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Surgical Management of IIIA/N2 Non-Small Cell Lung Cancer; A Systematic Review

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Abstract

Background: Non-Small Cell Lung Cancer (NSCLC) stage IIIA/N2 (cT1-3N2M0) represents a heterogenic group, and depending on the level of lymph node involvement, prognosis varies within this group. Optimal treatment is debated, and patients may have benefit from combined treatment modalities. The aim of this study was to assess the evidence regarding surgical treatment of stage IIIA/N2 NSCLC diagnosed before commencement of treatment.

Methods: A systematic literature search for Randomized, Controlled Trials (RCT) comparing various combinations of treatments with surgery. Extraction of relevant data was performed, including study characteristics, patient characteristics, quality of trials and survival outcomes.

Results: Five RCT's with a total of 1166 patients were included. Treatment modalities varied substantially. None of the included studies found a statistically significant improved median overall survival, and only one study found an improved progression free survival when patients received chemotherapy, radiotherapy and surgery. Results, however indicates better locoregional control with surgery.

Conclusion: Current clinical guidelines are not based on high-quality evidence. To assess the existing high-quality evidence on this subject, only RCT's were included in this review. Results of statistical significance on survival are lacking, and studies show poor methodical quality. Based on the evidence available, surgery is not superior compared to other treatment modalities. Further subgroup analyses are needed, as evidence points toward surgery being beneficial for a subgroup of patients, possibly those with single-station N2 disease. RCT's of high methodical quality are needed to determine optimal chemotherapy regimens, radiotherapy and concomitant surgical intervention.

Keywords: Non-small cell lung cancer; Surgery; Chemotherapy; Radiotherapy

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Introduction

Lung cancer is the most common type of cancer with approximately 1.82 million new cases per year [1], and Non-Small Cell Lung Cancer (NSCLC) accounts for approximately 84% of all cases [2]. For NSCLC, 5-year relative survival rate is 22.7% for all stages, however, variability is immense between stages as localized, regional and distant stages varies between 60.1%, 33.4% and 5.5%, respectively [2]. Treatment strategy predominantly depends on clinical staging (cTNM), especially N-stage along with the patient's comorbidity and performance level. Focusing on the N-stage only, patients with N0-N1 disease is according to guidelines [3] generally offered surgical resection without preoperative treatment, and followed by adjuvant therapy depending on tumor size, resectability and lymph node involvement.

Patients with N2 disease represent a very heterogenic group, and the optimal treatment is uncertain [4]. These patients may benefit from combined neoadjuvant or adjuvant treatment modalities – maybe even trimodality i.e. a combination of chemotherapy, radiation and surgery [5]. Whether N2 disease is intranodal or extranodal [6], single-station or multi-station, limited to one nodal zone, or presence of bulky lymph nodes (large, fixed lymph nodes), are factors to be considered in relation to choice of treatment [7].

The heterogeneity of patients with N2 disease have until now resulted in very diverse treatment strategies and consequently miscellaneous prognosis of the patients within this group [7]. Moreover,

Table 1: Study Characteristics and Outcomes.

First Author, Year, Reference	Country of Origin	No. of Patients (n)	Median Age of Patients (Year)	Staging Based on	Surgical Procedure Performed	Additional Interventions	OS, (95% CI)	DFS/PFS, (95% CI)
Albain et al. [10]	US and Canada	429	Group 1: 59 Group 2: 61	Biopsy samples by any of protocol-specified standard procedures (NS). CT or MRI of the brain.	Wedge resections, n=3 Lobectomies, n=98 Right-sided pneumonectomy, n=29 Left-sided pneumonectomy, n=25	Group 1: Concurrent induction chemotherapy (cisplatin and etoposide) and radiotherapy followed by surgery, n=216 Group 2: Concurrent induction chemotherapy (cisplatin and etoposide) and definitive radiotherapy, n=213	Group 1: 23.6 months (IQR 9.0-not reached) Group 2:22.2 months (IQR 9.7-52.7) p=0.24	Group 1: 12.8 months (IQR 5.3-42.2) Group 2: 10.5 months (IQR 4.8-20.6) p=0.02
Johnstone et al. [11]	US	75	< 60 years old: 51%	Histologic documentation by mediastinoscopy or anterior mediastinotomy	Thoracotomy without resection, n=3 Lobectomy or pneumonectomy, n=23	Induction chemotherapy (initially consisting of cisplatin, vinblastine and mitomycin-C. Modified regimen consisting of cisplatin and vinblastine) followed by randomisation to: Surgery arm, n=29 Radiotherapy arm, n=33	Surgery arm: 19.38 months Radiotherapy arm: 17.38 months (95% CI NR) p=0.46	14 months (95% CI NR)
O'Brien et al. [12]	United Kingdom, The Netherlands, Poland, Belgium	52	60	Mediastinoscopy/thoracotomy (n=42), needle biopsy/ aspiration cytology (n=8), clinical N2 disease because of vocal cord paralysis (n=2)	NS	Induction chemotherapy (paclitaxel and carboplatin) followed by randomization to Surgery, n=15 Radiotherapy, n=20	20.5 months (16.1-31.2)	NR
Shepherd et al. [13]	Canada	31	Radiotherapy alone: 52 Chemotherapy and surgery: 61	Biopsy	NS	Radiotherapy arm, n=15 Chemotherapy (cisplatin and vinblastine) and surgery arm, n=16	Radiotherapy arm: 16.2 months (10.7-32.3). Chemotherapy and surgery arm: 18.7 months (12.8-32)	NR
Van Meerbeeck et al. [14]	Belgium	579	61	Cytologic or histologic diagnosis. Mediastinoscopy, n=478 VATS, n=6 Thoracotomy, n=34 Needle procedure (transbronchial, transthoracic fine-needle aspiration or core biopsy), n=56	Right-sided pneumonectomy, n=38 Left-sided pneumonectomy, n=33 (Bi-)lobectomy, n=59 Exploratory thoracotomy, n=22 Remediastinoscopy, n=1	Induction chemotherapy (cisplatin or carboplatin, combined with at least one other chemotherapy drug) followed by randomization to: Radiotherapy arm, n=167 Surgery arm, n=165	Radiotherapy arm: 17.5 months (15.8-23.2) Surgery arm: 16.4 months (13.3-19.0) HR=1.06 (95% CI 0.84- 1.35)	Radiotherapy arm: 11.3 months (8.9-12.7) Surgery arm: 9 months (7.6-11.2) HR=1.06 (95% CI 0.85-1.33)

Abbreviations: CI: Confidence Interval; DFS: Disease Free Survival; HR: Hazard Ratio; IQR: Interquartile Range; NR: Not Reported; NS: Not Specified; OS: Overall Survival; PFS: Progression Free Survival; VATS: Video-Assisted Thoracoscopic Surgery

preoperative staging of the lymph nodes is problematic, since the various invasive methods are subject to inconsistent findings, based on the different presentations of N2-disease as described above. This can lead to faulty cTNM staging, and thereby "incorrect/sub-optimal" choice of treatment. However, patients with negative mediastinal staging (e.g. by invasive diagnostic procedures) of lymph nodes and classified as pN2 is often referred to as "minimal N2-disease" [8] and has a better prognosis compared to cN2 - not unlike survival rates for stage IIB, which is suggested to be related to limited lymph node involvement.

The aim of this study was to assess the existing evidence regarding surgery as an additional treatment modality of stage IIIA/N2 NSCLC diagnosed before commencement of treatment (cN2).

Material and Methods

Literature search

Publications were identified through searching the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Scopus and Embase (start 1980–July 2018). The following strategy was used to search PubMed and was adapted appropriately for the additional search engines:

((((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh])))) AND ("1980/01/01"[PDat] : "3000/12/31"[PDat]) AND English[lang])) AND (((((("Carcinoma, Non-Small-Cell Lung" OR "NSCLC")) OR "Lung Neoplasms"[Mesh])) AND ((("Pneumonectomy"[Mesh] OR "lung lobectomy")) OR surgery[Title])) AND ((("Overall survival" OR "Disease free survival" OR "progression free survival")) OR "Disease-Free Survival"[Mesh])) AND ("1980/01/01"[PDat] : "3000/12/31"[PDat]) AND English[lang]) Filters: Publication date from 1980/01/01; English

Based on titles and abstracts relevant to the topic, original articles were selected. Additionally, relevant articles were identified by review of references in key publications. An overview of the study selection process is displayed in figure 1 and is in accordance with PRISMA [9].

Data extraction

We extracted the following data from all included studies: author, publication year, Randomized Controlled Trial (RCT), country of origin, number of patients included, mean/median age of patients, method of staging, surgical procedure performed, additional interventions (chemotherapy and radiotherapy), Overall Survival (OS), Disease Free Survival (DFS), Progression Free Survival (PFS), characterization of N2 positivity (size/"bulky" or number of positive lymph node stations), recurrence patterns and treatment related mortality.

Assessment of study eligibility

The titles (and abstracts when available) identified through the literature search were reviewed. Any article that might meet the eligibility criteria was included. All studies were scanned for additional relevant references.

Eligibility criteria

Type of studies included RCT's assessing optimal treatment of patients diagnosed with stage IIIA/N2 NSCLC (according to TNM-classification), before commencement of treatment. Only one study arm included surgical intervention. Participants were >18 years of age, and only stage IIIA/N2 NSCLC was included. Types of surgical interventions included lobectomy, pneumonectomy, and wedge resection, exploratory thoracotomy, performed either through thoracotomy or Video-Assisted Thoracoscopic Surgery (VATS). Types of additional interventions included chemotherapy and radiotherapy.

Results

Description of included studies

As seen in Figure 1, five RCT's [10-14] were included in this review, with a total of 1166 patients, ranging from 31 to 579 patients (mean: 233; median: 75). Interventions varied between studies, and a description of the included studies is displayed in Table 1.

Staging

All included studies performed invasive mediastinal staging, and either cytologic or histologic documentation was obtained. One study [10] reported that Computed Tomography scan (CT) or Magnetic Resonance Imaging (MRI) of the brain was performed, none of the included studies reported on Positron Emission Tomographic Computed Tomography (PET-CT).

Chemotherapy and surgery compared to definitive radiotherapy (One Study)

Shepherd et al. [13] compared chemotherapy and surgery to definitive radiotherapy. In cases of complete resection, patients received the same chemotherapy postoperatively. No statistically significant difference was found between the two groups regarding median OS, which was 18.7 months (95% Confidence Interval (CI) 12.8-32) in the chemotherapy and surgery arm, and 16.2 months (95% CI 10.7-32.3) in the definitive radiotherapy arm.

Preoperative chemotherapy and definitive surgery compared to induction chemotherapy and definitive radiotherapy (Three Studies)

Van Meerbeeck et al. [14] randomized eligible patients after induction chemotherapy to either radiotherapy or surgery. No difference in outcomes were found between the two groups, median OS in the radiotherapy arm was 17.5 months (95% CI 15.8-23.2), and 16.4 months (95% CI 13.3-19.0) in the surgery arm, HR=1.06 (95% CI 0.84-1.35). Median PFS was 11.3 months (95% CI 8.9-12.7) in the radiotherapy arm and 9 months (95% CI 7.6-11.2) in the surgery arm, HR=1.06 (95% CI 0.85-1.33).

Johnstone et al. [11] randomized patients to either induction chemotherapy and surgery, or induction chemotherapy and radiotherapy. No statistically significant difference was found between intervention groups, median OS in the surgery arm was 19.38 months and 17.4 months in the radiotherapy arm, p=0.46. Median PFS was reported as 14 months for the entire study group.

O'Brien et al. [12] administered induction chemotherapy. Patients with response to induction chemotherapy, either partial or complete, were eligible for randomization to surgery or radical radiotherapy. This was a sub-study of the European Organization for Research and Treatment of Cancer (EORTC), trial 08941. Additional information regarding radiotherapy dosage and surgical interventions were not specified as the primary aim of this study was to evaluate toxicity and antitumor activity of carboplatin and paclitaxel. In all eligible patients, a median OS of 20.5 months (95% CI 16.1-31.2) was found.

Concurrent chemoradiotherapy followed by surgery compared to concurrent chemoradiotherapy alone (One Study)

Albain et al. [10] randomized patients between two groups, group 1 receiving induction chemotherapy and radiotherapy followed by surgery and group 2 receiving induction chemotherapy and definitive dose radiotherapy. No statistically significant difference was found in median OS between the two groups, 23.6 months (Interquartile range (IQR) 9.0-not reached) in group 1 and 22.2 months (IQR 9.7-52.7) in group 2, HR 0.87 (95% CI 0.70-1.10), p=0.24.

A subgroup analysis of overall survival found an improvement in median OS if lobectomy rather than pneumonectomy was performed, compared to matched patients in group 2 (33.6 months (IQR 15.6-not reached) *vs.* 21.7 months (IQR 10.1-46.0), p=0.002). Median PFS was found significantly improved in group 1, 12.8 months (IQR 5.3-42.2) *vs.* 10.5 months (IQR 4.8-20.6) in group 2, HR 0.77 (95% CI 0.62-0.96), p=0.02.

Characterization of N2 positivity

The included studies characterized N2 positivity using various methods (Table 2). Albain et al. [10] reported that approximately 75% in the two groups of patients had only one positive lymph node

Table 2: Overview of N2 Positivity, Recurrence Patterns and Treatment Related Mortality.

First Author, Year, Reference	Characterization of N2 Positivity	Recurrence Patterns	Treatment Related Mortality
Albain et al. [10]	Group 1: One positive lymph node station, n=153 (76 %) Other: 49 (24 %) Group 2: One positive lymph node station, n=146 (75 %) Other: 48 (25 %)	Fewer local-only relapses in group 1: 21 (10%) of 202) vs. 43 ((22%) of 194) in group 2. No difference in sites of first progression. Group 1: Primary tumour site only, n=5 (2 %) Hilar, mediastinal, or supraclavicular nodes only, n=14 (7 %) Primary tumour site and hilar, mediastinal or supraclavicular nodes, n=2 (1%) Brain, n=23 (11 %) Other distant site, n=75 (37 %) Group 2: Primary tumour site only, n=28 (14 %) Hilar, mediastinal, or supraclavicular nodes only, n=6 (3 %) Primary tumour site and hilar, mediastinal or supraclavicular nodes, n=9 (5 %) Brain, n=29 (15 %) Other distant site, n=81 (42 %)	Group 1: 16 deaths, ten of which was within 30 days of thoracotomy. 14 died after pneumonectomy, one after lobectomy and one did not undergo thoracotomy. Acute respiratory distress syndrome, n=9 Other respiratory, n=4 Cardiac, n=2 Haemorrhage, n=1 Group 2: Non-acute-respiratory-distress-syndrome respiratory, n=3 Other, n=1
Johnstone et al. [11]	Surgery arm: Bulky N2*, n=16 (55 %) Other, n=13 (45 %) Radiotherapy arm: Bulky N2, n=17 (53 %) Other, n=15 (47 %)	No significant difference in time to local failure. Radiographically complete response: Surgical arm, 67 % Radiotherapy arm, 39 %	Surgical arm: Late pulmonary toxicity, n=1 Pulmonary embolus, n=1 Radiation arm: Radiation pneumonitis, n=1
O'Brien et al. [12]	NS	NS	Infection during second-line treatment, n=2 Cardiovascular cause, n=1 Pulmonary hypertension 5 days post surgery, n=1 Unknown, n=1 No specification between treatment arms.
Shepherd et al. [13]	Radiotherapy arm: ≤1.5 cm, n=7 (47 %) > 1.5 cm, n=8 (53 %) Chemotherapy and surgery arm: ≤1.5 cm, n=8 (50 %) > 1.5 cm, n=8 (50 %)	Radiotherapy arm: Local relapse, n=6 Systemic relapse, n=4 Chemotherapy and surgery arm: Local relapse, n=8 Systemic relapse, n=1	NS
Van Meerbeeck et al. [14]	NS	Site of first relapse: Radiotherapy arm: Locoregional, n=71 (55 %) Distant, n=50 (39 %) Both, n=9 (7 %) Surgery arm: Locoregional, n=37 (32 %) Distant, n=70 (61 %) Both, n=8 (7 %)	30 day mortality, surgical arm: n=6 (4 %) Pneumonectomy, n=5 Exploratory thoracotomy, n=1 Radiotherapy arm: radiation pneumonitis, n=1

Abbreviations: CI: Confidence Interval; HR: Hazard Ratio; NS: Not Specified; PET-CT: Positron Emission Tomographic Computed Tomography
*Bulky N2: defined as visible on plain chest radiography

station. Johnstone et al. [11] defined bulky N2 disease as visible on plain chest radiography. In the surgical arm, 55% had bulky N2 disease, compared to 53% in the radiotherapy arm. Shepherd et al. [13] stated that 47% of patients had mediastinal nodes ≤ 1.5 cm in the radiotherapy arm, and 50% of patients in the chemotherapy and surgery arm.

Recurrence patterns and treatment related mortality

Table 2 provides an overview of recurrence patterns and treatment related mortality. Albain et al. [10] reported fewer local-only relapses in group 1, receiving surgery (10% *vs.* 22% in the non-surgical group). The initial site of progression was the brain only in 11% and 15% in group 1 and 2, respectively. At other distant sites, rates were 37% and 42% respectively. Treatment related mortality was higher in the surgical group. Johnstone et al. [11] reported that 67% of patients had radiographically complete response in the surgical arm, compared to 39% in the radiotherapy arm. O'Brien et al. [12] reported five treatment related deaths, however without specification between the two arms. Shepherd et al. [13] reported eight local relapses and one systemic relapse in the chemotherapy and surgery arm, compared to six local relapses and four systemic relapses in the radiotherapy arm. Recurrence patterns reported by van Meerbeeck et al. [14] showed that site of first relapse were more often distant in the surgery arm (61% *vs.* 39%) and more often locoregional in the radiotherapy arm (55% *vs.* 32%). Treatment related mortality within 30 days was 4% (n=6) in the surgery arm, and one death occurred in the radiotherapy arm.

Quality of included studies

An overview of the methodological assessment of the included studies is displayed in Table 3. Baseline characteristics were in general distributed evenly between intervention groups. One study [12] did not provide information regarding variations between intervention groups. One study reported a difference between intervention groups, however not statistically significant, consisting of overweight of squamous histologic features in one of the treatment arms (receiving chemotherapy and radiotherapy, chemotherapy regimen without mitomycin-C) (p=0.17) [11]. Two studies [10,14] stated that the

Table 3: Methodological Assessment of the Quality of the Included Studies.

First Author, Year, Reference	Achievement of Calculated Statistical Power (e.g. No. of Patients Enrolled, No. of Events)	Analysis by Intention to Treat	Randomization Procedure /Allocation Concealment	Patient Characteristics Well Balanced	Termination
Albain et al. [10]	Yes, after being revised during study period	Yes	A	Yes	-
Johnstone et al. [11]	No	NS	B	Yes	Terminated early because a large Phase II trial demonstrated the feasibility of preoperative concurrent chemoradiation in this group of patients
O'Brien et al. [12]	NS	NS	B	NS	NS
Shepherd et al. [13]	No	NS	B	Yes	Terminated early because investigators found the radiotherapy-alone arm inappropriate
Van Meerbeeck et al. [14]	No, but apparently without interference of statistical power	Yes	A	Yes	Terminated early because of slow accrual

Abbreviations: NS: Not Specified
A: adequate; B: unclear

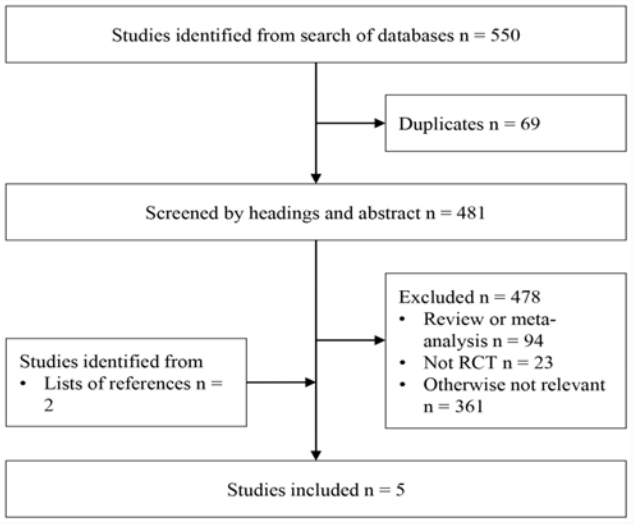

Figure 1: Study selection process.
Abbreviations: RCT: Randomized Controlled Trials

analysis was performed as an intention to treat analysis (ITT).

Procedure of concealment of group allocation was rated as adequate (A) when reported as central randomization, either computerized or using serial numbers, opaque and sealed envelopes or otherwise convincing methods. All other methods were rated as inadequate (C) (e.g. by pre-specified lists, case numbers or using date of inclusion or birth). When no clear description or only unclear description was reported, group allocation concealment was rated as unclear (B). Two studies [10,14] were rated as using adequate allocation concealment, and the remaining three studies [11-13] were rated as unclear.

Only one study [10] reported to have achieved sufficient power, although only after making amendments to the statistical design. One study [14] did not achieve calculated statistical power, but apparently without leading to interference of statistical power. Two studies [11,13] did not achieve calculated statistical power, and one study [12] did not provide information regarding this. Slow accrual was the reason for early termination in one study [14]. Authors felt it unethical to proceed with a solely radiotherapy arm in one study [13], and the study was terminated early. One study [11] was terminated prescheduled by another large Phase II trial that took precedence over this study, since the Phase II study demonstrated feasibility of preoperative concurrent chemoradiation in the same group of patients.

Discussion

High level of evidence can only be achieved based on RCT's, since there is an inherent risk of selection bias in observational studies, and therefore, only RCT's was included in this review. Since the purpose of this review was to investigate the evidence for surgery as part of the treatment, only RCT's with a non-surgical control arm was included. Current evidence-based clinical practice guidelines provided by the American College of Chest Physicians (ACCP) [4] is based on both RCT's and observational studies, and not all recommendations are strong, and/or based on high level of evidence. The subdivision of NSCLC is variable (e.g. single-station/multiple-station N2, minimal/clinical N2) and thereby choice of treatment, and obviously, prognosis varies [8].

A methodological assessment (Table 3) of the included RCT's was performed. Studies were statistically underpowered (except for one study [10]) and the low statistical power entailed risk of associations being coincidental. Analysis performed by ITT [15] was only provided in two studies [10,14], and the procedure of concealment of group allocation [16] was merely rated as adequate in the same two studies. Accordingly, the majority of the included studies were ranked as lower quality studies. We found a large heterogeneity between the included RCT's in terms of variety in interventions, and therefore it was not reasonable to perform meta-analysis. There were variations between single modality/bimodality/trimodality treatments, both between all included studies, and between test- and control-groups in the same study. Furthermore, there was variety in types of chemotherapy and various doses of radiotherapy. Sample sizes were in general small. All studies reported a median OS, but additional outcomes varied, e.g. some studies reported PFS, failure free survival or DFS. None of the included studies found statistically significant results regarding median OS and only one study reported a significant difference between interventions regarding PFS [10]. ACCP guidelines for staging [17] suggests, that routine imaging of the brain should be performed for patients with stage III NSCLC (preferably MRI, CT-scan if MRI is not available), regardless of a negative clinical evaluation. PET-CT should be performed to rule out

extrathoracic metastases. Invasive staging of the mediastinum should always be performed when suspecting N2 disease. Different methods for staging was used in the included studies, and the majority [10-14] did not perform brain imaging investigations or PET-CT as part of staging, and this raised a question of whether cerebral metastases or other distant metastases have been overlooked before commencement of treatment, and thereby explaining the poor effect of treatment for this group of patients. Optimally, only RCT's who performed PET-CT as part of staging would be included.

None of the included studies reported outcomes specific for the various subsets of N2, e.g. single-station or bulky N2 disease. One study [10] did however report one N2 nodal station positive at diagnosis vs. more than one as a statistically significant independent predictor of outcome (p=0.02). Furthermore, a relatively long median OS was found, which may be explained by the fact that the majority of patients had single-station N2 disease. The remaining studies [11,13] that provided characterization of N2 positivity, reported that the amount of "bulky N2" or N2>1.5 cm, was well balanced between intervention groups. Outcomes specified for the different variations of N2 disease could possibly strengthen the need for further subdivision of NSCLC [18], and surgery for a selected group of patients - e.g. single-station N2 disease [19]. Results indicated that surgery leads to better locoregional control [10,14] and radiographically complete response in a greater portion of patients [11]. One study [13] did however report that the majority of relapses were local in both groups.

Optimal surgical methods are debated, but aims at complete resection including systematic mediastinal nodal exploration [20]. Complete resection vs. incomplete resection was shown as a significant prognostic factor (HR=0.46, 95% CI=0.32-0.67) [14]. Lobectomy vs. pneumonectomy was also shown to be a significant prognostic factor (HR=0.59 95% CI=0.40-0.87) [14], as well as a subset analysis showed improved median OS when lobectomy was performed [10]. It has been suggested that pathologic down-staging after induction therapy is a stronger prognostic factor for survival, than complete resection [14,21,22]. Preferably lobectomy and perhaps segmentectomy should be performed, but not wedge resection [23]. In general, this review found treatment related mortality higher in the surgical arms, and pneumonectomy was associated with increased peri-operative mortality [10,14]. The mortality after pneumonectomy was evaluated as extraordinary high in the included references and should be reserved for carefully selected patients [24,25]. Surgery was performed through thoracotomy, and quality of surgery and lymph node dissection is not further described.

The RCT's included in this review had several shortcomings; poor methodical quality, lack of significant results, small sample sizes, different methods for staging and the heterogeneity of N2 disease all presented problems that made it impossible to draw firm conclusions regarding the use of surgery. Variations in interventions limited the basis for concluding the effect of a specific intervention. There is a risk that relevant studies have been missed in the literature search, because of strict inclusion criteria and only including RCT's with a non-surgical control arm in this review. The majority of studies included in this paper did not confirm their hypotheses, leading to the assumption that it is unlikely that some studies have not been published because of negative results. Therapeutic options have been improved, and a recent RCT showed great potential of immunotherapy in the treatment of unresectable stage III NSCLC in combination with chemoradiotherapy [26], and needs to be further investigated in relation to surgery. Recent published observational studies have shown statistically significant improved median OS [27,28] and PFS [28] for chemoradiation and surgery compared to definitive chemoradiation, and a statistically significant improved median OS for patients receiving surgery compared to radiotherapy, and further improved when the combination of preoperative radiotherapy and surgery was compared to radiotherapy [29]. As mentioned before, it is not possible to draw any conclusions based on these observational studies. Yet, it is not an easy task and not without limitations to perform a RCT: the need for resources (both financially and logistical), inclusion of a relatively high number of patients, the rapid development in diagnostic options and therapeutic options (e.g. immunotherapy) etc. However, these challenges are solvable and should not retain us for providing scientific documentation for the treatment of these patients.

In conclusion, it is not possible to deduce surgery as superior to treatment regimens without surgery based on the existing evidence. A trimodality approach of concurrent chemoradiotherapy followed by surgery showed improved median PFS, however, only in one study. An included study was with substantial heterogeneity. This review points towards better locoregional control, and surgery being beneficial for a subgroup of stage IIIA/N2 patients with single station lymph node involvement, which underlines the importance of methodological preoperative staging. Further RCT's of high quality is needed to determine optimal chemotherapy regimens, surgical procedure and whether targeted therapies can further improve survival, so clinical guidelines can be made based on high quality evidence. Survival analysis based on subgroups is needed to confirm trends toward selecting the group of patients that might benefit from surgery.

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