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Key Words: nonseminomatous germ cell tumor, thoracic metastases, lung metastases, surgery, pathologic concordance

Discussion

Presenter: Dr Laura L. Donahoe

Dr Kenneth A. Kesler *(Indianapolis, Ind)*. Dr Donahoe and her colleagues are to be congratulated on an excellent study. Their study gives us important messages that can't be understated. These are otherwise young and healthy patients with overall very good prognoses provided that the correct treatment strategies are taken, which typically include aggressive surgery after cisplatin-based chemotherapy to remove residual disease. Additionally, disseminated germ cell tumor patients need careful long-term follow-up, including serial CT scans and serum tumor markers with removal of recurrent disease, when appropriate, to maintain optimal outcomes.

There are a few items I would to discuss. First is the management of patients with elevated serum tumor markers after first-line cisplatin-based chemotherapy. Germ cell tumors that originate in the mediastinum have very poor response to second-line chemotherapy, but metastatic germ cell tumors from the testes to the lung or mediastinum with elevated markers after first-line chemotherapy have a 50% success rate of normalizing serum markers with second-line chemotherapy. Only approximately 20% of testicular cancer patients will have elevated serum markers after first-line chemotherapy, so half of these patients (or 10% of overall cases) will resolve viable germ cell cancer with second-line chemotherapy, which can significantly improve expected survival from the malignant curve up to the benign curve, as you nicely demonstrated. Accordingly, second-line chemotherapy can be very beneficial in select cases.

Fourteen patients in your series had pathologic evidence of viable germ cell cancer in the lung or mediastinum. I suspect that most of these patients presented to surgery with elevated serum tumor markers. Do you take patients with elevated serum tumor markers after first-line chemotherapy directly to surgery or do you offer second-line chemotherapy? If you do offer second-line chemotherapy, what is your regimen of choice, as there are a few options?

Dr Laura L. Donahoe *(Toronto, Ontario, Canada)*. Thank you very much for the question. For context, at our center, I work very closely with our medical oncologists and our urologist—myself and one of my partners. I do most of the germ cell surgery, and we have a multidisciplinary clinic with 2 oncologists and a urologist. In general, patients receive second-line chemotherapy if they have positive markers, but the benefit of our close working group is that we really discuss a lot of cases and take it on a case-by-case basis. So if somebody has mildly elevated tumor markers after first-line chemotherapy and, for instance, only a single site of intrathoracic disease, then that would be somebody who we would consider going to surgery rather than putting them through second-line chemotherapy.

But you know, we really discuss each patient—unless they have a very obvious high burden of disease. Protocol-wise, we use 2 cycles of TIP, and then high-dose carboplatin and etoposide, with autologous stem cell support for two cycles.

Dr Kesler. We also subscribe to your strategy of offering surgery to patients with intrathoracic disease and low-level serum tumor marker elevation. Many of these patients will normalize serum tumor markers after surgery even with "benign" teratoma pathology, and second-line chemotherapy can then be reserved for cases of persistent or recurrent marker elevation postoperatively.

Along these lines, I would like to know your specific surgical approach to patients with anticipated malignant disease, such as patients with chemorefractory or late relapse germ cell cancer and malignant (somatic) transformation into non–germ cell cancer. Our institution reported outcomes of this patient subset and found that resecting 4 or more areas of malignant disease had significantly worse

survival outcomes than resecting 1 area. We are therefore reluctant to offer surgery in cases where there are numerous areas of malignancy. While PET is typically not helpful for management of germ cell tumors, we have found PET useful to determine the location/number of malignant areas which in turn helps decide operability. Did you look at the number of malignant areas removed versus survival, or do you have a rough cutoff with respect to the number of malignant areas present and patient operability?

Dr Donahoe. Thank you. We have all of that data and the numbers look very nice—the simple resections from each case. But I would say that in each of these surgeries, I just looked at the worst pathology, but we resect multiple other lesions. So even though the worst pathology may have been malignancy, you're right, the question is how many sites and how many other locations they had resected at the same surgery.

We do have that data and will look at that for certain, because it will be interesting to look at the survival difference between number of sites resected with malignant disease. In terms of a cutoff number, I would say that we don't have an absolute cutoff; it's taken on a case-by-case basis. We are quite aggressive (and our oncologists are quite aggressive) with referring for surgery. Especially in a patient with salvage, we would resect if we can resect, provided that the patient can tolerate it. Even if it seems like a really large number of sites, if there really are no other options, we may try resecting. We have used PET scans in those cases to help differentiate, which we found very helpful. So again, if a patient has a large number of sites, there is no specific cutoff, but we would exhaust all systemic therapy options before proceeding to resection. But again, if it's a small number, we would be more willing to resect earlier.

Dr Kesler. Finally, I would like to discuss the role of contralateral pulmonary metastasectomy in the face of unilateral pulmonary metastasectomy pathologically demonstrating tumor necrosis only. I agree with your premise that it is an imprecise science to predict pathology in the lung and the mediastinum after chemotherapy. We can get some strong clues, however—for example, in patients with significantly elevated serum tumor markers is predictive of viable germ cell cancer. Patients with malignant (somatic) transformation (non–germ cell cancers) are a little trickier, as they are typically serum tumor marker–negative, but most of these patients will pathologically demonstrate non–germ cell cancer in orchiectomy or retroperitoneal surgical specimens. When patients have these factors suggestive of possible malignancy, we agree that an aggressive bilateral pulmonary metastasectomy approach is typically appropriate.

But in the usual scenario of patients who normalize their serum tumor markers after first-line chemotherapy, with no evidence of non–germ cell cancer in the orchiectomy or retroperitoneal surgical specimens, we do try to avoid the costs and morbidity of performing pulmonary metastasectomy for tumor necrosis only. Your data and other reports referenced in your manuscript have shown excellent—over 90%—pathologic concordance with tumor necrosis only identified in residual bilateral lung abnormalities. In the usual scenario, we typically perform unilateral metastasectomy in the lung most involved to minimize sampling error, and if pathology shows complete tumor necrosis, feel comfortable observing the contralateral lung. These patients will be carefully observed anyway with serial CT scans and serum tumor markers.

How do you do perform bilateral pulmonary metastasectomies? Do you operate on both lungs under the same anesthetic or use a staged approach where you know the pathology of one lung before operating on the other?

Dr Donahoe. Thank you. For the patients who have normal tumor markers and whom we can fairly confident that they do not have active malignancy, for most patients, we would do a staged approach. We have looked at our data in terms of simultaneous resection with doing retroperitoneum at the same time as doing the chest resection, but in general, for the lung, if they just have lung disease, we usually do a staged approach.

But we do have a number of patients who actually come from out of province, and in those patients, we've done them simultaneously just because of the logistics of having them travel a great distance for surgery. Of our patients, we have 3 who had bilateral lung resections with necrosis, and at least 1 of those was an out-of-province patient, so we wanted to facilitate that. We tend to do a staged approach, but again it's on a case-by-case basis.

Dr Kesler. Going back to the typical scenario, I don't see where your data conclusively demonstrate that observing the contralateral lung after unilateral pulmonary metastatectomy pathologically demonstrates tumor necrosis only adversely affects survival. I would like your thoughts on this, however. Again, congratulations on an excellent study.

Dr Donahoe. Thank you very much. I think we just want to alert people to the idea that every patient with metastatic disease in the chest should be considered for aggressive surgery. We had very few patients who had benign disease in one side and malignant disease on the other side. And in the patient who developed malignant disease afterward, it was a single nodule that grew a couple of months after his first surgery.

We want to raise the point that in all patients, it's not necessarily the same thing; even if patients had necrosis in the first instance, if they have a new growing nodule, you need to be aware that they need close follow-up and aggressive treatment. But as we discussed, in these patients who have residual disease bilaterally and normal tumor markers, I think we would also agree that we'd feel confident doing a staged approach, starting with one side (the worst side, as you mentioned). If it's just necrosis, then

we do close follow-up and resect if the nodules are growing. Thank you very much.

Dr Kesler. Thank you.

Dr Shanda H. Blackmon *(Rochester, Minn)*. Have you considered the role of circulating tumor cells or cell-free DNA in this population, especially when their tumor markers go down?

Dr Donahoe. We don't have any studies on that ongoing at this time, but that is a really interesting question.

Dr Blackmon. I think that's a great area for future exploration, especially for germ cell tumors. Of course, you might still want to resect remaining teratomas, but knowing if there was residual tumor might guide further chemotherapy.

Dr James D. Luketich *(Pittsburgh, Pa)*. I have a question regarding your follow-up. Is it primarily marker-driven? Every *x* number of months? Are they always getting CAT scans and PET scans in addition? Or do you wait for that marker first?

Dr Donahoe. For chest disease, we tend to follow up with CT scans for the first year or so, but in general it is marker-driven follow-up. We don't do any PET scans—again, we only use this in a select few patients preoperatively if we have extensive disease, and it's salvage just to see which lesions are more active. But even in follow-up, we don't do PET scans for these patients, and usually it's just a marker-driven.

Dr Luketich. I think outside of really busy centers like yours and Ken's, there's a lot of PET scanning that can be done at times. It can be confusing. Do you have any data about the role of PET scan and its limited role? And maybe it shouldn't be used at all; as you mentioned, you use it rarely. I think it probably gets used more frequently than it's needed elsewhere. Any general comments about how you're using it?

Dr Donahoe. I agree; we don't use it. It's not part of our workup at all. I've been involved for 4 years now, and I've done about half the patients we reported and I used it once, and that was actually not a patient in this series, and he was very salvage, with very widespread disease.

Dr Luketich. That was a very nice presentation, Dr Donahoe. Thank you, Dr Kesler, for your comments.