the patients who maybe very well suited for surgery are actually very rare and they can be hard to identify. There just are not that many out there and at our own center, even though I have several expert thoracic surgeons available who are very eager to do surgery on the appropriate patients, we have only had 2-3-4 patients over the last 5-6 years who have really been candidates for surgery and have undergone surgery for small cell lung cancer. And, in fact, most of those who have were actually not known to have small cell lung cancer until after their surgery. They underwent surgery for a nodule in the lung that was presumed to be a lung cancer, but was not known to be a small cell lung cancer beforehand. And that's often the way that we learn about patients having small cell lung cancer that is very limited stage: it's an incidental finding for people who have already had surgery.

Another key issue is that many patients who are seen by thoracic surgeons are not getting the kind of very attentive and thorough preoperative workup and staging studies that really would need to be done if we're going to routinely offer an approach like this for appropriate patients.

That whole concept is predicated on limiting this to the appropriate patients who would only be identified if thoracic surgeons are very vigorous in their selection.

In fact, as shown in the lower part of this slide, a pivotal study was published a few years ago in the *Annals of Thoracic Surgery* by Alex Little and colleagues. They looked at the results for over 11,000 patients who underwent surgery at a wide range of institutions in the United States. They found that of those 11,000 patients who underwent lung surgery, only 27% had a mediastinoscopy before surgery. Even of those who had a mediastinoscopy less than half the patients had any lymph nodes actually removed. They might have looked there but they didn't take any nodal tissue out, which is really not an effective way of screening for nodal involvement. Only 42% of the patients had any mediastinal nodes taken out during the course of surgery.

This is not ancient history, and this is at a wide range of centers throughout North America, throughout the United States and it just underscores the sobering conclusion that many patients are not getting the detailed and vigorous selection and proper staging that we would like patients to have when they undergo surgery. That would make me very cautious about surgery being done on not only the few arguably appropriate patients with small cell lung cancer, but many who would not be well served by this. If patients were to undergo surgery and have residual cancer left behind, that surgery was not a valuable one.

We also know that chemotherapy has been the cornerstone of treatment for patients with small cell lung cancer. It's often very responsive. At the same time we know that undergoing a big lung surgery does not make it easier to deliver that chemotherapy. This table comes from the postoperative experience in patients with non-small cell lung cancer, which is certainly emerging as an appropriate standard of care and has been for a few years, but the fact remains that it is a challenge to deliver the intended treatment as you would like.

As shown in the column in the middle on completed therapy, only about half to two thirds of the patients in most of these studies completed 3-4 cycles of post-operative chemotherapy. You can certainly imagine that in addition to the challenge of just giving chemo under any circumstance, the people who were still recovering from a big lung surgery may have particular challenges in recovering from the pain, the bowel issues, everything else related to a big surgery and then moving into chemotherapy after that.

So I would be very cautious about having any less-proven treatment like surgery compromise the ability to deliver a better proven treatment like chemotherapy in the setting of small cell lung cancer.

Now, there was an accompanying editorial in the *Journal of Thoracic Oncology* by an excellent and very highly regarded medical oncologist in Toronto, Dr. Frances Shepherd, and she raised the challenge of doing a large randomized, worldwide study for patients with very limited small cell lung cancer in which patients would be randomized to undergo surgery followed by chemotherapy, or non-surgical treatment with a combination of chemo and radiation. She acknowledged that this would require years of enrolling these rare patients and would require international collaboration.

Unfortunately, I really think that this approach is not feasible. These patients are really very unusual, and I think especially if we were to demand rigorous preoperative staging such as with a mediastinoscopy, we'd found that there are not enough patients to continue a global trial like this and actually expect to have it completed. At the same time, many physicians and certainly many patients would have their own feelings about whether they want to pursue or not.

The fact is that many people would find it not acceptable to have essentially a computerized coin flip dictate whether they undergo surgery or not. We have found that historically it's hard to do studies that randomize patients to a big issue like surgery or not. I think that would be a very significant challenge, and given the small numbers of patients who would be eligible for such a trial, I don't think it is something that we could ever hope to get a large scale answer to.

So in the meantime, I would say that surgery remains an option in the rare and well-selected patients preferably selected by very attentive surgeons who are skeptical about doing this in patients with mediastinal node involvement. I think it's appropriate to say that the benefit from surgery is still unclear. Patients with this stage of cancer may do very well and be cured with chemo and radiation and may be the very patients who do especially well even compared with the general statistics for limited stage small cell lung cancer, because they have a different biology that may keep the cancer small and localized rather than spreading over time, which is just not the typical pattern for small cell lung cancer.

I'll close with that. I'll address a couple of questions that have come in. One is if you knew someone had very early stage small cell lung cancer, would you recommend surgery?

I've betrayed my bias here. I think I would not be inclined to recommend it. I do think it is worth a discussion and something that I would discuss with the patient, and in fairness have them see and talk with a thoracic surgeon about the pros and cons of this. I think it is quite reasonable to do surgery if we are confident that someone could get through that and then get the established treatment of chemotherapy. But, if there was a patient in front of me who I was not convinced could get through that bimodality approach, I would consider chemotherapy to be the higher priority here.

Let me open this up to Dr. Weiss. What is your sense? Have you had any patients prospectively come to you with this, and/or have you had patients who after surgery have had small cell lung cancer and how have you approached it?

Dr. Weiss: So I'm not sure I can remember offhand the patient who has prospectively shown up with known, very limited stage small cell lung cancer. I think the patients I've seen are still small in number are patients who have incidentally been found to have small cell at the time of surgery. Patients who've gone on to get a full appropriate surgery for what was either believed to be a non-small cell lung cancer or for a mass that was too small to effectively get a biopsy in whom the surgery was effective for biopsy and then we found out after. The question was okay what do we do now? In the theoretical case of seeing a patient where in advance we know that there's a very limited stage I small cell lung cancer, I would not have a problem with surgery as long as there was determination to follow it up with chemotherapy.

I think the most key point here is the one that you've made most strongly and very well from your presentation in answering this question is that we don't know, we don't have large numbers of patients to really address that question with.

Dr. West: What about post-op and managing someone happens to show up after a surgery for say an unsuspected small cell that appears to be a stage I small cell, how have you approached those patients if you've had them?

Dr. Weiss: I have had a few of those. I think it goes back to the old trials in small cell lung cancer where small cell is a unique example in which in a chemoradiotherapy regimen, it's the chemotherapy that's actually doing the heavy lifting. Small cell is an extraordinarily chemo-sensitive cancer. So for my institution the approach has been to always follow-up with adjuvant chemotherapy regardless of the size of the cancer.

Dr. West: One other question is someone has said its great to know that the incidents of small cell lung cancer is declining, but why are we seeing that? Do you want to field some potential explanations for that?

Dr. Weiss: I have one guess, and I suspect its in the majority of thinking that it has a lot to do with trends in smoking. I think that the biggest affect maybe the effect of filters. Many people unfortunately are still smoking, but as the demographics break down people are smoking with filters more than ever before. The consequence of this is that its going to be the smaller particles that get through that tend to deposit more distally, far out in the periphery of the lung and that's going to predispose you more to a non-small cell lung cancer than to the small cell lung cancer that may be dependent on the larger more centrally deposited particles.

Dr. West: I agree that its highly likely to be directly related to smoking patterns. We just see far fewer patients who not only are no longer current smokers, but we see less long-time, multiple packs per day smoking which is not the invariable pattern with small cell, but most commonly in small cell its not only in smokers but in people who have smoked a lot for years.

In contrast, what we're seeing more of is never-smoker lung cancer and adenocarcinomas versus squamous cell carcinomas in patients with non-small cell lung cancer, and we know that squamous cell carcinoma, like small cell tends to arise in the middle of the chest, while adenocarcinomas tend to rise in the periphery of the lungs. That fits in with the concepts that smaller particulates are getting out further in the lungs when you smoke through a filter. When we were seeing more use of unfiltered cigarettes it makes more sense you'd have larger particulates causing cancers more centrally in the chest.

In fact, what we see with a review of adenocarcinoma versus squamous over time, and in different parts of the world and even in different demographic groups, it really matches with the time lag, the transition from unfiltered to filtered cigarettes. I think that's the leading expectation and I think along with that, we're probably going to see a continued decline in small cell lung cancer, which is great. But in the meantime it makes it quite challenging to do studies that are going to help us with addressing the optimal treatment approaches for patients with small lung cancer today.