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Key Words: lung cancer, induction therapy, surgery, radiation, chemotherapy

Discussion

Dr David R. Jones *(New York, NY)*. I have no disclosures. I would like to congratulate Dr Donington and her co-authors for an excellent paper and a superb presentation that examines essentially the safety of surgical resection following induction therapy with higher dose radiation in this highly selected group of patients with pathologically proven N2 non–small cell lung cancer. By combining 2 small prospective studies, the authors attempt to address a perceived fear

of increased morbidity and/or mortality associated with the use of radiation in the induction setting. I have 3 questions for Dr Donington and I will ask them individually.

Despite combining these trials, there are still only 93 patients in the analysis and 77 of these had a lobectomy. There was a significant increase in 30- and 90-day mortality in the 16 patients who had more than a straightforward lobectomy. Specifically, mortality was 19% at 90 days in those 5 patients who had a pneumonectomy, 5 patients with a bilobectomy and in the 2 patients with sleeve resections. How do you explain this increased mortality, what was the cause of death, and do you believe it is related to the induction regimen?

Dr Jessica S. Donington. We were a little surprised by the pattern of death; it was quite variable. There was a bronchopleural fistula after a pneumonectomy, but also someone who died from complications of a necrotic muscle flap, and one with pulmonary edema, so we saw this wide variety. We believe that the deaths may have been more a result of failure to rescue. Maybe it wasn't really directly our therapy but the fact that these patients had had induction therapy, be that radiation or chemo, and then went on to this bigger operation, overall it was difficult for them to overcome any complication.

Dr Jones. My second question relates to work from our group and others who have shown that a predicted postoperative diffusion capacity is associated with increased perioperative morbidity and mortality. In your manuscript and in your slides you apparently only looked at forced expiratory volume in 1 second. However, there are many studies that have show diffusion capacity is a predictor of increased morbidity in this patient population. Was that data element available to you in your analysis?

Dr Donington. No, it wasn't, unfortunately. In the 0229 trial, which was designed many years ago, I don't know that we all appreciated the value of diffusion capacity for carbon monoxide at that point. But I do agree going forward that would be important because it would also tie in the extent of resection and how much lung you were taking, and I agree going forward we discussed that as a preoperative factor that would need to be included.

Dr Jones. My final question really relates to the need to include radiation at all as part of the induction regimen. It is often difficult, if not impossible, for the surgeon to know the radiation volumes and doses and, more importantly, whether an extended resection may be needed, which is often is an intraoperative decision. Given the results of the prospective Swiss study where no additional benefit was observed with radiation relative to chemotherapy alone for overall or disease-free survival, would it not be reasonable to consider treating patients with induction chemotherapy alone and then using radiation in an adjuvant setting for persistent N2 disease or perhaps for an R1 or an R2 resection? I realize that in the Swiss Group for Clinical Cancer Research study the radiation was delivered sequentially and at a slightly lower dose of radiation, like 41 Gy. Can your study help me understand why this wouldn't be a preferred approach, particularly given the high mortality of 19% in this subset of patients?

Dr Donington. Thank you. I think there are a couple of important concepts. The first, which is important to understand, is that the treatment we gave our patients—chemotherapy and concurrent full dose radiation—is what patients get who are nonoperative. We gave them the best care out there, and for many institutions that is the standard of care. What we said is that surgery can improve survival above that if we can perform it safely. So I think that that difference is important. Giving patients sequential therapy does not provide the same level of mediastinal nodal clearance or pathologic complete response, and we know that both in the operative and nonoperative populations.

So I think this is an important approach to treatment, not only because it is where my group believes the best survival will be in those we try to treat prospectively but also for those young patients who are initially treated without a plan for surgery somewhere else and then present to our clinics. But I also think it is a dangerous combination if you think you are going to do an extended resection.

Dr Scott Swanson *(Boston, Mass).* Jessica, that was an excellent talk, and I agree with you that surgery is necessary to improve survival in stage IIIA, because chemo and radiation alone really doesn't do it. So my question is, with the conclusions you found, what are your recommendations about using induction targeted therapy and what are you going to do going forward with the extended resection, how do you use this data in your practice?

Dr Donington. In our practice currently for a patient who we believe—and I believe you can tell pretty well up front—and who we think is going to get a lobectomy, we treat them like this: a trimodality approach with chemotherapy, radiation, and resection. If I have a patient who looks like they are going to require a pneumonectomy or a bilobectomy, depending we will either treat them with induction chemotherapy alone followed by resection and the option for radiation after or definitive chemotherapy and radiation alone if we don't feel that they are a strong surgical candidate.

I believe this whole playing field is about to change as we now are starting to look at checkpoint inhibitors in the stage III setting.

Dr Walter Weder *(Zurich, Switzerland)*. Congratulations on this interesting analysis. I am surprised to see how high surgical mortality was in this study. If you look at the data from the Swiss study David Jones just mentioned, their surgical mortality for lobectomies and even for pneumonectomies was below 1%.

Dr Donington. Dr Weder, I knew I would be talking with you this morning. That is a wonderful trial that you participated in and the Europeans have done a beautiful job with these very complex treatment regimens. I think that an operative mortality after these complex resections of 4% isn't extraordinary, but 1.3% for lobectomy is, and I am going to stand by that data. The difference between 1.3 and 1 or 2 is very small and I think these are really good results, as good as what you published from Europe.

Dr Paul A. Ugalde *(Québec City, Quebec, Canada)*. Jessica, congratulations and great work. Yesterday we spent a lot of time discussing the management of N2 patients. I just wanted to understand again your concept on this. What you are telling us is that actually the ideal treatment for these patients is induction chemoradiation therapy as suggested by oncologists and radiotherapists and that we can add surgery to some of those patients. So as a concept is that what you are proposing?

Dr Donington. Yes, I believe we can add surgery to a majority of those patients. Again, anyone who I think doesn't require a bilobectomy or a pneumonectomy could safely have surgery added, and I believe that is their best chance for care. We might know for sure in 5 years or so when our data matures.

Dr Laureano Molins *(Barcelona, Spain)*. I enjoyed very much your presentation. What is not clear to me is did you restage the patients and some of them you just refused because they were pathological N2 but the others went into operation? So it is not clear to me what is the rule to discharge prior or not the patients for surgery.

Dr Donington. As the investigators, we couldn't agree either. The pre-resection invasive staging was done at the discretion of each institution. So not all patients underwent preoperative pathologic reassessment of their mediastinum. But for those institutions where that was their choice, then they did not bring those patients with residual nodal disease on to resection. That approach was the minority in this trial, where most patients were taken directly to resection. And I do hope to look at outcomes between those two groups at a later time, because now we have persistent N2 patients who were treated without surgery and those that went on, and that is an area of controversy still in our community.

Dr Gail E. Darling *(Toronto, Ontario, Canada)*. Jessica, that was fabulous. Thank you so much for bringing this forward and putting the data together. I had a question about the persistent N2 as well, because in the intergroup 0139, although the patients who had mediastinal sterilization had the best survival, there was improved survival even in those who had persistent N2, and going forward what would your recommendation be?

Dr Donington. As I said, I am working now to be able to do that analysis, because I still think that surgery is really important for that group of patients, and I don't like staging them and not bringing them to resection. I think that is the next analysis we need to do. This is unfortunately a fairly small subset that we are going to be looking at, 7 versus 20 or so, but hopefully it gives us at least some insight of where to go forward, because I don't think we have a lot of data in this area.

Dr Darling. What would your recommendation be to those of us in the room?

Dr Donington. I think that these patients should go to resection. A survival of 10% or 15%, which is what the literature tells us, is better than a survival of 0, which is what happens to those who don't go on to resection.

Dr Jones. I again congratulate you, as the other discussants have, on bringing this to our attention. You have clearly been able to demonstrate that thoracic surgeons can do a lobectomy after chemotherapy and radiation and it can be done safely. The real challenge is what do we do with that high mortality of 19% at 90 days in patients who get more than that and how do we better select those people up front? I also agree that the best treatment for persistent N2 disease is to remove the persistent N2 disease, and that means they need an operation.

Dr Donington. Thank you very much for your comment. I think we can choose these patients. And the 19% mortality, again, you are forgetting about that epidermal growth factor receptor antibody. It was really troublesome and none of us appreciated the toxicity that this causes in the lung, but we also saw this in an Radiation Therapy Oncology Group trial that didn't involve surgery (RTOG 0617). So although it is used in the head and neck and colon, it is probably not a good agent in lung and taking that out may have reduced our toxicity.