of another primary tumor site or metastatic spread beyond the mediastinum
Pulmonary function acceptable for surgery according to institutional criteria
Laboratory criteria (within 30 days of enrollment):
Absolute neutrophil count \( \geq 1500/\mu L \)
Platelet count \( \geq 100,000 \)
Total bilirubin and aspartate aminotransferase/alanine aminotransferase \( \leq 1.5 \) times the institutional upper limit of normal
Creatinine clearance \( \geq 50 \) mL/min (calculated using institutional standard)

Exclusion Criteria

Patients thought to be unable to medically tolerate surgical resection as assessed at the initial presentation
Hypersensitivity to cisplatin and/or etoposide
Patients with radiographic evidence of stage IVA thymoma (pleural or pericardial disease noncontiguous with the primary tumor site)
Pretreatment biopsy showing WHO type A thymoma when reviewed by institutional pathologists, unless obvious great vessel invasion and/or encirclement is present on the CT scan; it is understood that a WHO subtype might not be able to be assigned on the basis of the biopsy specimen in all cases
Previous radiotherapy to the chest that would preclude the administration of radiation using 3-dimensional conformal or intensity-modulated radiotherapy planning
Significant medical or psychiatric illness that would interfere with patient compliance
Patients whose 3-dimensional radiotherapy plan cannot meet the dose–volume constraint
Patients receiving other investigational drugs
Pregnant women or women of childbearing potential (women are not considered of childbearing potential if they are \( \geq 2 \) years postmenopausal and/or surgically sterile) who refuse to use effective contraception; will be determined on the judgment of the institutional principal investigators or designated associates
Failure to meet inclusion criteria

APPENDIX 2. INDUCTION REGIMEN
Cisplatin was administered by continuous intravenous infusion for 1 hour on days 1, 8, 29, and 36 at a dose of 50 mg/m\(^2\). The patients were hydrated both before and after cisplatin dosing with mannitol and saline. The use of colony-stimulating factors was prohibited. Etoposide was administered by continuous intravenous infusion for 1 hour on days 1 to 5 and 29 to 33 at a dose of 50 mg/m\(^2\). Dosage modifications, including reductions and delays, were incorporated into the protocol for hematologic toxicity, if the creatinine clearance decreased to \(< 50 \) mL/min, and/or grade 3 or 4 nonhematologic toxicity.

Preoperative radiotherapy began within 24 hours of chemotherapy initiation using either a 3-dimensional conformal–or intensity-modulated radiotherapy–based plan. The radiation dose was 4000 to 4500 cGy at 180 to 200 cGy/fraction (weeks 1-5; Monday through Friday). The treatment target included the entire thymus and the gross tumor, with a 2 to 2.5-cm margin. To minimize toxicity, dose–volume constraints were incorporated into the radiation plan for the lungs, esophagus, heart, and spinal cord. Radiotherapy interruptions were permitted for febrile neutropenia, grade 4 mucositis or esophagitis, and grade 3-4 pulmonary toxicity.

Postoperative Treatment

Patients undergoing adjuvant chemotherapy alone received cisplatin by continuous intravenous infusion for 1 hour on days 1 to 3 and 29 to 31 at a daily dose of 33 mg/m\(^2\). Patients were hydrated both before and after cisplatin dosing with mannitol and saline. Etoposide was administered by continuous intravenous infusion for 1 hour on days 1 to 3 and 29 to 31 at a dose of 100 mg/m\(^2\). Patients undergoing adjuvant chemoradiotherapy (patients with incomplete resection) received the same treatment protocol used in the preoperative setting, except that only an additional 2000 to 2500 cGy of radiation (180 to 200 cGy/fraction; ending during the third treatment week) was administered to the sites of residual disease. In these cases, the chemotherapy dose for the second postoperative cycle was increased to the level administered in the absence of radiotherapy (cisplatin 33 mg/m\(^2\) and etoposide 100 mg/m\(^2\) on days 29-31).

Discussion

Dr Frank C. Detterbeck (New Haven, Conn). Bob, nice presentation. I want to thank you for pulling this off. This was really Bob’s trial that he initiated, and I think to pull off a multicenter trial with multiple institutions is quite an accomplishment, and I think that is great. There are really not all that many prospective series out there. I think that is 1 of the strengths of this study—it is a multicenter trial, and it is prospective. I think another major strength is that the patients are really quite well characterized by the radiographic findings. I think all too often we are limited by reading reports. One walks away from the report, saying, “well, that is interesting, but I really do not have a strong clue about what these patients really looked like and whether a patient I am
seeing is going to be similar to what was reported.” Thus, I think those are the real strengths of what you reported, and, certainly, the lack of any recurrence in those who underwent complete resection is pretty exciting.

My first question is about the choice of chemoradiotherapy versus chemotherapy. I did a brief review of the studies that have been published on induction chemotherapy, certainly patients who were not quite as well characterized but had stage III thymoma or thymic carcinoma, and I think that your complete resection rate was pretty similar, 77% versus 75%. Your survival was pretty similar at 5 years, 71% versus 74%. However, your CPR rate was lower, 0% versus 18% in the other studies, and the partial response rate was lower also, about 46% versus 89%. So I am not necessarily seeing a benefit as I would have expected from chemoradiotherapy, and I am wondering about your thoughts about that.

Dr Robert J. Korst. Thank you, Dr Detterbeck.

We had the same impression as well. There have been a couple of CPRs in at least 1 of the other prospective clinical trials of this disease, but we did not see any, despite the addition of another locally acting agent. We did, however, have 5 near CPRs in the patients with thymic carcinoma. I think from a toxicity standpoint, we are in the ballpark with chemotherapy alone. I do not think our study had significantly more toxicity than some of the other published data. The studies, however, were drastically different in terms of the stages included and other inclusion criteria. The patients had been deemed unresectable in the other 2 prospective studies, but that is a highly subjective term. In addition to that, the chemotherapy agents were different. One of the studies was actually a chemotherapy and prednisone study. Thus, it is really difficult to make comparisons. What we tried to do with the present study was to try and make some of these factors as objective as possible, such that in the future, when other studies are done, the data can be compared.

It is hard to say I am going to change my practice because of a 22-patient prospective, single-arm trial, but it is all we have in thymoma. I have always treated with preoperative chemotherapy for locally advanced thymoma; however, the data for the thymic carcinoma are intriguing. Of the 7 patients, 4 had a near CPR. It is also the patients with thymic carcinoma who also had the most significant radiographic response. Therefore, if I had a patient with thymic carcinoma who presented to me and met these criteria, I would probably treat them with chemoradiotherapy up front.

Dr Detterbeck. My next question is where do we go from here? This is an intriguing trial, 20 patients. It is slightly more difficult to really know for sure whether it is chemoradiotherapy versus chemotherapy, et cetera, et cetera, what is really the way to go and how do we get more science behind what we should be doing as we move forward.

Dr Korst. Well, what we really need to do is band together and start doing trials in this rare disease. I can tell you that I stopped this trial around to anyone who would listen 5 years ago, and the response was always similar, which was, “We are going to see 2 patients this year. It is really not worth our while to get this through our institutional review board.” We have to change that, and if we can change that, we can start investigating all types of questions for these patients.

Dr Scott J. Swanson (Boston, Mass). I really enjoyed it, Rob. Without seeing the scans, it is hard for us to know what you were looking at. How comfortable are you that these patients had unresectable disease before treatment and is there some other minimally invasive method we should use to ensure that? Because if 4 or 5 of these patients had resectable disease before this treatment, perhaps they did not need this intensive therapy up front.

Dr Korst. Well, that is clearly a good point, and I will be the first to tell you that unresectability was not an inclusion criterion. There were some patients who, if you looked at the scan, you would say, “I could probably take that out,” and then there actually were some patients who had terrible disease. The remainder of the patients were all kind of on that fence. One third of the patients had clear-cut great vessel or organ invasion, indicating an intraluminal tumor. It is hard to make comparisons in this disease because my “unresectable” might not be your “unresectable.”

Dr Swanson. I have 1 last follow-up question. Carcinoma sounds clear and clear-cut invasion sounds clear. If you have a patient you are not so sure about now but who fits these criteria, would you give them the induction therapy or would you try to resect them, you know, off the protocol?

Dr Korst. If I was treating off the protocol, I think what I would do is probably treat with preoperative chemotherapy for patients with marginally resectable disease at this point, unless they were a patient with carcinoma or perhaps B3, for whom I would use chemoradiotherapy.

Dr Swanson. So nobody progresses. You do not lose the ability to resect anybody.

Dr Korst. No one progressed.

Dr Shaf Keshavjee (Toronto, Ontario, Canada). I have just a comment to Scott’s question. When you consider the survival curves of thymoma and you consider the ones that we resect that recur later, that was sort of the target we were looking at, the high risk of recurrent tumors or a high risk of incomplete resection. So, the patients who you see clearly do not have resectable disease and “let us try and treat them and see whether we can make them resectable” were not really the target for this trial. It was more the high-risk larger tumors in general, but not necessarily just large, and then showing invasive or aggressive features, to see whether we could improve on that. The pleasant surprise was how well the thymic carcinomas behave with this induction therapy. So, those were 2 important nuances.

Dr Jacques-Pierre Fontaine (Tampa, Fla). Of the 23% of your patients who did not undergo an R0 resection, what percentage were able to receive postoperative radiotherapy for those positive margins, seeing that they all had already received 4000 to 4500 cGy preoperatively? As a follow-up question, if your trial does not show an increased rate of R0 resectability or a change in survival compared with previous series, albeit not truly comparable, why not simply give them induction chemotherapy only, resect, and treat your R1 and R2 resections with higher doses of uninterrupted postoperative radiotherapy, which would be more effective than lower doses or interrupted doses of radiation?

Dr Korst. Of the patients who did not undergo an R0 resection, 1 underwent debulking and died postoperatively, but the other 4 were treated.
Dr Fontaine. So, they were able to undergo radiotherapy despite the initial radiation?

Dr Korst. They were able to be treated. Again, it is a matter of philosophy. The purpose of the trial was to try to enhance our rate of complete resection by adding another local modality. It is unfortunate that the trials are really not comparable. The other trials excluded patients with thymic carcinoma. One third of our patients had carcinoma. You just cannot compare the patients.

Dr Dirk Van Raemdonck (Leuven, Belgium). With regard to your pretreatment staging, did you do thoracoscopy in any of these patients or in all patients to exclude stage IVA disease?

Dr Korst. No. It was all done radiographically. A single patient was found to have stage IVA disease once they had undergone resection. Also, we had 2 patients who had stage IVB because of nodal disease.

Dr Joshua R. Sonett (New York, NY). It was a great endeavor and great project, with results that I think will be extremely helpful. One question that I have encountered is trying to sort out the large thymomas that will not respond to induction therapy and, thus, should avoid induction. Thus, using pathology or molecular studies, we need to separate out who should receive therapy for thymoma. I have had a number of patients with very large thymomas that had very disappointing results from induction chemotherapy. I am wondering whether you could glean anything from your data that indicates which of those thymomas responded and which did not, because if they are not going to respond, clearly, the whole debate about whether to go straight to surgery or give them induction is less relevant.

Dr Korst. Most type A thymomas can be resected. I think the WHO histologic type plays a large role in the decision. However, the carcinoma or B3 cases, I think those are the ones for which one must entertain the idea of induction therapy.