Letters to the Editor


We have read with great interest the paper from L. J. Wirth and co-workers reporting their experience with a multimodality treatment for locally advanced non-small cell lung cancer (LA-NSCLC; Ref. 1). In this report, the authors described the findings of a complex and multidisciplinary approach to stage III (a and b) NSCLC, exploring its feasibility with a Phase I dose escalation study design. In this setting, however, an analysis of the possible “induction” potential (i.e., tumor clinical and pathological response) of this protocol along with the possible effects on survival have been realized.

This experience is very similar to the one that we realized 2 years ago and reported previously (2, 3). Thus, we have drafted some reflections integrating the substantially common background and outcome with recent evidence and recommendations regarding the general approach to LA-NSCLC (4, 5).

First of all, we see the point that the definition of LA-NSCLC has not been homogeneous in the last 2 decades. Even if this may seem a collateral issue, it is actually the rationale for why the majority of small and large trials exploring therapeutic strategies for LA-NSCLC include patients with very different cancers. For this reason, the interpretation of results has been, and is still, somewhat confused. A functional definition as the one reported by Macchiarini et al. (5) does not resolve the problem of patient stratification inside clinical trials, especially when surgical indication follows chemotherapy and/or radiation treatment.

In an extreme simplification, in fact, it is widely accepted (even in the absence of proper consolidated results from Phase III randomized trials) that LA-NSCLC with clinical stage IIIa for a T,N1 or T1–2N2 condition could be “ideally” cured by a multimodality chemotherapy or chemo-radiation approach, eventually followed by surgery (and in carefully selected patients, adjuvant chemotherapy). On the other hand, when clinical IIIb cases for a T4 or N3 status are at stake, there is much more confusion.

Continuing along the lines of simplification, we could assert that this heterogeneity exists because, whereas in the first group of patients (IIIA), the fact that the induction treatment is chosen on the basis of “operability”, in the second group (IIIB), the treatment is chosen to modify “resectability,” which is a more immediate objective (subjective from the surgeon’s point of view) and strict parameter, and operability stands second in line.

Following the recent “guidelines” of Machtay and Jeremic (4), we can say that a direct surgical indication could exist in very selected T,N1–2 cases (with poor long-term results and a 5-year survival rate at <20%) at the price of extended and aggressive surgical approaches, whereas N3 cases are generally not considered eligible for surgery at all.

The potential impact of a “neoadjuvant” approach for T4 and/or N3 cases on clinical tumor response and survival has been investigated in the past. A certain correlation among local control (clinical tumor response and, thus, clinicopathological downstaging) and survival seems to effectively exist (5–10), especially if downstaging is obtained at the N level (7).

In our experience (2) and in that reported by Wirth et al. (1) several stage IIIb patients were included in the Phase I study (designed as dose finding); clinical response to the multimodality treatment was “incidentally” so good as to have some of those initially judged inoperable and unresectable re-enter the chance for complete surgical resection.

This evidence supported the idea that the two multimodality approaches (1, 2), even if designed as Phase I studies, proved to have an induction potential; moreover, a possible benefit on long-term survival could be hypothesized in the light of previously cited consolidated experiences (5–10).

If we focus on the very group of IIIb patients studied by Wirth et al. (1), we see that one clinical T,N0 case who experienced a partial response to a chemo plus chemoradiation protocol, one clinical T,N3 case with partial response as well and one clinical T,N3 case with a preoperative question of progression of disease were all deemed to have achieved such satisfactory downstaging at restaging as to have re-entered operability and resectability and were operated on. The first and the second cases experienced significant pathological downstaging [with complete pathological response (clinical partial response) and with complete absence of tumor in the specimen of the latter] whereas the third was upstaged to stage IV because of intra-operative and pathological evidence of a neoplastic nodule in a lung lobe different from that of the primary tumor site.

We would like to amicably invite the authors to clarify some aspects of the following results:

(a) re-staging (T and N statuses in adjunct to the stage) should be disclosed so as to make the reader better understand the process of surgical indication;

(b) in particular, it would be interesting to understand why the T4 patient got this clinical status and what was her restaging situation. In this setting, in fact, an important difference exists if a patient is T4 because of an assumed neoplastic nodule in a different lobe of the same lung or because of a direct infiltration of, let’s say, the main branch of the pulmonary artery. Moreover, if this is the case, it is extremely difficult to outline the criteria (essentially attributable to technical heterogeneity and interobserver variability) for upgrading a case from T3, because of a simple contact between the tumor and the mediastinal pleura around the vessel, to T4, because of a clear vessel infiltration. This kind of difficulty is magnified when the assessment is made after chemotherapy or chemo-plus-radiation treatment has been administered when, at the moment of the restaging, the morphology of the therapy-induced biological effect is checked and interpreted (11).

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(c) furthermore, we assume that the two N3 cases had had their mediastinal controlateral nodal involvement status assessed via pathological verification of mediastinoscopic biopsy material indicated on a clinical suspicion. A comprehensive definition of the clinical N3 status (which stations and how many, now many nodes, etc.) would be welcome; moreover, because both cases experienced a pathological downstaging at the N3 level (one to N0, and one to N2) we would like to know how this was assessed: clinically only (computed tomography scan, positron emission tomography, and so forth); by re-do mediastinoscopy? pathologically by controlateral lymphadenectomy at operation? If re-do mediastinoscopy was performed, it would be of interest if the authors could discuss this procedure after such a complex chemotherapy plus chemoradiation protocol in the light of very important issues such as technical feasibility, biopsy reliability, and so forth, which, in our turn, we have reported (3) and discussed (12).

In this setting, in fact, we have experienced significant technical difficulty in re-do mediastinoscopy procedures performed after concurrent chemoradiation treatment (two patients): in both cases, the pre- and paratracheal plans were nullified, and the senior surgeon who performed the operation was not entirely sure to have re-biopsied the same area as in the first step (at the moment of mediastinoscopy); the pathologist disclosed a significant difficulty in assessing the nature of the specimen (neoplastic versus scar) at the frozen-section examination and could confirm the eventual absence of tumor only after a complete and definitive examination of the specimen.

We would like to close this short and friendly comment by asking the authors whether, in light of their experience, they agree to the specimen.

In this setting, we feel strongly that an evidence-based consensus through the analysis and discussion of proper and focused clinical research experiences is still needed.

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References
Reply

As noted in the commentary by Cesario et al. (1), an evidence-based consensus on the role of surgery in multimodality treatment for stage IIIIB non-small cell lung cancer (NSCLC) (excluding patients with pleural effusion) is indeed needed. These authors point out that several studies that have examined outcomes of patients with IIIIB disease treated with neoadjuvant therapy followed by surgery, including our Phase I study, typically considered surgery only in patients with clinical downstaging from neoadjuvant therapy (2, 3). The best evidence for this approach is provided by the Phase II Southwest Oncology Group (SWOG) 8805 study, in which 126 patients with stage IIIA or B NSCLC received induction cisplatin and etoposide plus concurrent thoracic radiotherapy (2). Resection was attempted in patients without progressive disease. Fifty-one patients (40%) had stage IIIIB (T4 primary or N3 nodes) disease. In this subset, resectability was 80%, and 3-year survival was 24%, similar to results for the stage IIIA group. The strongest predictor of survival after surgery was nodal status at the time of resection. In patients with pN0 disease at resection, 3-year survival was 44%, versus 18% in patients with involved nodes (P = 0.0005). The fact that this survival difference was seen in patients with both IIIA and IIIIB disease suggests that treatment decisions should not only take anatomic staging into account but should also consider tumor biology and response to therapy. Thus, some patients with stage IIIIB disease, for whom guidelines typically recommend combined chemoradiotherapy without surgical resection (4), may, by virtue of an excellent response to neoadjuvant treatment, be able to enjoy the benefits of resection, as would a patient with similarly responsive stage IIIA disease. The final report of the randomized intergroup trial 0139 (RTOG 93-09), investigating the outcomes of patients with stage IIIA NSCLC from combined chemoradiotherapy alone versus chemoradiotherapy followed by surgery, is pending (5). Preliminary data suggest similar overall survival in both groups of patients but improved progression-free survival in the surgical arm. Further analysis may shed light on who will benefit from the full multimodality approach to therapy for locally advanced NSCLC.

Based on our results, in which 3 of 12 IIIB patients were deemed resectable, and the SWOG 8805 data, we agree with Cesario et al. (1) that surgical resection after neoadjuvant therapy can be considered in selected patients with stage IIIB (T4 primary or N3 nodes) after neoadjuvant therapy. The patient in question with T4 disease had radiographic evidence of invasion into the mediastinum on presentation, not a satellite nodule or carinal involvement that might meet the more typical guidelines for resectability. The question remains how to best identify patients who may benefit from surgery. In our Phase I study, all patients were restaged by computed tomography (CT) alone after both induction chemotherapy and chemoradiotherapy. Of the 14 patients eligible for surgery based on restaging CTs showing the equivalence of stage IIIA disease or better, 7 of the preoperative CT scans did not accurately predict the postoperative pathological stage. Of these, six patients were downstaged to N0 status or had a pathological complete response to neoadjuvant therapy, indicating that restaging by CT alone is not fully reliable.

Alternative approaches to restaging include positron emission tomography (PET) and repeat mediastinoscopy. PET restaging is attractive because it offers the possibility of both characterizing locoregional response to neoadjuvant therapy and identifying clinically unrecognized distant metastatic disease, thereby sparing those patients unnecessary treatment (6). Unfortunately, the data available to date include unacceptable numbers of false positives and false negatives for PET restaging alone to be considered a standard approach to determining resectability of stage III NSCLC after neoadjuvant therapy (7, 8). Repeat mediastinoscopy, as Cesario et al. (1) have observed, can be technically challenging in the postchemoradiotherapy setting and is therefore not routinely performed. As a result, it is difficult to recommend a standardized approach to restaging after neoadjuvant therapy in patients with stage IIIIB NSCLC to determine resectability. Nevertheless, the favorable outcomes that can be seen in selected stage IIIB NSCLC patients in response to trimodality therapy do indicate that further study in identifying appropriate surgical candidates is clearly needed.

References

Reply

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