Review Article

N2-IIIA non-small cell lung cancer: a plea for surgery!

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Abstract: Management of stage IIIA-N2 non-small cell lung cancer is still matter of ongoing controversy. The debate is flawed by the heterogeneity of this group of patients, lack of strong evidence from controlled trials, diverging treatment strategies, and hesitating estimation of prognosis. Surgery is credited a survival advantage in a trimodality setting. For many teams, N2 is by principle managed with induction chemotherapy, followed by surgery if the patient is down-staged. However, surgery remains a suitable option even in case of persistent N2. On the other hand, outcomes are comparable, regardless whether chemotherapy has been given as induction or adjuvant treatment. Hence, upfront surgery without invasive staging, followed by adjuvant therapies, appears reasonable in resectable single station N2 disease, simplifying patient care and reducing cost. We expect that molecular biomarkers will improve estimation of prognosis and patient selection in the future.

Keywords: Non-small cell lung cancer; stage IIIA-N2; multimodality treatment; surgery

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Introduction

The classic debate in favour or against surgical resection of N2 disease is sentenced to go on for a while. Although a substantial number of patients are concerned, there is a lack of strong evidence. The few available phase III trials published in peer-reviewed journals, which all have some imperfection, are largely exceeded in number by several subsequent meta-analyses and review articles. Because of the well-described difficulties to set up randomized controlled trials (RCT) in the context of thoracic surgical practice, research is increasingly based on clinical registries or population based administrative databases (1). The latter are not limited by patient accrual, which is a capital problem for RCTs, and probably better reflect real life than trials. Trials attempt to protect of any bias, but patients included are uppermost selected, and obviously healthier. Feeding of clinical databases is founded on voluntarism, and quality monitoring may be questioned (2). Beyond diverging methodological approaches, where the one attempts to select the ideal and unbiased patient, while the other strives to snapshot real life, several confounding factors impede comparison of treatment outcomes and long-term survival obtained by various treatment strategies in N2 disease.

Despite several subsequent revisions of the TNM staging system, the N2 descriptor still federates into one single category a very dissimilar group of patients with sharply differing prognosis, ranging from microscopic N2 to bulky disease with perinodal infiltration (3,4). At the one end of the spectrum, the disease is obviously resectable, and sometimes even diagnosed retrospectively on pathology specimens, while at the other end the disease appears as

unresectable at baseline owing to diffuse infiltration of the mediastinum. Hence it appears difficult to set up trials with homogeneous patient groups and sufficient accrual.

While the disease is the same, it is striking how treatment strategies differ between Europe and North America (5). A comparative study of the databases of the Society of Thoracic Surgeons and the European Society of Thoracic Surgeons obviates that North American Surgeons favour induction therapy, prefer to limit resection to down-staged patients, and avoid pneumonectomy; European surgeons are eager to perform upfront surgery and are less reluctant to perform pneumonectomy; the proportion of N2 disease was almost twice as high in the European database (6). The editorial on transatlantic perspective by Rocco *et al*. cites several single centre studies anticipating or supporting the results from this database study (5).

The confusion has increased in the early 2000s following the publication of two trials, which are frequently cited as arguments against surgery. Actually, the predominantly disseminated interpretation may be debated. Betticher *et al*. published a phase-2 trial on induction therapy with docetaxel-cisplatin in biopsy-proven N2 disease followed by resection; the authors observed a marked difference in survival between those patients with persistent ypN2 and those who had been down-staged. They concluded that resection should be limited to those patients who were down-staged after induction (7). This recommendation creates a new problem named invasive restaging after induction, with inherent cost, loss of time to treatment, and additional uncertainties. We can further oppose to this recommendation that it sentences patients with persistent N2 to a treatment that has shown its inefficacy, while they still might take some advantage of a curative resection.

The EORTC collaborative group published a trial including patients with marginally resectable N2, which compared induction chemotherapy followed by surgery to induction chemotherapy followed by radiation therapy. Survival was similar in the two arms, which led the authors to conclude that surgery should be avoided (8). However, critical revision of the data of the surgical arm revealed that 50% of resections were incomplete. Hence, we might alternatively conclude that (I) chemotherapy cannot increase operability in inoperable patients; (II) that an incomplete resection offers no survival advantage; and (III) that the effect of chemotherapy is weak, because regardless the local treatment, most patients eventually die from metastatic progression.

Another important bias is unsteady quality of surgery. In most trials evaluating combined modality treatments, there are strict definitions of quality criteria and control regarding chemotherapy or radiation therapy while no mention is made about quality criteria for surgery and quality monitoring. Only a single trial quoted quality criteria for surgery (9). In addition, the majority of multicenter trials are characterized by a relatively low caseload per centre, which adds the adverse effect of low centre volume on outcomes after surgery. Further, it is unclear whether a radical lymph node dissection has been performed routinely in all patients. Uncertainty about lymph node dissection is a major hint of interpretation, because node dissection is an independent prognostic factor improving survival: according to the meta-analysis by Takagi *et al*., including four randomized trials comparing sampling and formal dissection, the hazard ratio of radical lymph node dissection was 0.86, i.e., slightly more favourable than the hazard ratio of peri-operative chemotherapy! When removing the ACOZOG trial because of its methodological limitations, hazard ratio decreased to 0.69 (10).

Despite conflicting statements and attitudes, there are clear arguments in favour of surgery in stage IIIA-N2, which we will develop in the following sections. The main questions to discuss are whether surgery offers any added value to chemotherapy and radiation therapy, how to care for patients with persisting N2 after induction, whether upfront surgery can be justified, and which prognostic markers might be helpful for adequate patient selection.

Surgery increases survival in a trimodality setting!

The largest bimodality trial, comparing chemotherapy followed either by radiation therapy or surgery, concluded that there was no difference in survival (8). However, it should be repeated that this trial included patients with marginally resectable disease, and that half of the patients in the surgical arm were considered as incomplete resections.

The Albain trial published in 2009 suggested that trimodality treatment, adding surgery to radio-chemotherapy, might be beneficial to patients with stage IIIA-N2 lung cancer. While overall survival was similar, there was a strongly significant advantage to the surgical arm with reference to survival without progression (log rank P=0.017; HR 0.77). It was felt that the survival advantage with surgery was flawed by tremendously high post-operative mortality after pneumonectomy, which was 25% after standard pneumonectomy and rose to 50% after

extended pneumonectomy. When focusing survival studies to patients subjected to lobectomy, there was a highly significant 1-year difference in median survival: median survival rose from 22 months in the non-surgical arm to 34 months in the surgical arm, and the 5-year survival rate doubled from 18% to 36% (11).

The most recent meta-analysis on multimodality treatments in stage IIIA – N2 disease published by McElnay *et al*. in 2015 confirmed that there is no obvious advantage in favour of surgery in the bimodality setting, comparing induction chemotherapy followed by surgery or radiation therapy. On the opposite, surgery increased survival in trimodality settings, with a hazard ratio of 0.87 (12). We may hypothesize that the advantage might be even increased in specialized high volume units (13).

It is reasonable to operate persistent N2!

The final message of the Betticher study, at least as it is repeated worldwide since 15 years, states that operating N2 persisting after induction therapy is meaningless (7). The authors demonstrated a sharp difference in survival between persistent N2 and down-staged patients. However, applying this rule may end up with the paradoxical situation where an ineffective chemotherapy is simply continued. We know also that a second line chemotherapy following an ineffective first line is credited a response rate of 17%. Further, we can imagine that in selected patients with single stage N2, the down staging may happen during mediastinoscopy, leading to the hypothesis that nodal down staging is globally overestimated. Last but not least, if we found decision to operate on down staging, we create the need for a repeated invasive staging procedure. PET/CT fails to accurately predict persistent N2 after induction therapy: reviewing 101 patients explored with repeated PET/CT after induction for N2, Ripley *et al*. demonstrated that roughly half of PET avid nodes were free of tumour, and conversely half of PET silent nodes contained residual tumour. Concurrently, they calculated relatively deceiving indicators, with a sensitivity of 59%, a specificity of 57%, and a diagnostic accuracy of 57% (14).

The first authors to challenge this paradigm were Port *et al*., reporting in 2005 on a case series with documented N2 subjected to induction chemotherapy. The rate of down staging was slightly lower compared to the Betticher series with 19 patients only among 52 resected (36%). Overall 5-year survival after resection was estimated 23% (median 31.3 months); for patients down-staged to N0 or N1, it was estimated 30% (median 36.7 months); for persistent N2 patients, 5-year survival was 19% (median 29.7 months) (15). In 2009, a report from the Leuven group, pooling 85 patients, concluded that there was no significant difference in survival between down-staged and persistent N2 patients (16). Our group reported on 153 patients who underwent pneumonectomy. Up-front surgery was performed in 93, who got various modes of adjuvant therapy; 60 underwent surgery after induction chemotherapy, 28 of whom were persistent N2. Median survival for upfront surgery N2, down-staged and persistent N2 was 15, 27 and 28 months respectively; 5-year survival rates were 12.4%, 34.8% and 32.2% respectively (17).

Ripley *et al*. reported that PET avidity after induction chemotherapy was neither related to overall survival nor to disease free survival. Further, persistent N2 and stage IIIA respectively did not adversely affect survival in their cohort of 100 patients (14).

We may summarize that surgery is an option for patients with persistent N2, provided that a complete resection can be performed.

Upfront surgery is an option!

Although there is no striking evidence in support, many of available guidelines claim that a multimodality strategy based on induction chemotherapy is the gold standard for resectable N2 disease. This opinion based attitude has been challenged by Boffa *et al*., having reviewed the National Cancer Database to compare the two strategies; the authors concluded that there was no survival difference, regardless whether chemotherapy acted as induction or adjuvant treatment (18). As one paradox may hide another one, it is well known that compliance to treatment is above 90% in neo-adjuvant protocols, and less than 65% in adjuvant protocols, yet the survival benefit of either strategy is the same.

In this context, upfront surgery followed by adjuvant chemotherapy, potentially completed with radiation therapy, offers several advantages to the patient. The patient will come fitter to surgery, after a reduced time from diagnosis to treatment. The patient will avoid uncomforting and hazards of invasive staging procedures, and shorten anxiety retrieved from never-ending pre-treatment work-up. This pragmatic approach will at the same time shorten health care expenditures (19).

Legras *et al*. have outlined feasibility and excellence of

results of upfront surgery with radical node dissection. Outcome was particularly favourable in patients with single station, so-called skip-N2 node metastases, i.e. without invasion of N1 nodes, for whom 5-year survival was 34%. Overall survival in their cohort was 25%. Intermediate prognosis with a 21% 5-year survival rate was observed in patients with either multi-station skip N2 disease or single station non-skip N2. Worst prognosis was seen in association with multiple stations, non-skip N2 (4).

Obiols *et al*. demonstrated that patients discovered with unsuspected N2 at operation, after appropriate mediastinal staging, have still an acceptable prognosis approaching 40% at 5 years and should undergo a resection with curative intent (20).

Prognostic factors and patient selection

Control of peri-operative mortality and morbidity, and medium term survival, are conditioned by appropriate patient selection. As mentioned above, an anatomical complete resection combined with a radical node dissection is mandatory (4,10). Feasibility of an R0 resection is founded on medical imaging and subsequent TNM coding. However, the decision to proceed with surgery should take into account various other prognostic factors outside of the TNM system.

Factors without direct relation to tumour biology may significantly influence prognosis. Fitness for treatment is a lucid example of a factor that may adversely interfere with early and medium term outcomes. The joint task force on patient fitness driven by both European Respiratory Society and European Society of Thoracic Surgeons has standardized pre-treatment evaluation of respiratory function (21). Similarly, the American College of Cardiologists has set up guidelines for cardiac evaluation; cardiovascular comorbidity accounts not only for post-operative complications and mortality, but also for medium term demises (22). Denutrition increases post-operative morbid-mortality (23). Patient's motivation is difficult to evaluate, but certainly a key-player as well.

Referring to tumour biology, the current TNM classification does not take into account even simple morphologic characteristics heralding a poor prognosis, such as angio-invasion, neoplastic thrombi in lymphatics, and capsular disruption. A survey by our group demonstrated that the ratio of invaded lymph nodes on the dissection specimen exceeding one third has an ominous significance on the whole, and for N1 and N2 separately. Following induction chemotherapy, unlike persistent N2, an unfavourable lymph node ratio appears as an adverse prognostic factor (24).

Microscopic N2 represents a subgroup with improved prognosis. In a series of 982 pN2 patients, 31.5% had only microscopic node metastases. Five-year survival was 31% for the whole cohort. Microscopic N2 was credited an improved survival, with a median survival of 42 months and a 39% 5-year survival rate; in comparison, median survival was 23 months, and 5-year survival 21% in patients with macroscopic N2. In multivariate analysis, microscopic N2 appeared as an independent prognostic factor with a hazard ratio of 0.681. Interestingly, adjuvant treatments had a deleterious impact on survival in microscopic N2 (3).

Molecular biology studies increasingly deepen our insight into tumour biology and potential for local recurrence and metastatic progression, but also sensitivity to treatments. Comparing survival in patients with adenocarcinoma, it appears that the wild type responds to an intermediate prognosis for both overall survival and time to progression; prognosis is significantly better in presence of EGFR mutation, and significantly worse in presence of KRAS amino acid substitution (25). When comparing different types of KRAS amino acid substitution, it appears that the G12V type heralds a particularly catastrophic outcome (25). Patterns of progression are associated with mutations: lung metastases are more frequently observed with the wild type; EGFR mutation is related to brain and liver metastases; KRAS G12C is related to bone metastases; KRAS 12V is related to pleural and pericardial metastases (26). Sensitivity of brain metastases to radiation therapy is increased in case of EGFR mutation, while G12V announces resistance (27).

We may speculate that choice of treatments and strategies will considerably be modulated by existing and new biomarkers in the future.

Conclusions

We conclude that surgical treatment based on anatomic resection with radical lymph node dissection within a multimodality strategy may reasonably be offered to selected patients with stage IIIA-N2 non-small cell lung cancer, in whom an R0 resection may be anticipated, and who qualifies for appropriate fitness.

When induction chemotherapy is chosen, it appears reasonable to proceed with resection even in case of persistent N2, provided that a complete resection can be achieved. Hence, restaging can rely on simple CT scan to

exclude progression; there is no need to perform invasive restaging procedures or hazardous PET/CT scans.

Upfront surgery in baseline resectable disease, followed by adjuvant therapies, offers equal results, but appears to be simpler for the patient, time saving and cost effective.

The pending development of novel biomarkers is expected to improve selection of those patients who will take benefit from surgery.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Yang CF, Hartwig MG, D'Amico TA, et al. Large clinical databases for the study of lung cancer: Making up for the failure of randomized trials. J Thorac Cardiovasc Surg 2016;151:626-8.
2. Murthy SC, Blackstone EH. Research based on big data: The good, the bad, and the ugly. J Thorac Cardiovasc Surg 2016;151:629-30.
3. Garelli E, Renaud S, Falcoz PE, et al. Microscopic N2 disease exhibits a better prognosis in resected non-small-cell lung cancer. Eur J Cardiothorac Surg 2016;50:322-8.
4. Legras A, Mordant P, Arame A, et al. Long-term survival of patients with pN2 lung cancer according to the pattern of lymphatic spread. Ann Thorac Surg 2014;97:1156-62.
5. Rocco G, Nason K, Brunelli A, et al. Management of stage IIIA (N2) non-small cell lung cancer: A transatlantic perspective. J Thorac Cardiovasc Surg 2016;151:1235-8.
6. Seder CW, Salati M, Kozower BD, et al. Variation in Pulmonary Resection Practices Between The Society of Thoracic Surgeons and the European Society of Thoracic Surgeons General Thoracic Surgery Databases. Ann Thorac Surg 2016;101:2077-84.
7. Betticher DC, Hsu Schmitz SF, Tötsch M, et al. Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicenter phase II trial. J Clin Oncol 2003;21:1752-9.
8. van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst 2007;99:442-50.
9. Nagai K, Tsuchiya R, Mori T, et al. A randomized trial comparing induction chemotherapy followed by surgery with surgery alone for patients with stage IIIA N2 non-small cell lung cancer (JCOG 9209). J Thorac Cardiovasc Surg 2003;125:254-60.
10. Takagi H, Matsui M, Umemoto T. Alice in wonderland of mediastinal lymph nodes. J Thorac Cardiovasc Surg 2011;142:477-8; author reply 478-9.
11. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 2009;374:379-86.
12. McElnay PJ, Choong A, Jordan E, et al. Outcome of surgery versus radiotherapy after induction treatment in patients with N2 disease: systematic review and meta-analysis of randomised trials. Thorax 2015;70:764-8.
13. Samson P, Patel A, Crabtree TD, et al. Multidisciplinary Treatment for Stage IIIA Non-Small Cell Lung Cancer: Does Institution Type Matter? Ann Thorac Surg 2015;100:1773-9.
14. Ripley RT, Suzuki K, Tan KS, et al. Postinduction positron emission tomography assessment of N2 nodes is not associated with ypN2 disease or overall survival in stage IIIA non-small cell lung cancer. J Thorac Cardiovasc Surg 2016;151:969-77, 979.e1-3.
15. Port JL, Korst RJ, Lee PC, et al. Surgical resection for residual N2 disease after induction chemotherapy. Ann Thorac Surg 2005;79:1686-90.
16. Decaluwé H, De Leyn P, Vansteenkiste J, et al. Surgical multimodality treatment for baseline resectable stage IIIA-N2 non-small cell lung cancer. Degree of mediastinal lymph node involvement and impact on survival. Eur J Cardiothorac Surg 2009;36:433-9.
17. Mansour Z, Kochetkova EA, Santelmo N, et al. Persistent N2 disease after induction therapy does not jeopardize early and medium term outcomes of pneumonectomy. Ann Thorac Surg 2008;86:228-33.
18. Boffa DJ, Hancock JG, Yao X, et al. Now or later: evaluating the importance of chemotherapy timing in resectable stage III (N2) lung cancer in the National Cancer Database. Ann Thorac Surg 2015;99:200-8.
19. Lim E, McElnay PJ, Rocco G, et al. Invasive mediastinal staging is irrelevant for PET/CT positive N2 lung cancer if the primary tumour and ipsilateral lymph nodes are resectable. Lancet Respir Med 2015;3:e32-3.

20. Obiols C, Call S, Rami-Porta R, et al. Survival of patients with unsuspected pN2 non-small cell lung cancer after an accurate preoperative mediastinal staging. Ann Thorac Surg 2014;97:957-64.
21. Brunelli A, Charloux A, Bolliger CT, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). Eur Respir J 2009;34:17-41.
22. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. J Am Coll Cardiol 2007;50:1707-32.
23. Thomas PA, Berbis J, Falcoz PE, et al. National perioperative outcomes of pulmonary lobectomy for cancer: the influence of nutritional status. Eur J Cardiothorac Surg 2014;45:652-9; discussion 659.
24. Renaud S, Falcoz PE, Olland A, et al. Mediastinal downstaging after induction treatment is not a significant prognostic factor to select patients who would benefit from surgery: the clinical value of the lymph node ratio. Interact Cardiovasc Thorac Surg 2015;20:222-7.
25. Renaud S, Falcoz PE, Schaëffer M, et al. Prognostic value of the KRAS G12V mutation in 841 surgically resected Caucasian lung adenocarcinoma cases. Br J Cancer 2015;113:1206-15.
26. Renaud S, Seitlinger J, Falcoz PE, et al. Specific KRAS amino acid substitutions and EGFR mutations predict site-specific recurrence and metastasis following non-small-cell lung cancer surgery. Br J Cancer 2016;115:346-53.
27. Renaud S, Schaeffer M, Voegeli AC, et al. Impact of EGFR mutations and KRAS amino acid substitution on the response to radiotherapy for brain metastasis of non-small-cell lung cancer. Future Oncol 2016;12:59-70.

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