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Mortality associated with pneumonectomy after induction chemoradiation versus chemotherapy alone in stage IIIA-N2 non-small cell lung cancer

To the Editor:

I read with great interest the recent article of the Toronto group on improved results of induction chemoradiation followed by surgery for selected patients with stage IIIA-N2 non-small cell lung cancer.¹ Uy and colleagues¹ are to be congratulated for their detailed analysis and honest data reporting regarding this difficult subset of patients with N2 disease for whom the optimal treatment remains to be defined. As in the Intergroup-0139 trial,² Uy and colleagues¹ adopted an induction therapy of concurrent chemotherapy and radiotherapy, followed by surgical resection if there was no progressive disease on restaging. In 11 cases (27.5%), pneumonectomy was necessary. As previously observed in the INT-0139 trial, mortality in this setting was high: 27% overall, and even 50% for complex pneumonectomies. Causes of death were adult respiratory distress syndrome and postoperative hemorrhage. After induction therapy followed by

pneumonectomy, higher incidences have been reported for empyema, bronchopleural fistula, and adult respiratory distress syndrome than are seen after standard resection without induction therapy.³

Uy and colleagues¹ referred to European Organization for Research and Treatment of Cancer trial 08941, results of which were recently reported.^{3,4} In this multicenter trial, patients with histologically proven stage IIIA-N2 non-small cell lung cancer were treated with induction chemotherapy—without radiotherapy—and in case of response were subsequently randomly assigned to undergo either surgery or radiotherapy. Pneumonectomy was performed in 46.8% of patients; the 30-day mortality in this subgroup was 6.9%, which was much lower than those reported by Uy and colleagues¹ and in the INT-0139 trial.² Similar results as in the EORTC 08941 study were recently published by a group from Strasbourg; they reported a 30-day mortality of 6.7% in a series of 60 patients undergoing pneumonectomy after induction chemotherapy.⁵

Although Uy and colleagues¹ did not specifically comment on this issue, the type of induction therapy—chemotherapy versus combined chemoradiotherapy—may be important in explaining this mortality difference. Unfortunately, there are no randomized studies directly comparing induction chemotherapy with chemoradiotherapy with respect to outcome after surgical resection for locally advanced non-small cell lung cancer.

Although a pneumonectomy can be safely performed after induction chemotherapy, it remains a high-risk procedure after induction chemoradiotherapy, especially when a complex procedure has to be performed on the right side. Coverage of the bronchial stump with viable tissue is essential to prevent the dreadful complication of bronchial stump dehiscence.

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Reply to the Editor:

Dr Van Schil's letter clearly enunciates the concern of many surgeons that the combination of chemotherapy and radiation for induction increases the risk of subsequent surgical intervention, whereas the use of induction chemotherapy alone does not. Although the report from Martin and colleagues,¹ as well as the data from the Intergroup 0139 trial,² support this concern, we believe this not to be the case. In our experience, as outlined in our report, the mortalities all occurred early in our experience with this protocol. There were no mortalities in the last 34 patients, including those undergoing pneumonectomy. In doing the chart audit, we noted that the mortalities in the patients undergoing pneumonectomy occurred in patients with large, bulky central tumors, in whom the hilar dissection could be anticipated to be difficult. In retrospect, we would now not consider such patients for resection. Based on our own experience, we do not think that induction chemoradiation results in excessive risk for resection if patients are selected appropriately. Furthermore, this is supported by the work of Sonett and colleagues,³ who used even higher doses of radiation without any operative mortality.

In selecting patients for trimodality therapy, we believe that both the primary and

nodal disease must be technically resectable before induction. In particular, the nodes should not be fixed to the airway, nor should the proximal hilar vessels be obliterated by the nodal disease. The latter is determined based on the computed tomographic appearance, and the former is assessed at the time of mediastinoscopy. This speaks to the importance of mediastinoscopy in assessing the mediastinum, not just for the purpose of biopsy of the lymph nodes, which could be done by using endobronchial ultrasound, but also to assess resectability of the nodes.

Patients must be appropriately selected for surgical intervention based on their cardiopulmonary reserve, and it is worthwhile to repeat functional testing after induction to ensure that the induction regimen has not compromised the patient's cardiac or pulmonary function.

The timing of resection is important because beyond 6 to 8 weeks after completion

of radiation, fibrosis becomes progressively more severe and increases the difficulty of the dissection.

In our experience the combination of chemotherapy and radiation leads to higher response rates, with significant downstaging beyond what one expects with induction chemotherapy alone. Furthermore, the R0 resection rate using combined therapy is also increased.

In our center induction chemoradiation remains the preferred induction regimen for select patients with N2 disease. We do not think that induction chemoradiotherapy prohibitively increases the risk of pneumonectomy, and in fact, it provides an opportunity for curative resection in selected patients with N2 disease.

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