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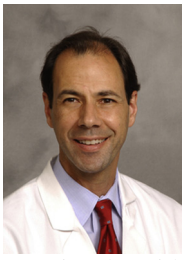
Key Words: small cell lung cancer, adjuvant chemotherapy, adjuvant radiation, prophylactic, cranial irradiation

Discussion

Presenter: Dr Nicolas Zhou



Dr Thomas A. D'Amico *(Durham, NC)*. Congratulations to Dr Zhou and his colleagues for this important multi-institutional study. The role of surgery and the management of small cell lung cancer continue to evolve. Recent studies have demonstrated that surgery for early-stage small cell was associated with improved long-term survival when

compared with concurrent chemoradiation and that adjuvant therapy improves survival. Despite these findings, the rate of surgery in these patients has not appeared to increase. Analysis of outcomes of the surgical treatment of small cell lung cancer are difficult to interpret because the treatment guidelines do not replicate the guidelines for non–small cell lung cancer, and the diagnosis of early-stage small cell lung cancer is often not available at the time of decision making regarding surgery. In this multi-institutional study, Dr Zhou and his colleagues analyzed the outcomes of patients after surgical resection for limited-stage small cell lung cancer and both node-negative status and the use of adjuvant chemotherapy are identified as important predictors of survival. More than half of patients had T1 tumors and without an established diagnosis of small cell lung cancer, preresectional pathologic mediastinal lymph node assessment would not be expected.

However, approximately 40% of patients were found to have node-positive disease at the time of surgery, with long-term survival of approximately only 15% and it is uncertain whether induction therapy would have improved the survival of these groups. With that in mind, I have these questions for Dr Zhou: The National Comprehensive Cancer Network guideline algorithm for patients who are clinical T1 N0 or T2 N0 small cell lung cancer is the following: Pathologic mediastinal lymph node assessment followed by surgery for patients who are not N2. In your study, 15% of patients were T3 or T4, 19% were N1, and 19% were N2.

Although some of the patients are certainly upstaged at surgery, this would not explain the majority of patients who are beyond T2 N0. Would you explain your algorithm to select patients for surgery?

Dr Nicolas Zhou *(Houston, Tex).* Thank you for your question. So we collected surgically resected data for small cell lung cancer from various institutions. Therefore, we cannot comment 100% accurately on why some patients had surgical resection for N2 disease or not. There may be several reasons that this happened. First, when you look back at the literature, there are several phase 2 trials in the 1990s that showed that there was survival benefit for limited stage disease patients after surgery—even in those patients who are stage IIb to IIIa. So it is within reason that some patients have surgical resection, even if they were known to have N2 disease.

Secondly, some of these patients may have been initially diagnosed as atypical carcinoid or non–small cell lung cancer with neuroendocrine features, and a lot of times, the histology of the cancer was determined intraoperatively. So for those patients, the surgeon does not have the luxury of knowing beforehand that this is small cell lung cancer.

So we do assume that some of these were resected upfront and were either upstaged or the diagnosis was changed on a fine pathology. Lastly, we also included patients who were mixed histology as long as a small cell lung cancer was the driving histology for survival. So all those factors may have contributed to why some N2 disease patients had resection.

Dr D'Amico. I'm sorry: You said as long as the small cell component was the driving feature of survival?

Dr Zhou. Yes.

Dr D'Amico. How do you know that in advance?

Dr Zhou. Just based on historical survival for each histology.

Dr D'Amico. Okay. Regarding adjuvant therapy: the National Comprehensive Cancer Network guidelines recommend adjuvant chemotherapy for all patients after surgical resection and adjuvant chemotherapy has already been demonstrated to improve survival, from studies from the National Cancer Database. Why did only 68% of your patients receive adjuvant chemotherapy?

Dr Zhou. Thank you. This came to us as a surprise as well. It is something that we will point out in the print publication. When we looked at patients who receive adjuvant chemo binodal stage, we found that those with N0 disease, 69% of them received chemo. And for those with N1 disease, 87% of them received chemo. For N2 disease, only 45% received chemo. So that is kind of puzzling.

It could be that with some of the higher referral centers, perhaps when patients get diagnosed with N2 disease, they either forego chemotherapy to receive other treatments or receive chemo back home instead of at the treating institution, so that could have contributed some missing data.

Dr D'Amico. Thank you. Regarding prophylactic cranial irradiation, how was this determined to be utilized? In your study, it was used in only 43 patients, yet nearly twice that many were beyond stage I and might have been considered.

Dr Zhou. Thank you. PCI and limited small cell lung cancer is an area of controversy. While some studies showed that the benefit was survival, some studies really highlight the side effects of PCI whole brain radiation.

There was a large meta-analysis of 7 clinical trials with nearly 1000 patients that showed that in small cell lung cancer (and these were mainly limited-stage disease), it was a 4.5% overall survival benefit. However, a recent Japanese trial in 2017 showed that the use of PCI made no difference in progression-free survival and the group that was on a surveillance arm actually trended toward a better survival.

So clinically this is controversial and our institution tends to evaluate each patient on a case-by-case basis and really weigh the benefit of survival versus the side effects. It was 1 of our study's aims to map out the rate of PCI and its effects. As we can see, even in major institutions, decisions regarding PCI are individualized. Some patients may refuse it and elect to get brain radiation only when metastasis occurs. So

unfortunately, we don't we don't think that we have enough statistical power to answer this question.

Dr D'Amico. Finally, it's very important to have institutional studies in addition to the national database studies in order to develop guidelines for small cell lung cancer. It requires multi-institutional series due to the relatively small number of surgical patients at any 1 institution. So congratulations, once again to you and your coinvestigators. Can you please briefly summarize how this study may inform the development of future guidelines and improve the care of patients with early-stage small cell lung cancer.

Dr Zhou. Thank you. And we thank all of our collaborative partners in this endeavor. We think that this study strengthens the claim that adjuvant chemotherapy has survival benefit in limited-stage small cell lung cancer, regardless of whether patients have nodal disease or not. As for adjuvant chest radiation, we did not find that it was an independent predictor of survival once patients have local disease control. As for PCI, we did not find that it reduced the recurrence rate of brain metastases and it was not an independent predictor for survival. Small cell lung cancer is on those diseases that the resection rates are generally very low in any 1 institution, similar to primary chest wall tumors or thymomas. This collaborative effort or retrospective data is important, but moving forward, it should be beneficial to create a well-annotated, multi-institutional database.

The benefit of resection in small cell is evident, from multiple retrospective studies. And right now, atezolizumab has demonstrated survival benefit in extensive stage disease and other poly ADP ribose polymerase inhibitors have also shown promise. So all these novel agents are soon to be studied in limited stage small cell lung cancer, but those trials are likely to be done in patients with radiation such as stereotactic body radiation therapy and not have surgery be a part of it. So we ought to make sure that surgeons are aware of these novel agents and have a seat at the table when trials are designed for small cell lung cancer, especially limited-disease small cell lung cancer.

We believe that surgery offers a tremendous benefit in these patients and offers value not only in local and regional disease control, but also the pathology, the responses to therapy, and translational studies. So we see a lot of benefit for collaborative work in this area.

Dr D'Amico. Brief question: I think you mentioned that there was no difference noted in survival—and as you said surprisingly—between N0 and N1. Was that correct?

Dr Zhou. Yes, for overall survival.

Dr D'Amico. Indeed, and along those lines, can you comment on the median number of lymph nodes that were taken during the pathologic analysis? And do you think that was a problem that maybe just not enough nodes were taken to ensure that you were truly N0? Could you comment on that?

Dr Zhou. I appreciate the question; that is something that we want to look at. But unfortunately, not all institutions have those data, so we cannot comment completely on overall how many lymph nodes were taken for each patient.

Dr D'Amico. I see. Thank you.