



Challenges of Managing Frail and Elderly Patients with Lung Cancer, Part 1: Considerations for Adjuvant Therapy, with Drs. Paul J. Hesketh & Karen Kelly

Dr. West: Hello and welcome everyone my name is Jack West, I'm a Medical Oncologist and the President and CEO of GRACE, the Global Resource for Advancing Cancer Education.

I'm happy to be here with two great colleagues of mine from other parts of the country to talk about challenges of treating elderly and frail patients with lung cancer.

With me today are Dr. Paul Hesketh, who's a Medical Oncologist, and Director of Thoracic Oncology at the Lahey Clinic just outside of Boston in Burlington, Massachusetts; and also Dr. Karen Kelly from Kansas University Medical Center in Kansas City. She is a medical oncologist with an internationally recognized expertise in lung cancer.

Here are the declared conflicts of interest for each of us on the program.

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We're going to cover several cases that highlight the challenges of treating lung cancer in a frail, often elderly patient population.

So the first case is in the setting of early stage, non-small cell lung cancer. This is a 77 year-old woman who was referred to me for consideration of adjuvant chemotherapy after resection of an early stage, a stage two non small cell lung cancer a few years ago.

She's actually a lifelong never-smoker and has a history of hypothyroidism and atrial fibrillation, and she had presented to an outside emergency room with some right chest discomfort, and that led to a CT angiogram to look for a possible pulmonary embolus. That wasn't seen, but the scan did reveal a 1.6 centimeter pleural-based lesion in the superior segment of the right lower lobe, and I'll show that a little later.

She was subsequently referred to a pulmonologist, and she didn't actually see him for a few months, but by the time she came back a repeat CT was done that showed that the nodule had grown in that interval of a few months to two centimeters. She also had a PET/CT done around that time that showed that there was significant uptake, hyper-metabolism consistent with a high probability of a cancer, with the standard uptake value of 7.6. And there was no other evidence of increased uptake in any of the lymph nodes of the chest, or distantly.

She had good lung function tests, as shown in the bottom of the slide, that are measures of whether a patient is likely to tolerate surgery or not, and she ended up going on to surgery.

This is the scan showing her lesion in the bottom portion of the slide here; this is the base of her right lung; and this is really along her back.

She underwent what's called a wedge resection, where the surgeon removed just a portion of the lung tissue where the cancer was, and at the point it was to establish the diagnosis of a presumed cancer, and after that he had her undergo what's called a completion lobectomy.

So she he had her entire right lower lobe removed, and with that I'll start with the first question of whether, Paul or Karen, you think that you would clearly recommend a lobectomy, or do you personally, or at your institution when talking about such cases, question whether all patients should have a lobectomy, versus which ones might do as well with a wedge resection? And I would say that could be based on the size of the cancer, or how aggressive it seems to be, as well as potentially the age of a patient.

Dr. Hesketh: I think it's a very important question, because I think the simple answer is we don't know a definite answer yet. But clearly this is an issue that's being studied, and I think the question really is, "Can we take a lung cancer out and have a successful surgery for cure and not have to sacrifice as much lung as we normally would when we take an entire lobe?"

And I think that we have some clues that would suggest that, in fact, that might be the case. Because, basically, there is some data that would suggest that -- I know that the SEER data looked at this, and we have some analysis of that that actually showed that there was no difference in outcome whether one did a segmentectomy or wedge versus a full lobectomy.

And I think, more importantly, this is being studied prospectively by one of the National Cancer Institute sponsored groups known as the CALGB; and there is a study underway right now in which patients are being randomized with small lesions, such as this patient, which are kind of located in the distal, the peripheral part of the lung, which this lesion is. And they're randomized to either receive the standard full lobe resection or to basically have a smaller resection. Where there's either a so called wedge or a so called segmentectomy: both less lung being removed than with the standard lobectomy. So I think that right now it's an open question.

I think that my own feeling, and my own approach is that if the patient has concern, if we have concerns about the patients' pulmonary status post operatively and we think that they're somewhat marginal, then I think that is a reasonable thing to consider. My own feeling would be that if the patient has excellent pulmonary function, until we have the results of the prospective study underway, I probably would still recommend a lobectomy. And this patients' lung function is excellent and she certainly could tolerate a lobectomy without difficulty.

Dr. West: With the degree of comorbidities, other medical problems that could be perhaps a greater issue than perhaps her cancer, or in her case not that much, but would the issue of how much or how little other medical issues a person have factor significantly into your thoughts on this?

Dr. Hesketh: I think it clearly could. I think the primary issue is probably the extent of pulmonary reserve, but clearly if the patient had significant cardiovascular issues or significant other comorbid problems, I think this patient has a history of atrial fibrillation, but she basically is a never smoker which probably explains why her pulmonary function is so good. And she doesn't seem to have a lot of other medical problems, so I think at least in her case it would seem like the standard operation is still a very reasonable one.

Dr. West: Karen, what are your thoughts?

Dr. Kelly: Yes, I just want to add a couple of things. I agree with what Paul has said, and I think our evaluation of this patient who -- really, you know her age is 77, but I think the thing that's going to come out throughout this hour conversation -- is that age alone shouldn't really impact very much on the decision-making process. That you have to really consider other factors in addition to age, but age itself, most likely most of the time, I guess, perhaps we might argue that a little bit when they're in their 80's, but I think we could argue that there is data to say that patients can undergo a surgery successfully even in that age category as well.

But two important points I want to make here is that she really is in excellent health, as you said from the pulmonary function, and I think that we would have, as Paul said, recommended a lobectomy, because she really doesn't have any negative physiological factors for undergoing a lobectomy. And she has some other concerning factors. I think having perhaps a SUV value of 7.6 to me is a little concerning.

I think that the other very, very important issue that I want to raise, and I think this patient really highlights this is staging. When you do just a wedge resection, many times we don't get any lymph nodes at all, and had this patient only had this wedge resection we wouldn't have known about that lymph node that was involved that has now changed her staging.

I think the other important thing here that I also get concerned about, and I'm sure we'll talk about it, is the fact that she did have pleural invasion, albeit these are very minor things, albeit very important and negative prognostic factors for her, so I think accurate staging here is very critical in this patient. She herself, I think in looking at her, is fine. Tumor-wise I think she does have some negative prognostic factors.

Dr. West: That's interesting, because definitely the issue of getting more versus less information about pathologic staging is a real factor. Consistently we see that patients who are pathologically staged do better than the patients who have stage basically estimated based on scans, because scans can underestimate the extent of disease. And by the same token a more limited surgery is going to yield less material to make a precise staging. And then, as you said, the standard

uptake value on the PET scan, as well as the degree of interval change over a few months, is suggestive that this isn't an exceptionally indolent cancer.

She ended up having pathology reviewed, that showed a 1.8 centimeter adenocarcinoma with some features of bronchioloalveolar carcinoma peripherally. It was moderately differentiated overall, and there was a rare focus of tumor involving the visceral pleura, so even though this was a smaller tumor, this was designated T2, and there was a single lymph node out of ten that were resected that had a microscopic focus of adenocarcinoma in it that was 4 millimeters.

And so with that, there's a question that may not be very age-specific, but what would your thoughts be about her staging and the recommendation or your enthusiasm for post operative therapy? Either chemotherapy or EGFR-based therapy or both? She is stage II with a microscopic focus in a single node and a smaller tumor. So, Karen, what are your thoughts?

Dr. Kelly: Well, and she does have that limited pleural invasion. Again, I think there are several retrospective analyses that does show that does show that this is a poor prognostic factor, albeit minor, I still think we have to take them on face value. So my recommendation, or my conversation with this patient, clearly does include chemotherapy.

I think that we all know from the LACE meta-analysis, as well as the more recent meta-analysis from the Non-Small Cell Lung Cancer Collaborative Group that was published in Lancet recently this year, shows that patients who receive adjuvant chemotherapy do get a benefit. And we know that this particular group, those patients who had N1 disease and N2 disease, really do have the most benefit.

Now when we look at the adjuvant trial that was conducted from Canada, the JBR.10 trial, they had done a subset analysis of patients, of the elderly patients, and showed that overall, patients over the age of 70 did do as well in terms of their survival, but they did have some concerns with their toxicity.

They also did this very tiny subset analysis of patients over the age of 75, although I think there were only about 12 patients per arm in that limited subset, that did show significant harm to those patients in overall survival. But that is such a small number of patients I don't think that we can really make too much out of that, but to inform the patients of those results. I think overall that if there's a patient who should most likely receive chemotherapy, in my opinion I think I would typically probably do a dose modification, and I'd be interested about what Paul's thoughts about this are, because toxicity really is the primary issue here that we're concerned about here. And so I think that I would typically, in these elderly patients, consider doing really a dose modification from the beginning. Like I said, I'd be interested in what you all do.

Dr. Hesketh: Well I agree that I would definitely have a discussion with the patient in which my recommendation would be to consider adjuvant therapy. Interestingly, that's really done unfortunately in the absence of much data with regard to the older patients, and I think that one of the consistent themes, Jack, that will be coming

back to time and time again with all the cases is that unlike the younger patients, we really have a paucity of data on which to base our recommendations. And I think that the LACE meta-analysis that Karen referred to, which looked at all of the adjuvant studies, was very important in showing the overall benefit for chemotherapy in the entire population. But when you actually look at the number of elderly patients that was included, it was extraordinarily small. So I think we right now have a paucity of data on which to make sort of evidence-based recommendations.

That said, in the real world you have to make a recommendation for a given patient, and I think that I would look again at the patient's physiologic status; the age is a consideration, but I think it's less important than what the patient's physiologic status is. And this patient appears to be in reasonably good shape. We don't have information about things like her renal function and her other organ function, her nutrition status, etc. But assuming that she has good renal function and her other organ function is intact, then I definitely would recommend adjuvant therapy.

In terms of what therapy to utilize, I think again it really depends on how good a shape she's in, because as we know the evidence supports a cisplatin-based adjuvant regimen. And people may be a bit leery and nervous about using cisplatin because of its potential renal toxicity in someone who's 77, but if this individual is fortunate enough to have had very preserved renal function, then I would still consider using cisplatin, probably combined with an agent such as pemetrexed, given her histology.

And I think one of the advantages of using cisplatin as opposed to, say, carboplatin, is that it's going to be less suppressive of her bone marrow and, as long as her renal function is ok, she's likely to have less toxicity in terms of her blood counts and the risk of infection. So I think we'd have to have a little bit more information as to what regimen to recommend, but clearly my discussion would be favoring adjuvant therapy, yes.

Dr. West: And age, even in somebody who is in their late 70's, would not preclude you from at least considering a cisplatin-based regimen over carboplatin as a general policy.

Dr. Hesketh: That's correct. I've always been a relative cisplatin fan, even at times where that didn't seem to be the most popular choice, but as we know, the data now is sort of coming back to that agent, at least in terms of what's available. So as long as her function is ok and her renal function is sufficient, I would consider that. I might, as Karen suggests, maybe use a somewhat lower dose of cisplatin, but I think that probably would still be my preferred regimen if I thought I could get away with it safely.

Dr. Kelly: I think I agree. I would recommend a cisplatin-based regimen. I think that this is the setting where cisplatin really is the platinum of choice when you're going for a cure in this patient population. And as Paul already alluded to, if her renal function is fine -- I think you have to monitor -- I do think these patients should be monitored a little bit more closely, because even in the LACE meta-analysis and the more recent meta-analysis, toxicity can be an issue here. And I think

that that is really the more worrisome thing in these particular patients, is really toxicity.

And their ability to complete the treatment, even in the JBR.10, the LACE meta-analysis and even the more recent analysis, the elderly patients did not receive all their drugs and yet they still did great from a survival point of view. But didn't do so well from toxicity point of view, and certainly I think we absolutely need to minimize toxicity in this, in all patients, but particularly in the elderly, who may have a more severe magnitude of toxicity as has been demonstrated. I think that's one thing that we can say the data will support: they do tend to have more toxicity.

So I agree completely with a cisplatin-based regimen. I do tend to maybe start off a little bit, just tweak the regimen a little bit. I think it's important to remember that most of us probably don't use the regimens that were used in these clinical trials. I know that I typically don't use the dosing (I don't think anyone does -- I could stand corrected), the dosing that was used in the JBR10 trial with the cis/vinorelbine, so I think tweaking the doses here a little bit or changing to pemetrexed/cisplatin would be reasonable as well, but certainly a platinum-based regimen I would recommend.

Dr. West: It's not going to be unusual for an older patient to have a renal function that is more marginal – a creatinine of 1.5 or 1.6. In such cases, would you be inclined if you would otherwise be recommending adjuvant chemotherapy to recommend a carboplatin doublet, still consider cisplatin but monitor more closely, or would you say well the data are with cis, so it's cis or it's nothing?

Dr. Hesketh: In that situation, Jack, I think that most of us are pretty pragmatic, and I think that if the renal function is somewhat impaired and we think we're going to get into trouble with cis, then I think it's perfectly reasonable to use carboplatin in that situation. Because to start out with cis when you know you're potentially going to get in trouble and have all kinds of issues with renal failure which compromises subsequent chemotherapy administration, I think you're much better off if you can start with carboplatin and successfully get in four cycles then if you start out with cisplatin in a marginal patient and then have excessive delays and not end up getting in any kind of reasonable therapy. So I think that we don't have data for it, but I think it's a reasonable concession to make if the renal function is not excellent.

Dr. Kelly: Yes, and I think, Paul, you said that very well. I agree 100% -- I would do the same. You would just switch out to carboplatin, as you would most likely in any patient regardless of their age who have that issue.

Dr. West: Right. I wonder also if somebody came and you felt that they would benefit from adjuvant chemotherapy but they were leery about toxicities and felt you didn't want to scare them away from it, really the question is whether a carbo doublet is better than nothing even if it's a compromise.

Dr. Kelly: I think if it's not renal toxicity, I think you raise a good point, because again it is about getting the drugs in and that's why I made the comment of really maybe tweaking the doses from cycle one in the beginning. Because you want to be

able to get these doses in; you want them not to have the problems of delayed dosing, weeks of delay, having toxicities that these patients will say that they're not going to do it again. I think this is a patient population that's also very pragmatic. If they're getting toxicities that are significant, as we've seen and the data will show us, they're not going to be as likely to want to continue on. They're going to be the patients that say, "Gee I'm done with this."

Dr. West: That was interesting: in the age-based analysis of the Canadian study, it was a combination of protocol-based stopping it and patients saying, "*I'm done with that*", more likely in older patients than younger patients, and yet they both still get the benefits.

Dr. Hesketh: Just to emphasize one thing that Karen said before, and I can't overemphasize enough: if you're going to be treating these folks, I think more monitoring rather than less is critical, because in some settings patients are given therapy and they may come back in the interval between cycles or they may not even in some settings. I think if you were giving something like cisplatin, for example, in a patient who you were concerned about to this extent, I often would have them come back even in the same week, two or three days later. Because if they're going to get into trouble with their renal function, that's going to happen immediately, and better to find it out two or three days later than to have them come one or two weeks later and find out that they're in renal failure at that point. So I think when you review this with a patient, you've got to say, "we're going to follow you extraordinarily closely, and it's going to take a greater commitment on your part, time wise probably, to get through this successfully. But if we do that we're going to have a greater chance of not getting into major difficulties."

Dr. Kelly: I agree 100%. I watch my patients very closely. I think a minimum of once a week, but having them come back a few days later for that monitoring of that creatinine is something that I do as well. So I'm glad to see that others are doing that.

Dr. West: What about somebody who isn't necessarily older but has a performance status that is more marginal? A performance status of two by our standard scale, but has, say, multiple nodes involved that would make you extremely inclined to recommend chemo. We have essentially no data on what to do for someone with a marginal performance status, whether they're old or younger. So what have you done? How would you approach a patient who is maybe receptive but concerned about the detrimental effects? Are you concerned about doing more harm than good or would you extrapolate the adjuvant data we have to a more shaky clinical population?

Dr. Hesketh: Well, I think for the most part, if the patient has been able to go to a full resection as this patient has, I mean they're pre operative performance status must have reasonable for them to have been considered for the operation. I think the issue then becomes, do the patients get into post-operative complications that then impairs their performance status so that they're considerable worse after the surgery than they were before?

And I think that gets into a very problematic area, and I think we've all seen patients who have gotten into that situation where there's just been a more

delayed recovery, there's been more pulmonary impairment than perhaps was anticipated. There's been an infectious complication or there's been a leak of lymphatic fluid within the chest or something like that, and I think there the issue is if the patients status has really been impaired to a significant degree, in most cases what happens is there's then a prolonged delay for the patient to then recover.

And I think if the delay really becomes inordinate, such that it's more than say 6 months or something, you really have to wonder what the value of chemotherapy is in that situation, because you don't really have any data supporting a very delayed administration of adjuvant treatment. So I think that in that type of patient, unfortunately some of those folks, probably the majority that has that kind of presentation, I ultimately probably don't end up giving them adjuvant therapy.

Dr. West: Karen what's your thought?

Dr. Kelly: Well, typically if a patient is beyond three months from their surgical resection -- and I use that, because sixty days was the guideline in the some of the studies, so I add another month there -- so if it's three months, they're beyond three months, I just don't have any data to say we should give these patients adjuvant chemotherapy. However, if there are patients who within six weeks are still having a poor performance status post surgery, I think that is telling you something. That if they haven't tolerated surgery that well, most likely they're not going to be able to tolerate chemotherapy. I think that is a sign that they don't do well. Now if they have a poor performance status for another reason, that perhaps doesn't really matter; but I do think that patients with poor performance status, we don't really have any data at all or extremely limited, but that's a patient population where I think we can harm them more than we can help them. And I tend to lean on the side of not recommending adjuvant chemotherapy for those patients.

Dr. West: Yeah, I do think it's important that we remember the value of adjuvant chemotherapy, though we are all believers that it is very clinically meaningful, it is still above and beyond the potential curative effects of the resection. So we've seen, whether it's with the earliest stage patients, smaller tumors that in a group of people who may have less to gain, we can do more harm than good perhaps. So that's just something that we need to be aware of, that we could end up doing something deleterious for them.

We didn't talk about EGFR therapy, and in truth I hadn't sent her cancer off for EGFR mutation testing. This was a few years ago. But what would your thoughts be now about somebody who either had completed adjuvant chemotherapy and might have read or heard or thought about this or who did not pursue chemotherapy? Would you be inclined to consider EGFR-based therapy?

Karen, I should say, since you are the chair of the RADIANT trial that is looking at Tarceva versus placebo for a somewhat selected population, although it's not the group with the EGFR mutation that we might be most tantalized to consider this for, but would you be, would either of you be inclined to give EGFR based therapy outside of a protocol setting? Perhaps based on molecular testing?

Dr. Kelly: My answer is at this time no. I just think we do not have really the data that would support this. There are certainly true believers in this approach, and I just don't think we have any real evidence, except small bits of evidence, to say that this is the right thing to do. I think that maybe, and I don't know this for sure, that we will hear the results from the Canadian trial, perhaps this year at ASCO that gave gefitinib in this setting. So I would be anxious to see what those results are. If we don't have them this year, we'll have them shortly, and I would like to see those results before I would, outside of a clinical trial, recommend giving this lady EGFR therapy even if she was mutation positive.

This is a different setting than patients with metastatic disease. She has an opportunity to be cured with surgery alone, and we can't forget that: that she still does have an opportunity to be cured without any further therapy. So giving her EGFR therapy with mutation positive, how long do you give it for? These patients do end up with significant side effects; the rash, the diarrhea -- patients do struggle with this, and when you're asking them to take it for a year or two, I can tell you that that's a challenge for patients.

I think sometimes chemotherapy, knowing that it's only going to be 4 cycles and they're done, patients even struggle with that. But they're more willing probably to say, "Look, I need to go back to my life, and I don't want to think about this cancer." I think we all know that when we did these adjuvant studies, patients really, unless it was proven, they didn't want to take these types of medications. Because it still impacts their life, and when the surgeon says, "I got it all -- you're cured", they just want to go on with their life and forget they ever had cancer. So I think without having a lot more evidence I would not recommend this off of a clinical trial.

Dr. West: Well, it is interesting that in the metastatic setting, the people who were on it for a year or two are usually delighted to stay on it, but they're getting the feedback that it's helping them, and it's a fundamentally different situation than somebody you don't know if they are already cured and would be doing just as well and without side effects for a longitudinal therapy.

Paul, what are your thoughts, because certainly there are folks, thoughtful people in New York and Boston and other parts of the country and world who are intrigued by and perhaps pursuing this if not extremely avidly promoting it.

Dr. Hesketh: Right. Right.

Well you're right I think there are groups such as the group at Sloan Kettering in New York who have some provocative retrospective data, where they looked at the patient's who had been resected and found the patients who had EGFR mutations and then basically saw how they did. They were all treated with a variety of different things; again this was just a retrospective analysis, so some of them had gotten adjuvant, either Tarceva or Iressa, or some had gotten standard chemotherapy. Some didn't get anything, and what they did find in this, again -- retrospective look -- is that the patients that did get the Tarceva or Iressa-type therapies seemed to do better than the chemotherapy patients.

So that's intriguing -- it's very interesting -- but I would agree with Karen: I don't think it's enough right now to try to recommend this as a standard approach we're going to take. Remember another important thing about the patient's who have these mutations: we know from the advanced disease setting where the therapy, such as Iressa, has shown real value sometimes used as initial therapy, that those patients who have the positive mutations also are very sensitive to chemotherapy. If anything they're more sensitive to chemotherapy than patients who do not have the mutation. So it's likely that these patients are still going to benefit from the proven value of chemotherapy and may in fact even benefit more than a patient who doesn't have the mutation.

I think that my own feeling is that even if I have that information, and I think that it's probably worth getting it for future reference, but if I have that information I'm still going to give them standard chemotherapy. And if there's more data that comes out before I get to the point where I have to give them something in addition I might consider it, but right now I'm not routinely giving people and adjuvant treatment with a Tarceva-type medication. Because, again, I don't even know how long I should keep them on -- should I keep them on a year, two years, or three years?

I think that Karen's study is going to be critically important to give us some idea as to whether there's any value to adjuvant Tarceva because -- correct me if I'm wrong Karen -- but I'm sure you're looking at mutations in these patients as well. So you'll have a group of patients in which you'll be able to look at what happened with the patients who had mutations versus those that didn't. So I think that as we get more information, we might feel a little more comfortable, but right now I'm not routinely doing this. And from a very practical standpoint, there might be issues even trying to get it paid for by third party payers because it's really not approved for use in this setting.

Dr. West: The final question on this general topic is about molecular markers like ERCC-1 or chemotherapy sensitivity testing. Are these markers anything that you have used or would use to help clarify where you would stand in an equivocal case, or perhaps recommend against it based on a high ERCC-1 level predictive of resistance, or would you say that the data that have come out are still retrospective and quite limited and not useful to you for clinical decision making right now? Karen: your thoughts?

Dr. Kelly: I don't think that the ERCC-1 testing should be done routinely. I think even though there's provocative data from the IALT study, and others as well, it is retrospective. The methodologies that have been used in all of these studies are different, and we really don't have a validated ERCC-1 test.

So, as you know, there are I believe three randomized trials in the adjuvant that are prospectively looking at being ERCC-1 positive or negative. And we'll get to this answer. I think that we cannot really recommend this at this time. I think that when you're looking at trying to make a decision about whether someone's going to be resistant or sensitive to chemotherapy based upon this one factor, I think that that is probably a little bit challenging. Because remember, if we don't give them platinum-based chemotherapy we don't have an alternative to give them. Then you're saying that we know that those patients who are high may be more

likely to have a better prognosis, and so then you would offer them nothing. And I think people would be uncomfortable with that right now, since that part, that piece is a challenge. So I think that we can't recommend that.

Now chemotherapy sensitivity testing, I think, has improved over the years in that methodology as well, but again I have never found it really to be something that I've advocated. When I've used it occasionally, it really didn't pan out for my particular patients and wasn't helpful, but that's just my own experience.

Dr. West: Paul, any different thoughts?

Dr. Hesketh: I would agree. I know these tests are out there, and people are checking them and whatnot, but I just wouldn't use that as a basis for deciding whether I'm going to give chemotherapy. Right now I don't routinely check the ERCC-1 levels on these patients, and I think we need to see more information before we do that. And most likely it's going to have to be combined with other factors to really try to make that decision. I think it's very hard to do that on the basis of one test.

Dr. West: Well, I'll say I did make the distinction in the slide of two potential ways to use it, and one would be broadly across a group of people and the other would be in a more equivocal case. And I'll say that I have used that in situations where I could really fall on either side. Someone with a stage Ib cancer, particularly someone who may be a more marginal performance status person, and in such cases where you could potentially do harm by guessing wrong, I have used that.

But I would make a distinction between overstepping or reversing what I would otherwise consider to be a clear standard of care, and helping to decide which side of a fence you might fall on when you could really go either way based on the clinical data in front of you.