



Pneumonectomy in stage IIIA-N2 non-small cell lung cancer

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Abstract: Stage IIIA-N2 non-small cell lung cancer is a very heterogeneous group of patients and the different therapeutic approaches for IIIA-N2 disease are still debated in particular when pneumonectomy has to be performed considering the expected low long-term survival and the worse post-operative outcome. In literature, there are different studies and randomized trials comparing the results of pneumonectomy in patients with and without induction therapy, showing different outcomes. Although several studies favor a definitive chemo-radiotherapy treatment in patients with IIIA-pN2 non-small cell lung cancer, through our results and the literature was showed that pneumonectomy could be considered a valid surgical option in well-selected patients based on the acceptable long-term survival and the low rate of post-treatment morbidity.

Keywords: Pneumonectomy (PN); non-small cell lung cancer (NSCLC); chemotherapy

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Stage IIIA-N2 non-small cell lung cancer (NSCLC) is a very heterogeneous group of patients with different therapeutic strategies and prognosis. “Resectable” N2-NSCLC patients could be candidate to surgery in case of stable or respondent disease to induction therapy (IT), with a good long-term survival (1-3). However, the different therapeutic approaches for IIIA-N2 disease are still very much debated between surgeons and oncologists, in particular when pneumonectomy (PN) has to be performed considering the expected low long-term survival and the worse post-operative outcome, in particular after IT. This highlights a substantial variability in the surgical and clinical management of those patients. Thus, patients with stage IIIA-N2 NSCLC candidate to PN are often excluded from surgery and candidate to a more conservative approach such as definitive chemo-radiotherapy.

Even if the incidence of post-operative complications following PN dropped sharply compare to the past

considering the new progresses in surgical technique and in post-operative care (4,5), PN is still considered a challenging procedure and its role remains controversial, due to the implemented use of multimodality approach in advanced stage lung cancer and the increased risk of surgical complications after IT ranging between 14% and 43% (6-9).

In literature (*Table 1*), there are different studies and randomized trials comparing the results of PN in patients with and without chemotherapy and showing different outcomes, mostly due to the different neoadjuvant therapies rather than the treatment strategy itself (6,7,10-14,16,17).

American groups performed induction chemo-radiation therapy in 58.7% of the case according to the Society of Thoracic Surgeons General Thoracic Surgery Database, compare to only 8.2% of the European trials (French General Thoracic Surgery Database—EPHITOR) (14,15), and this could be the reason of the higher post-operative morbidity and mortality. The Southwest Oncology Group

Table 1 review of the literature of patients underwent PN

Authors year (reference)	Type of study	N	IT rate	Morbidity	30-day mortality	5-year OS
Patel <i>et al.</i> 2002 (10)	Abstract	115	45%	–	4%	18.8 months median OS
Van Schil <i>et al.</i> 2005 (11)	Multicenter randomized trial	69 (all N2)	100%	9% only BPF	7%*	–
Gilligan <i>et al.</i> 2007 (12)	Multicenter randomized trial	145	45%	7%; 10%*	4%; 5%*	–
Thomas <i>et al.</i> 2008 (13)	Randomized trial	104	100%	33%	6%; 14% [§]	–
Albain <i>et al.</i> 2009 (6)	Multicenter randomized trial	54	100%	–	26%	22%
Pisters <i>et al.</i> 2010 (7)	Multicenter randomized trial	45	47%	–	0%; 17%*	–
Shapiro <i>et al.</i> 2010 (14)	Retrospective, STS GTDB	1,002	27%	30%	5%	–
Thomas <i>et al.</i> 2015 (15)	Retrospective, EPITHOR group	4,498	27%	33%	9%; 6%*	–
Broderick <i>et al.</i> 2016 (16)	Retrospective	1,033 (866 cN2)	71%	–	0%; 8%*	31%; 33%*
Casiraghi <i>et al.</i> 2019 (17)	Retrospective	233 (all N2)	64%	13%; 23%*	2%; 3%*	32%

*, after IT; [§], after chemo-radiotherapy. PN, pneumonectomy; IT, induction therapy; STS GTDB, Society of Thoracic Surgeons General Thoracic Database; OS, overall survival; BPF, bronchopleural fistula.

trial showed a 16.7% mortality rate in the PN group after IT compare to no mortality in the surgery-alone group; the outcomes were even worst in case of preoperative chemo-radiotherapy (7). In the Society of Thoracic Surgeons General Thoracic Surgery Database (14) induction chemo-radiotherapy was an independent risk factor for major post-operative events after PN as well as in the INT 0139 trial (6), in which IIIA-pN2 patients undergoing PN after platinum-based induction chemotherapy and radiotherapy had a 25.9% 30-day mortality rate.

On the other hand, the European trials, such as the French Thoracic Cooperative Group (10) and the MRC LU22/NVALT 2/EORTC 08012 multicenter randomized trial (12), did not show any significant increasing in mortality rates after IT. In the EORTC 08941 trial, the 30-day mortality of PN after IT was 7% (11,18), similar to the 5.7% of the EPITHOR and even lower than the post-operative mortality of patients (8.6%) who did not have IT (15). Besides, the German Lung Cancer Cooperative Group showed a post-PN mortality after 3 cycles of cisplatin and etoposide of 6% compare to 14% of patients treated with preoperative chemo-radiotherapy (13).

In our recent retrospective study (17) on 233 patients undergoing PN for N2 NSCLC, the 30-day and 90-day mortality rates was 2.5% and 8.8%, respectively, without any significant correlation to IT on survival, probably due to the fact the most of the patients had just induction chemotherapy, and only 6.1% concomitant chemo-

radiotherapy. Even in our older studies, the post-PN (after IT) mortality was described to be below 5%, but up to 10% after extended PN, due to higher surgical (bronchopleural fistula) and respiratory complication rates (17,19). Kim *et al.* (20) recently published a meta-analysis showing a significantly higher mortality for right sided PN, up to 11% after IT, probably related to a higher likelihood of bronchopleural fistula.

Indeed, PN is often associated to major post-operative morbidity, especially after IT and right PN, such as respiratory complications and post-operative bronchopleural fistula, which are the major cause of death in those patients. Thomas *et al.* (13) showed an overall postoperative complication rate of 33%, and a post-operative related mortality due to respiratory complications and bronchopleural fistula of 20.8% and 34%, respectively, mostly related to right-sided surgery more than IT.

In a study published by Patel in 2002, 115 patients undergoing PN, of which 52 patients (45%) after IT, had a 30-day mortality of 6% on the right side and 3% on the left side. Besides, IT was related to a higher risk of post-operative cardiac complications, but not to the incidence of bronchopleural fistulas. Their median survival was 18.5 months for the right-sided and 19.1 months for the left-sided interventions (10).

However, both in ours (17) and in other recent studies (13,21) major postoperative morbidity rate was considered acceptable after IT, even when induction chemo-

radiotherapy was included. This could be probably related to the systematic use of vascularized flaps, in particular after right post induction PN, which reduced the incidence of bronchial stump fistula (6,17,21).

Besides, some retrospective studies described poorer outcome after PN, even without IT (22-25), compare to lobectomy due to the stage of the tumor (centrally located), and to the higher early mortality after surgery (25). Also, Spaggiari in 2016 (26), published a retrospective study on 141 patients with “potential” resectable stage IIIA-pN2 after IT, describing a slightly better survival in the lobectomy group compare to PN, even if not statistically significant.

Considering the long-term survival, Casiraghi *et al.* (17) showed a 3- and 5-year OS of 43.4% and 31.6%, respectively, with no difference in survival between patients undergoing IT and patients who did not. In particular, poorer prognosis was associated to the number of N2 stations and to the extended resection, suggesting the importance of a correct patients’ selection.

Broderick *et al.* (16) analyzed 1,033 patients stage IIIA NSCLC (886 patients clinical N2) from the National Cancer Database showing for the T1-T3N2 patients an overall 5-year survival of 29.4%, 31.3% in the neoadjuvant group compare to 24.8% in the adjuvant group. In particular, the author did not find any difference in survival between all stage IIIA patients treated with neoadjuvant or adjuvant chemo-radiation, and the subset of IIIA patients with N2 disease.

In conclusion, although several studies favor a definitive CT/RT treatment in patients with IIIA-pN2 NSCLC, through our results and the literature was showed that PN could be considered a valid surgical option in fit patients based on the acceptable long-term survival and the low rate of post-treatment morbidity; however, patients who underwent extended resections with multiple N2 involvement had a poorer prognosis, emphasizing that an accurate patient selection should be a prerequisite for extended surgery.

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Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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