



A more upfront role for surgery in the management of stage IIIA (N2) non-small cell lung cancer?

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There is no consensus on the role of surgical management in stage III(A) N2 disease but there are several alternative strategies which vary across the World. The variation reflects the lack of high grade evidence and the debate surrounding the results of the randomized trials that have been completed. However, there are certain principles that can be accepted.

Firstly, N2 disease is a heterogeneous group with metastasis confined to a single nodal station (N2a) having a significantly longer survival than that in multiple nodal stations (n2b) (1) after resection. Indeed, the relatively poor prognosis from N2b should preclude intentional resection in this stage. Therefore, it is imperative that we define what is resectable N2 disease. The IASLC have attempted a definition which comprised: free resection margins proved microscopically; systematic nodal dissection or lobe-specific systematic nodal dissection; no extracapsular nodal extension of the tumour; and the highest mediastinal node removed must be negative (2). These recommendations can be applied when operating before or after induction therapy and suggest in the latter context that there is no need to resect the volume of lung that was involved initially, only enough to subsequently obtain negative resection margins.

There is universal agreement that surgery for N2 disease must be part of multimodality therapy which has included chemotherapy and radiotherapy but latterly also now incorporates immunotherapy with checkpoint inhibitors.

Induction chemotherapy

The SAKK trials (3) demonstrated no significant difference in progression-free survival or overall survival from induction chemoradiotherapy followed by surgery over induction chemotherapy followed by surgery. The NCCN

guideline concludes that the benefit from preoperative chemotherapy is similar to that of postoperative chemotherapy and either approach is justified. It does, however, make note of evidence that more patients complete the full treatment regime when chemotherapy is given preoperatively compared with postoperatively.

Induction chemoradiotherapy

Surgery can be performed safely after radical chemoradiotherapy and was found, in the Intergroup 0139 trial, to lead to a survival benefit if the resection can avoid pneumonectomy and there has been complete nodal downstaging (ypN0) (4).

The ESPATUE trial, similarly, found comparable rates of survival in stage IIIA non-small cell lung cancer (NSCLC) treated by either definitive chemoradiotherapy or surgery after induction chemotherapy with five-year overall survival of over 40% in both groups (5).

Induction chemoradiotherapy + immunotherapy

The recently published outcomes of the PACIFIC trial (6) suggest that immunotherapy with checkpoint inhibitors may play a significant role in the management of stage III NSCLC. In this study, the addition of the checkpoint inhibitor durvalumab following chemoradiotherapy in stage III significantly improved median progression-free survival when compared with placebo (16.8 vs. 5.6 months). Overall survival data are awaited, whilst other ongoing trials of checkpoint inhibitors, such as PEARLS (NCT02504372), are seeking to determine whether checkpoint inhibitors have a role following surgical resection in earlier stage

disease including stage IIIA (N2).

Induction immunotherapy

PDL-1 blockade by these checkpoint inhibitors is more likely to be effective when the primary tumour and lymph nodes are still present (7) thus initial studies of its use in induction in N2 disease have been encouraged and are starting to report. Concerns remain regarding side effects which may delay or prevent subsequent resection. In the NEOSTAR study, patients with stage I–IIIA (single N2) received three doses of nivolumab 3 mg/kg or nivolumab 3 mg/kg plus ipilimumab 1 mg/kg q2w followed by surgery (8). Five of the 31 patients initially scheduled for surgery did not proceed to resection (one with grade 3 hypoxemia, two with high surgical risk, two no longer resectable). In the LCMC 3 study surgery was delayed in one patient due to grade 3 immune-mediated pneumonitis (9). The major pathological response (MPR) rate (as defined by <10% viable tumour cells) has been found to vary from 22% to 45% but this cannot be predicted from clinical staging as a few as 10% of patients had objective responses on post-treatment CT-scans (10). Even the outstanding preliminary results from induction *chemoimmunotherapy* in the Spanish Lung Cancer Group study NADIM, where major pathological complete responses were seen in over 50%, could not be predicted before resection from conventional imaging (11). Thus predictions that immunotherapy may replace surgery in the treatment of N2 disease may be premature.

Operate on all resectable N2

Lim *et al.* (12) based a strategy on the assumption that no published trial has shown evidence in favour of excluding surgery as part of multimodality management of N2 disease. In their interpretation the six randomised trials comparing surgery and chemotherapy versus chemoradiotherapy failed to show any evidence in favour of nonsurgical management and have suggested that surgery should be performed for all non-fixed and non-bulky N2 disease thus obviating the need for invasive mediastinal staging before upfront surgery. This rather simplistic approach, whilst attractive in the way it may reduce costs, fails to address the poor outcome of those undergoing resection of pN2b disease (13).

Primary surgery in N2a + adjuvant chemotherapy

I favour a more selective but nevertheless primarily

surgical approach to N2a disease. On the basis of similar postoperative survival I propose to treat N2a disease as one would do N1b with upfront surgery followed by adjuvant chemotherapy. We, together with others, have found median survival of between 3 and 4 years for patients by using this selective approach (13,14). Independent prognostic factors have been found to include: age, smoking status, pathologic N2 status, margin, and adjuvant chemotherapy.

This approach has met with criticism (15). Quite correctly it is stated that the IASLC database contains only surgical patients who have presumably undergone extensive intraoperative lymph node sampling ensuring accurate classification of nodal status. The challenge is that this N2 disease represents a different population to those with clinically apparent N2 on preoperative imaging in whom the outcomes may be inferior. In answer to this I would advocate that surgery for cN2a is only performed after exclusion of N2b by invasive mediastinal staging, preferably by mediastinoscopy and lymph node dissection. In these cases the surgeon is looking to confirm negative nodes in other stations so should use the method with the best negative predictive value i.e., video assisted mediastinal lymphadenectomy (VAMLA) (16).

Furthermore, these authors favour the use of induction rather than adjuvant chemotherapy (15). Here the evidence is far from clear-cut. Lim *et al.* published an indirect comparison meta-analysis of 32 randomized trials involving 10,000 participants which demonstrated no difference between postoperative compared to preoperative chemotherapy in all resectable disease (relative hazard ratio of 0.99) (17). In the randomized NATCH Trial (18) there was an insignificant survival difference between the three arms: (I) preoperative chemotherapy (paclitaxel/cisplatin) and surgery; (II) surgery alone; (III) surgery and postoperative chemotherapy. However, this trial contained a high proportion of stage I disease.

In analyses of large American databases a study of cIII-N2 NSCLC from the National Cancer Database failed to identify a survival advantage of preoperative chemotherapy, over post-operative chemotherapy (19). In a study of over 3,000 patients with cN2 disease in the Society of Thoracic Surgeons database (20), the 5-year survival was no different (at 35%) for patients treated with induction therapy or upfront surgery. The 5-year survival of the subset of Upfront Surgery patients who were confirmed to be pN2 (i.e., no clinical over-staging) was 29% (which was significantly less than the Induction group, $P=0.037$), but the comparison is likely to be biased due to an inability to

eliminate over-staged (better prognosis) patients from the Induction group.

Rocco *et al.* (21) noted the Transatlantic difference in N2 management; in the United States most centres prefer to use chemotherapy in the neoadjuvant setting (22) whilst in Europe upfront surgery is often used in those cases with single-station non-bulky N2 disease. It may be no coincidence, therefore, that It has been noted from the data in the 8th TNM revision that the survival for pN2 is significantly higher in US than in Europe: 42% *vs.* 22% (23).

There is a suggestion that superior survival is due to better initial staging but I would suggest that patient selection is a major factor. If we imagine the treatment of N2 disease to be akin to corralling a herd of wild horses then induction therapy is effectively letting them all loose and then using a lasso to recapture them and bring them to stable. Recapturing them is not as easy as one may think. Only 1 in 3 (24) patients returned to surgery again after induction chemotherapy in Cerfolio's prospective experience but these "slower horses" have a good prognosis (won't escape again). But what happens to the wilder horses that run free? Would they not have been better advised to keep them in the surgical stable from the outset?

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