Original Article

Is sleeve lobectomy safe after induction therapy?—a systematic review and meta-analysis

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Background: Sleeve lobectomy (SL) is a lung-sparing procedure, which is accepted as a valid operation for centrally-located advanced tumors. These tumors often require induction treatment by chemotherapy and/or radiotherapy to downstage the disease and thus facilitate subsequent surgery. However, induction therapy may potentially increase the risk of bronchial anastomotic complications and related morbidity. This meta-analysis aims to determine the impact of induction therapy on the outcomes of pulmonary SL.

Methods: We compared studies of patients undergoing SL or bilobectomy for non-small cell lung cancer (NSCLC) with and without induction therapy. Outcomes of interest were in-hospital mortality, morbidity, anastomosis complication and 5-year survival. Odds ratio (OR) were computed following the Mantel-Haenszel method.

Results: Ten studies were included for a total of 1,204 patients. There was no statistical difference for between patients who underwent induction therapy followed by surgery and patients who underwent surgery alone in term of post-operative mortality (OR: 1.80, 95% confidence interval (CI): 0.76–4.25, P value =0.19) and morbidity (OR: 1.17, 95% CI: 0.90–1.52, P value =0.237). Anastomosis related complications rate were 5.2% and appears increased after induction therapy with a statistical difference close to the significance (OR: 1.65, 95% CI: 0.97–2.83, P value =0.06). Patients undergoing surgery alone showed better survival at 5 years (OR: 1.52, 95% CI: 1.15–2.00, P value =0.003).

Conclusions: SL following induction therapy can be safely performed with no increase of mortality and morbidity. However, the need for induction therapy before surgery is associated with increased anastomotic complications and poorer survival prognosis at 5 years.

Keywords: Sleeve lobectomy (SL); induction therapy; anastomosis complication; survival; thoracic surgery

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Introduction

The main approach to manage non-small cell lung cancer (NSCLC) with a curative intent remains surgical resection. For centrally-located NSCLCs, pneumonectomy is indicated if several lobes or if central broncho-vascular structures are involved. Alternatively, pulmonary sleeve resection is a parenchyma-sparing surgical procedure that was proven to be valid in centrally-located NSCLCs (1,2).

This approach has the advantage of providing complete tumor resection while avoiding pneumonectomy. Initially proposed for NSCLC patients with poor cardiopulmonary functions, sleeve lobectomy (SL) has now replaced pneumonectomy even in patients with excellent cardiopulmonary functions, when technically feasible. Several studies or meta-analyses have demonstrated better post-operative outcomes and better quality of life in favor of pulmonary sleeve resection in comparison with pneumonectomy, with equivalent oncological outcomes (3-6). However, SL has been associated with higher distant recurrence rates than pneumonectomy in disease with nodal involvement (N1 or N2) (7,8). Thereby, induction treatment by either chemotherapy and/or radiotherapy is currently used to reduce the size of the tumor to potentially avoid the pneumonectomy and facilitate parenchyma-sparing procedures. Induction therapy is often needed before SL, to decrease the risk of subsequent recurrence, minimize the tumor size and ultimately facilitate complete resection. However, induction therapy may cause fibrosis and treatment related changes, which make dissection of lobar bronchus or artery and reconstructive procedure more difficult and complex (6), and raise concerns about the effects of chemotherapy and/or radiotherapy on vascular and bronchial anatomy (9,10) and airway healing. The aim of this meta-analysis was to assess the impact of induction therapy on sleeve resections, focusing on (I) post-operative 30-day mortality, (II) 30-day post-operative morbidity, (III) anastomotic related complications and (IV) overall survival.

We present the following article in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist (available at https://dx.doi.org/10.21037/jtd-21-939).

Methods

Data sources and search strategies

Electronical searches were performed on the MEDLINE using OVID, EMBASE and Google Scholar databases for articles published between January 1st 2000 and December 31st 2020. Two investigators (LEC and MG) independently carried out the literature search. A search protocol was established prior to any research. The search terms used are described in Appendix 1.

References from articles were also reviewed. Disagreements were resolved by a discussion between the two investigators. If no consensus was reached, the study was removed from the pool. The search was limited to human studies with no limit in sample size. Cochrane Library databases were also reviewed to search any previous meta-analysis on the subject. Findings were executed and reported following the PRISMA statements. Data collection was then performed independently and in duplicate by the two authors.

Selection criteria

Literature search results were screened for title and abstract referring to pulmonary sleeve resection in the context of induction chemo- and/or radiotherapy. Then, only full articles published in English were kept. Our exclusion criteria were: (I) article only available in the form of abstract, book chapter, case-report or narrative review; (II) full articles not available in English. The remaining articles were reviewed and studies with available relevant data were pooled. During this step, studies designed as observational studies, randomized clinical trials or non-randomized clinical trials meeting the following criteria were included: data were separately available for patients undergoing induction therapy or surgery alone with end-points or outcomes expressed as percentages or means with standard deviation, and patient benefiting from a pneumectomy were distinguished from patients undergoing a SL or bilobectomy. Finally, the quality of each individual study was assessed using the STROBE checklist.

Data extraction

Postoperative outcomes were compared between patients undergoing induction therapy followed by surgery and patients undergoing surgery alone. Parameters of interest were postoperative mortality, postoperative morbidity, anastomosis-related complications and 5-year survival. Mortality was defined as any death during in-hospital or 30 days after surgery.

Post-operative morbidity was defined as any post-operative complications arising after surgery including anastomotic complications. Anastomotic complications were defined as any stenosis or dehiscence at the site of the anastomosis and broncho-pleural fistula (BPF) or broncho-vascular fistula. Characteristics of each population were extracted and included average age, predominant sex, number of participants in each group, type of sleeve resection performed, oncological parameters, type of disease (benign or malign), staging (for cancer patients only), number of patients undergoing pre-operative chemotherapy alone, radiotherapy alone or combined therapy. The studies characteristics (retrospective or prospective study) were reported.

Statistical analysis

We computed the pooled odds ratio (OR) for each parameter, using the Mantel-Haenszel method. If one group displayed 0 patient for a given parameter, we used the Haldane-Anscombe correction consisting in adding 0.5 to each group for computing the OR. If both groups displayed 0 patient, we excluded the study for the computation of the parameters. We computed the confidence interval (CI) on a 95% base and reported the P value of each CI. We considered a P value <0.05 to be significant. The variance used to compute the CI was obtained from the log of the pooled OR as presented by Robins *et al.* (11). If a substantial lack of homogeneity with a I^2 values over 60% and a significant P value (see next section) was observed, a random-model (DerSimonian and Liard method) was applied. In this case, the inverse-variance-weighted method was chosen to obtain OR and 95% CI of the pooled OR, using the inter-study variance.

Heterogeneity assessment and publications bias

Q-Cochrane statistic was computed to assess the heterogeneity between studies. We chose the I^2 value as the reference to quantify it. For P values <0.05, we considered that we could not exclude a lack of homogeneity in the pool of study. Our reference for interpreting the I^2 value was 0% to 30%: might not be important; 30% to 60%: may represent moderate heterogeneity; 60% to 75%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity; following the Cochrane recommendation (12).

We used funnel plots to investigate potential publication bias with 95% CIs. We followed the Stern and Egger's method plotting the log OR on x-axis and standard error (SE) on y-axis. Interpretation of funnel plots was performed visually by searching for any asymmetry or suggestive lack of studies in any side around the null OR, which could indicate a publication bias.

Statistic computations were performed with Excel and R software. Display in forest plot and funnel plot were visually generated using the package "meta" in R.

Results

Study selection

After the first screening across databases and exclusion of duplicate studies, we identified 283 potential articles. Details of the selection of the studies are provided in *Figure 1*. Finally, we could pool 9 studies.

Among these 9 studies, 7 were retrospective (13-19) and 2 were prospective studies (20,21). All of these articles reported the details for post-operative mortality, morbidity and the rate of anastomotic complications. Caso *et al.* (15) and Veronesi *et al.* (22) reported no patient mortality in either group and so were excluded from computation for this parameter. In the same manner, Caso *et al.* (15) did not witness any anastomotic complications and the study was also excluded from the pool. Seven studies (13,15-20) presented the 5-year survival rate and were included in the pooled ratio. Details of parameters and design from individual studies can be found in *Table 1*.

Population of interest

The pooled population was composed of 1,204 patients for a mean age of 60.3±5.2 years. Among them, 930 were male (77.2%). A total of 352 patients (29.2%) were included in the induction group. Of those, 187 patients (53.1%) received a combined radio-chemotherapy induction therapy, 161 patients (45.7%) received chemotherapy alone and 1 patient (0.28%) radiotherapy alone. The 3 remaining modalities were not reported (NR). All patients presented lung cancer except five patients who presented pulmonary metastasis from renal cell cancer, schwannoma, muco-epidermoid cancer, colon cancer metastasis and inflammatory myofibroblastic tumor. The pre-operative and pre-induction tumoral stage were reported for 1,138 patients with a majority of stage II (500 patients, 43.9%), followed by stage III (421 patients, 37.0%) and stage I (172 patients, 15.1%). Of the remaining patients, 36 presented a stage IV (3.2%) and 9 a stage 0 (0.8%). Patients' characteristics are reported in *Table 2*.

In-hospital mortality

Five studies (13,14,16,18,20) contributed to the pooled estimate for mortality (*Figure 2*). We excluded 2 studies that reported the 90-day mortality (17,19). Overall mortality rate ranges from 0% to 3.8%. The OR was equal to 1.80

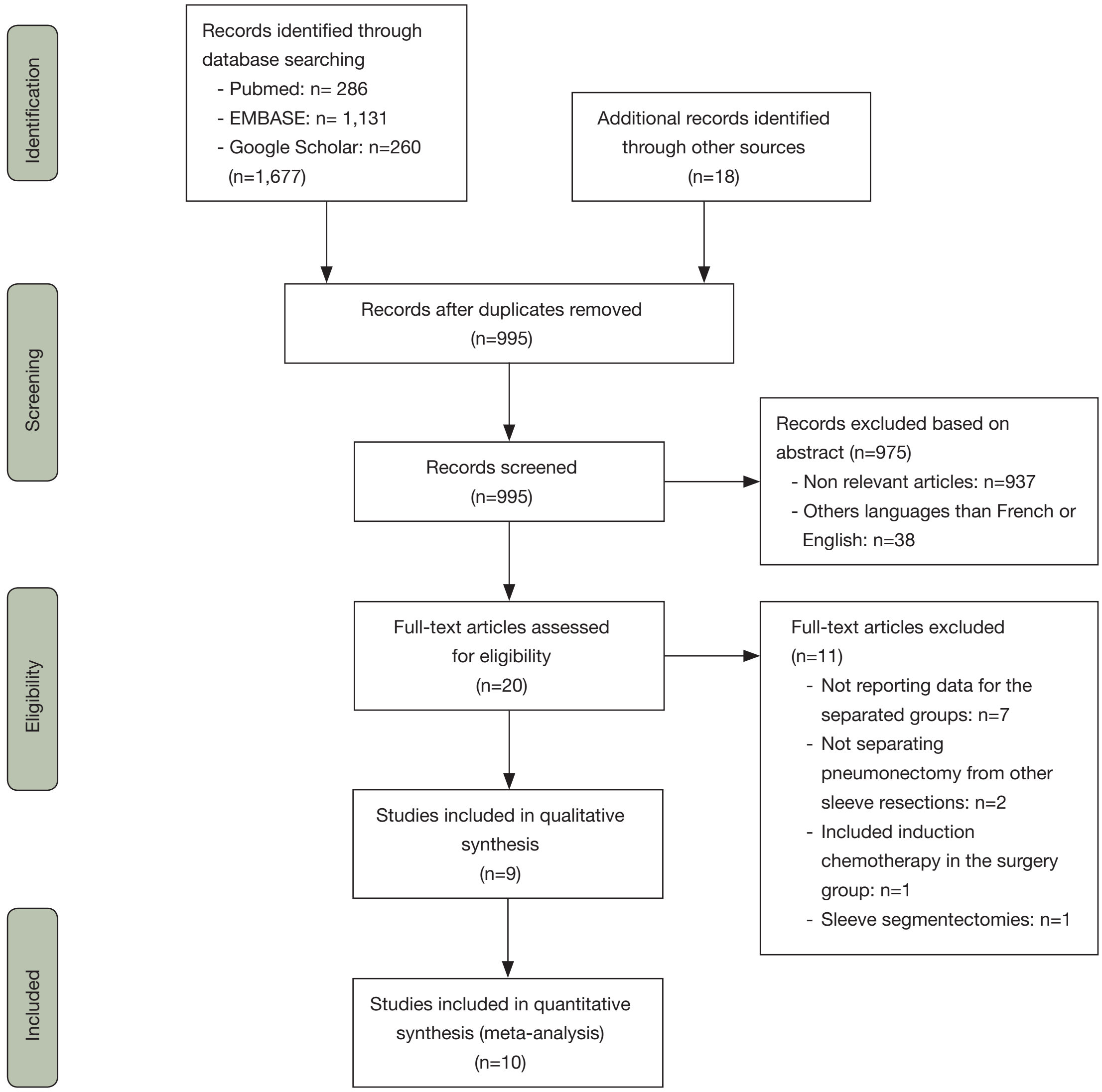

Figure 1 Parameters and design of individual studies included in the meta-analysis.

with a 95% CI from 0.76 to 4.25 (P value =0.19). No lack of homogeneity was observed (I^2=0%, P=0.499482) across the studies.

Morbidity

Nine studies (13-20,22) were pooled for the parameter of morbidity, ranging from 23.9% to 50.5% with an estimate OR of 1.17 (95% CI: 0.90–1.52, P value =0.237) (*Figure 3*). No lack of homogeneity was observed (I^2=0%, P=0.960317) among the studies.

Anastomotic complications

Eight studies (13,14,16-20,22) reported on anastomotic complications. The overall rate of anastomotic complications was 5.2% (63/1,204). The estimate OR was 1.65 (95% CI: 0.97–2.83, P value =0.06) (*Figure 4*). No lack of homogeneity was observed (I^2=15.2%, P=0.311066) across studies. Anastomotic complications rates ranged between 0% and 18% in both groups. A total of 25 patients over 352 undergoing induction (7.1%) and 38 of the 852 patients in surgery alone group (4.4%)

Table 1 Parameters and design of individual studies included in the meta-analysis

First author, year of publication	Design	Surgery performed	No. of patients (SA/IT)	Mortality (SA/IT)	Morbidity (SA/IT)	Anastomosis complications (SA/IT)	Five-years survival (SA/IT)
Bagan, 2009 (13)	RCC	SL	159 (74%/26%)	2%/2%	25%/21%	3%/0%	65%/74%
Burfeind, 2005 (14)	RCC	SL, BP	73 (74%/26%)	4%/0%	35%/42%	0%/5.2%	NR
Caso, 2018 (15)	RCC	SL, double SL	15 (73%/27%)	0%/0%	38%/50%	0%/0%	80%/100%
Comacchio, 2019 (16)	RCC	SL	159 (69%/31%)	0%/2%	27%/35%	18%/18%	36%/35%
Gonzalez, 2013 (17)	RCC	SL	99 (72%/28%)	3%/4%	49%/54%	3%/11%	45%/28%
Koryllos, 2020 (18)	RCC	SL	501 (73%/27%)	2%/5%	41%/47%	3%/8%	47%/34%
Milman, 2009 (19)	RCC	SL, SBL	64 (67%/33%)	5%/0%	47%/43%	4.7%/0%	48%/41%
Gómez-Caro, 2012 (20)	PC	SL	79 (67%/33%)	6%/0%	30%/35%	2%/0%	76%/33%
Veronesi, 2002 (22)	PC	SL, SBL	55(51%/49%)	0%/0%	43%/37%	0%/3.7%	NR

Numbers of patients (%) in surgery group/numbers of patients (%) in induction group. BP, bronchoplasties; SA, sleeve lobectomy alone group; IT, sleeve lobectomy with induction therapy; RCC, retrospective clinical cohort; SL, sleeve lobectomy; NR, not reported; SBL, sleeve bilobectomy; PC, prospective cohort.

Table 2 Demographics and oncological details of individual studies

First author, year of publication	No. of patients	Mean age (SD or range)	Male patients	Cancers	Stages (0/1/2/3/4)	Induction therapy (C/R/X)	Induction criteria
Bagan, 2009 (13)	159	57 (±11)	67%	NSCLC	–/30%/38%/30%/3%	100%/–/–	N2, T3, T4, need for size reduction
Burfeind, 2005 (14)	73	58 (11–78)	60%	Any malignant etiology	–/33%/27%/25%/4%	21%/–/79%	N2, hilar M1, T4, mediastinal invasion
Caso, 2018 (15)	15	49 (±27)	33%	Various tumors	20%/33%/20%/20%/7%	1C, others : NR	NR
Comacchio, 2019 (16)	159	66 (36–84)	79%	NSCLC	2%/11%/73%/11%/3%	76%/2%/22%	N2
Gonzalez, 2013 (17)	99	62 (29–83)	76%	NSCLC	3%/25%/37%/35%/–	43%/–/57%	Potentially resecable T1–3N2M0
Koryllos, 2020 (18)	501	64 (NR)	70%	Lung cancer	–/4%/42%/50%/4%	30%/–/70%	N2, advanced mediastinal involvement
Milman, 2009 (19)	64	60 (±10.6)	73%	NSCLC	–/23%/27%/44%/6%	–/–/100%	NR
Gómez-Caro, 2012 (20)	79	64 (38–83)	89%	NSCLC	–/24%/53%/23%/–	–/–/100%	N2
Veronesi, 2002 (22)	55	63 (44–76)	85%	Lung cancer	NR	89%/–/11%	N2, T4, SCLC

C/R/X, chemotherapy/radiotherapy/combined chemotherapy and radiotherapy. SD, standard deviation; NR, not reported; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

presented anastomotic complications. Bagan *et al.* (13) reported 3 cases of anastomotic complications (1 BPF and 2 anastomotic stenosis) (3%) in group surgery alone and none in the induction group. Burfeind *et al.* (14) observed only 1 case of BPF after induction therapy (5.2%). Comacchio *et al.* (16) reported 5 cases of BPF (4% in induction group *vs.* 2.7% in surgery alone), 9 cases of early anastomotic stenosis (4% in induction *vs.* 6.3% in surgery alone) and 15 cases of late anastomotic stenosis (10% in induction *vs.* 9% in surgery alone). Gómez-Caro *et al.* (20)

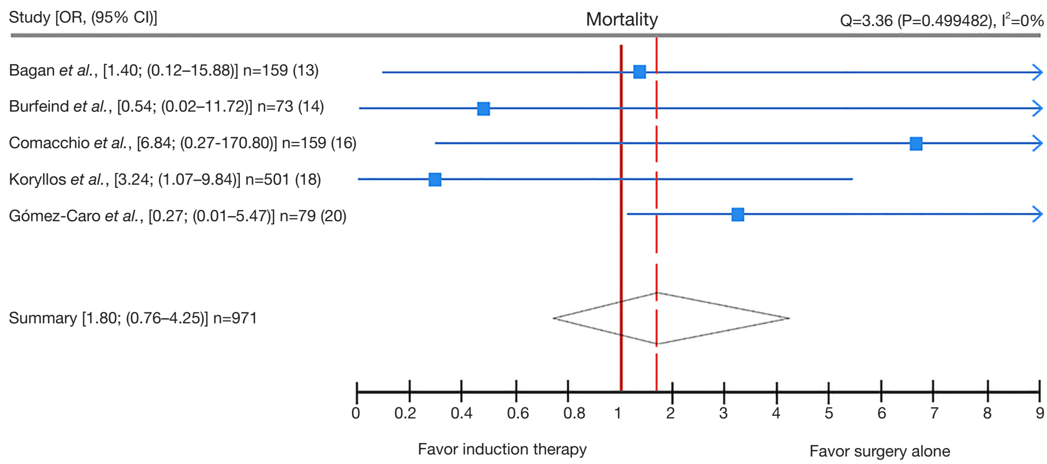

Figure 2 Forest plot showing the mortality OR after induction therapy with surgery or surgery procedure alone (13,14,16,18,20). OR, odds ratio; CI, confidence interval.

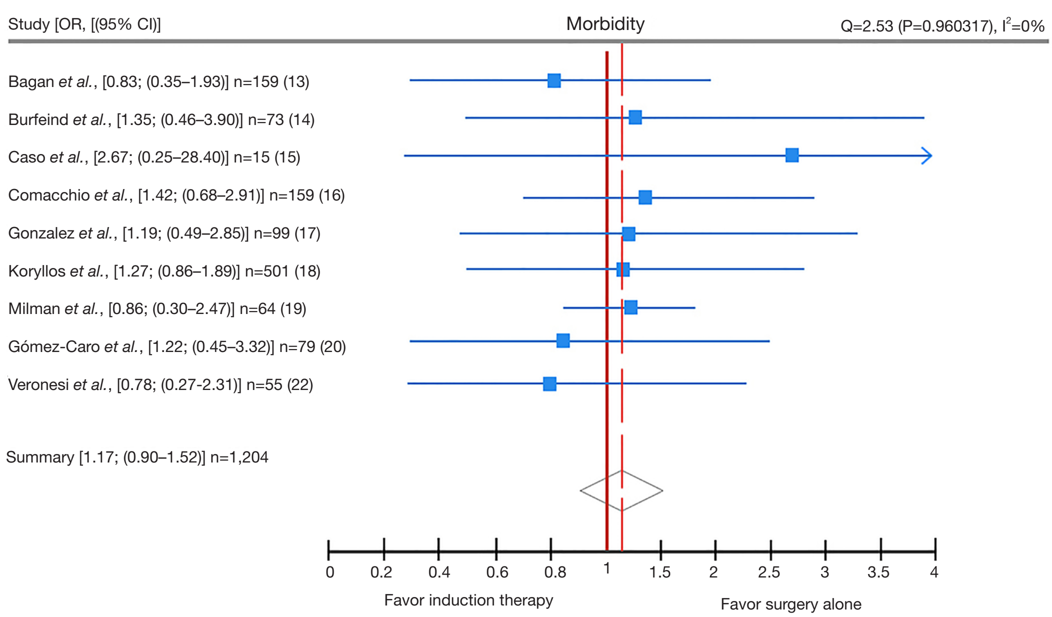

Figure 3 Forest plot showing the morbidity OR after induction therapy with surgery or surgery procedure alone (13-20,22). OR, odds ratio; CI, confidence interval.

presented only 1 case of BPF in the surgery alone group (1/53 *vs.* 0/26)). Gonzalez *et al.* (17) reported bronchial anastomosis complications occurred in 3 patients (10.8%) with neoadjuvant therapy (2 BPF and 1 stenosis) and in 2 without (2.8%) (1 BPF and 1 stenosis) (P=0.3). Koryllos *et al.* (18) observed a total of 21 anastomosis insufficiencies (8% induction *vs.* 2.7% surgery alone), described by the authors as necrosis or perforation of the bronchial wall. However, no detail over the nature of each of it was given. Milman *et al.* (19) reported 1 case of anastomotic stenosis, 1 case of broncho-pulmonary artery fistula after surgery alone (4.7%) and none in induction group. Finally, Veronesi *et al.* (22) observed 1 cases of late stenosis after induction therapy (3.7%). The estimated rate of BPF and early or late anastomotic stenosis (excluding the study of Koryllos due to missing

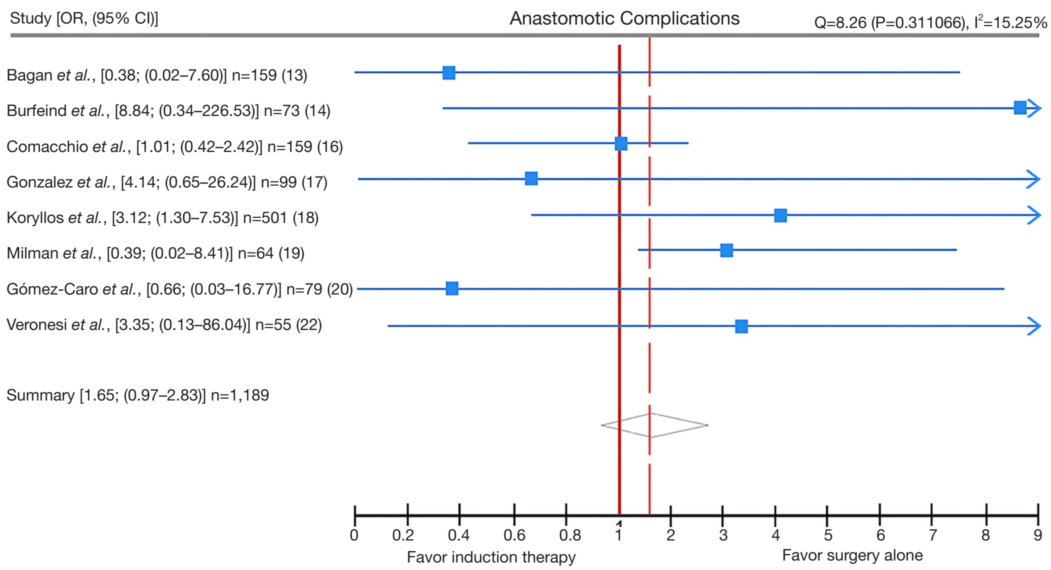

Figure 4 Forest plot showing the anastomosis complications OR after induction therapy with surgery or surgery procedure alone (13,14,16-20,22). OR, odds ratio; CI, confidence interval.

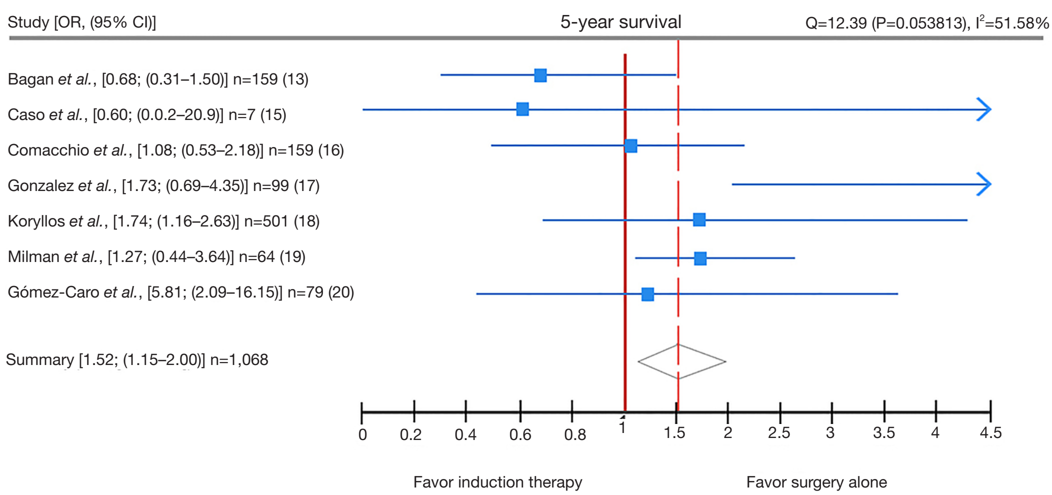

Figure 5 Forest plot showing the 5-year survival OR after induction therapy with surgery or surgery procedure alone (13,15-20). OR, odds ratio; CI, confidence interval.

informations) was 16/691 (2.3%) and 31/691 (4.5%) respectively.

Five-year survival

The 5-year survival was reported in seven studies (13,15-20) and varied from 20% to 76% in the surgery-only group and from 28% to 100% in the induction group. The pooled OR was 1.52 (95% CI: 1.15–2.00, P value =0.003) (*Figure 5*). No lack of homogeneity between studies have been observed (I^2=51.6%, P=0.053813).

The funnel plots for the mortality, anastomosis complications and 5-year survival did not display any asymmetry. However, regarding the pool for morbidity, a suspicion of small studies or publication bias could not be excluded.

Discussion

Sleeve pulmonary lobectomy is preferred over pneumonectomy for centrally located NSCLCs, provided that a complete resection can be achieved. Several studies have shown that SL presents similar survival and recurrence rates for adjusted tumor stage and is associated with lower post-operative mortality and morbidity and better quality of life compared with pneumonectomy (1-4,6). However, recurrences remain frequent in sleeve resection procedures and neo-adjuvant radio-chemotherapy may be proposed to reduce the size of the tumor and thus enhancing chances for a complete resection and decreasing distant or local relapse rates. Conversely, induction therapy has been associated with major complications if followed by pneumonectomy (21). Pre-operative chemotherapy allows treatment by lobectomy in otherwise non-resectable lesions and patients unable to tolerate a pneumonectomy (23). However, sleeve resections feasibility after induction therapy is often questioned because the procedure requires a reliable anastomosis (24-27).

Our meta-analysis pools the results of 1,204 patients who underwent pulmonary sleeve resection with (n=352) and without induction treatment (n=852) offering an analysis of the main post-operative outcomes.

After SL, reported postoperative mortality and morbidity rates range between 2–5% and 15–47%, respectively, even if SL is combined with additional surgical procedures such as pulmonary artery, superior vena cava, or chest wall resection or performed in elderly patients for whom a lung-sparing procedure is associated with lower mortality (10,14,28,29). Mortality is often comparable between patients with or without radio-chemotherapy. In our review, all of the studies showed a comparable mortality ranging from 0% to 5.5% for the induction group and 0% to 4.7% in the surgery alone group. With an OR of 1.80, a 95% CI from 0.76 to 4.25 and corresponding P value of 0.19, we found that it was not significantly different between these two groups. In our study, mortality represents respectively 3.3% (9/272) of patients in the induction group, and 1.86% (13/699) of patients in surgery group. In either case, these rates are acceptable and comparable to the ones found in the literature.

Occurrences of general morbidities after the intervention also seem comparable between induction patients and surgery alone patients. No significant difference occurred in individual studies included in this meta-analysis. Morbidity rate ranged from 21.4% to 54% in induction group and 27% to 49% in surgery alone group. The pooled results evidenced an OR of 1.17, a 95% CI between 0.90 and 1.52 and a P value of 0.237. Reported SL or bilobectomy complication rates were 32.9 and 45.8%, respectively (30). Pooled rates from our meta-analysis are evaluated to 36.8% in the surgery group (314/852) and 40.6% (143/352) in the induction and surgery group. Again, morbidity rates were not significantly increased by induction therapy. However, induction treatment, especially radio-chemotherapy, has been the subject of controversy if applied in the context of SL. Induction-related injuries of the bronchial microvascularization may potentially predispose to airway complications, such as bronchopleural or bronchovascular fistula and bronchial stenosis. Bronchovascular fistulas may occur occasionally, but BPFs are more common, with a reported incidence of 1% to 5% after SL (1,7,10,28,29). The reported incidence of stenosis at the site of bronchial anastomosis ranges between 1% and 4% (10,28,29,31). These complications may result from inappropriate surgical procedures, such as mechanical tension at the level of the anastomosis or bronchial devascularization during dissection, or from nutritional deficiencies or advanced tumor stage (32). Induction therapy may additionally compromise bronchial healing as a result of radio-chemotherapy-induced microvascular injuries and desmoplastic tissue reactions.

Anastomotic complications rates derived from our meta-analysis ranged between 0% and 18% in induction group as in surgery alone group. We observed almost statistical differences (P=0.06) between the two groups with increased anastomotic complication rate in the induction therapy group. Risk factors inducing worse outcomes at the site of the anastomosis have been described by several studies. The main one after induction therapy is the impact of radiotherapy alone on bronchial tissue. As shown by Yamamoto *et al.* (9), radiation seems to negatively impact healing capacity of the tissue. Interestingly, these authors observed that whereas chemotherapy seems to have a little effect on blood flow, radiations significantly worsen healing potential of the surrounding tissue. In our meta-analysis, Comacchio *et al.* (16) and Koryllos *et al.* (18) supported the view that radiotherapy bears a potential harmful effect in the context of sleeve resection. Comacchio *et al.* pointed out mediastinal radiotherapy as a risk factor for bronchial complications. They observed a statistically significant difference in terms of anastomotic complication rate between patients undergoing induction chemotherapy and patients undergoing pre-operative chemo-radiotherapy or radiotherapy alone (10.8% *vs.* 41.6%, respectively, P=0.01), indicating that the radiotherapeutic component might be one of the causes behind this difference. Similar findings were reported by Koryllos who reported equivalent rates of anastomotic complications after no pretreatment and chemotherapy (2.7% and 2.4%, respectively), but increased rates of anastomotic complications after radiotherapy (10.4%) (P=0.002). Rea *et al.* (10) also found an increased incidence of BPFs after radiotherapy. More recently, Rodriguez *et al.* (33) investigated the impact of chemoradiotherapy compared to surgery or surgery with neoadjuvant chemotherapy in sleeve patients. They observed that neoadjuvant chemoradiations increased pulmonary airways complications. In line with these observations, some authors proposed to reconsider the pertinence of pre-operative radiotherapy since it does not result in survival differences when compared to post-operative radiotherapy alone (34) and it seems to increase the rate of anastomotic complications. Conversely, some studies speak in favor of induction therapy: pre-operative chemo-radiotherapy allows to avoid a positive resection margin, which has been identified as a predictive factor of anastomotic complications (10,35). Induction radiotherapy should be cautiously discussed when considering a SL due to the increased rate of anastomotic complications.

Anastomotic complications have often been reported to be manageable with bronchoscopy and successfully treated. The rate of BPF and early or late anastomotic stenosis was 2.3% and 4.5%, respectively. We observed a total of 12 re-operations (14-18,20), with four cases of BPFs, one case of persistent air leak, one case of anastomotic stenosis and one case of broncho-arterial fistula. The remaining re-operations were performed by Koryllos *et al.* (18) with no detail over the indication. Gonzalez *et al.* (17) and Koryllos *et al.* (18) performed a sleeve bilobectomy (SBL) and a middle lobe and intermediate bronchus resection respectively, with new anastomosis in order to avoid a pneumonectomy. Again, the main management of anastomotic complications remained bronchoscopy with a total of 34 bronchoscopies and led to the resolution of the insufficiency, excepted in one case that needed a completion pneumonectomy (16). In addition, 16 complications required a stenting procedure. It is noteworthy that Koryllos *et al.* did not perform bronchoscopy, but successfully managed 16 anastomosis insufficiencies (of 21) by intensifying antibiotics (18). Among all complications, two were fatal. The patient who presented a broncho-arterial fistula reported by Milman *et al.* (19) died after the completion by pneumonectomy, while a fatal BPF was reported by Comacchio *et al.* (16). Each one occurred early in the post-operative care.

The other point of frequent discussion is the need to cover the bronchial anastomosis. Several techniques have been developed for this purpose, including the intercostal pedicle flap, the pleural and pericardial flaps, the pericardial fat pad flap, the pedicled pericardiophrenic graft, and the omentum. This point was not analyzed in our meta-analysis. However, most authors recommend routine coverage of bronchial anastomosis of post-inductive sleeve resections. On the other hand, Storelli *et al.* (31) have reported on 25 patients undergoing SL after induction therapy without bronchial complications, despite the fact that no anastomosis wrapping had been performed.

Our review reported a significant difference of survival between surgery and induction groups. With a pooled OR of 1.52, surgery alone seems to favor the 5-year survival rate as compared to induction followed by surgery (P value =0.003). Indeed, when induction is associated with sleeve lobectomies, studies show similar survival (19), or even worse survival in the induction group compared to surgery alone group (20). Moreover, reduced function of remaining lungs has been observed in context of induction therapy because of its chronic effects. This impacts long-term outcomes (36), even when one considers factors enhancing long-term survival linked to induction therapy, such as a negative resection margin (37) or mediastinal downstaging to N0 (16,37). In addition, decreased 5-year survival can also be explained by the imbalance in tumor staging between induction group or surgery alone group (18), since the induction group will pool patients with more advanced disease, thus poorer prognosis.

There are several limitations to our meta-analysis. First, the design of the included studies might have induced a selection bias. Also, the studies did not display the rate of avoided pneumectomies notably avoided cases by benefiting from induction therapy. In addition, difference in outcomes between upfront pneumonectomy and SL with induction therapy (IT) was not assessed. Then, the heterogeneity of information reported in the studies did not allow us to constitute a solid pool of patients undergoing radiotherapy alone and fully investigate its specific effects. Thus, our conclusions on anastomosis complications should be interpreted with caution, due to the limited number of patients included. In the same spirit, no distinction was made between the different modalities of induction therapy. Survival analysis should be cautiously interpreted due to the absence of data regarding the individual oncological status such as tumor stage, including tumor size and lymph nodal metastasis, involvement of hilar structures. Finally, and in addition to the compulsory limitations of an aggregated meta-analysis, we could only pool a small number of studies with only two reporting data at the patient level, which limited the inference that could be made from our statistical analysis. Consequently, the results of this meta-analysis did not provide the level of risk for an individual patient, and the aim of this study was restricted to observation of outcomes after exposition.

In conclusion, SL for NSCLC can be safely performed after induction chemotherapy and/or radiochemotherapy, with similar mortality and morbidity but with an increased risk of airway complications especially after induction radiotherapy and poorer survival prognosis at 5 years.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/jtd-21-939). MG serves as an unpaid editorial board member of *Journal of Thoracic Disease* from Feb 2021 to Jan 2023. JYP reports grants from Chercher & Trouver, Oncoswiss and Novartis. The other 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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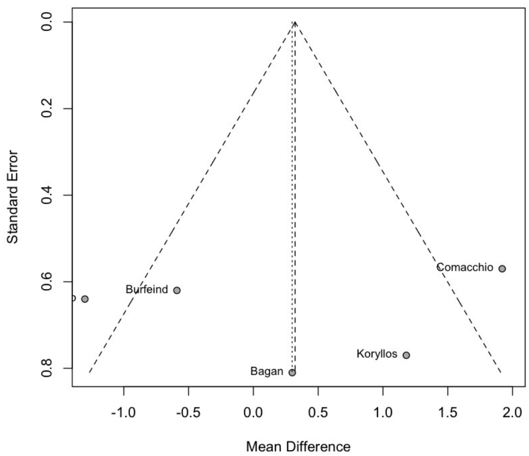

Figure S1 Funnel plots for the mortality outcome. Individual circles indicate studies included in the aggregated pool. The position of these circles along the horizontal axis represents the effect-estimate in log of the OR. This is plotted against the inverse of the SE of the log-OR which is an estimate of study precision. Asymmetry is suggestive of small study or publication bias causing overestimation of the effect size in a meta-analysis. OR, odds ratio; SE, standard error.

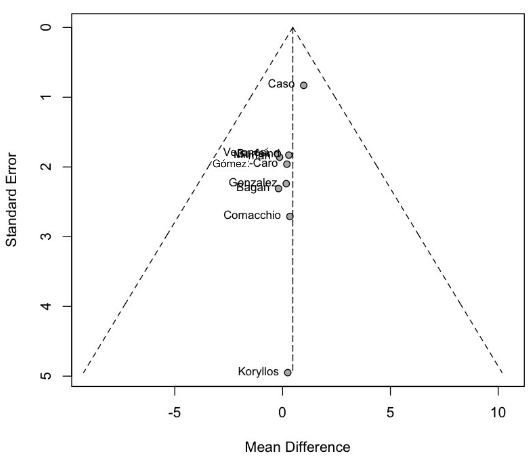

Figure S2 Funnel plots for the morbidity outcome. Individual circles indicate studies included in the aggregated pool. The position of these circles along the horizontal axis represents the effect-estimate in log of the OR. This is plotted against the inverse of the SE of the log-OR which is an estimate of study precision. Asymmetry is suggestive of small study or publication bias causing overestimation of the effect size in a meta-analysis. OR, odds ratio; SE, standard error.

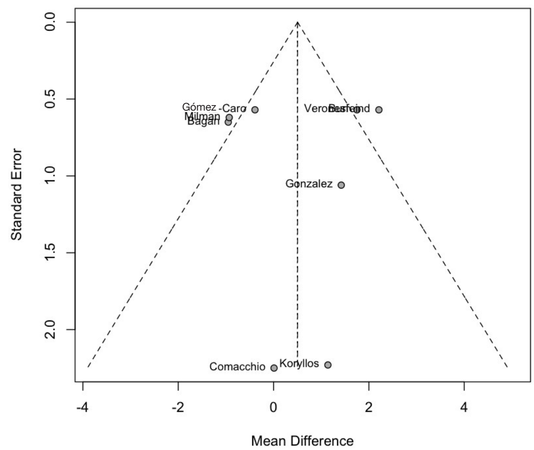

Figure S3 Funnel plots for the anastomosis complications outcome. Individual circles indicate studies included in the aggregated pool. The position of these circles along the horizontal axis represents the effect-estimate in log of the OR. This is plotted against the inverse of the SE of the log-OR which is an estimate of study precision. Asymmetry is suggestive of small study or publication bias causing overestimation of the effect size in a meta-analysis. OR, odds ratio; SE, standard error.

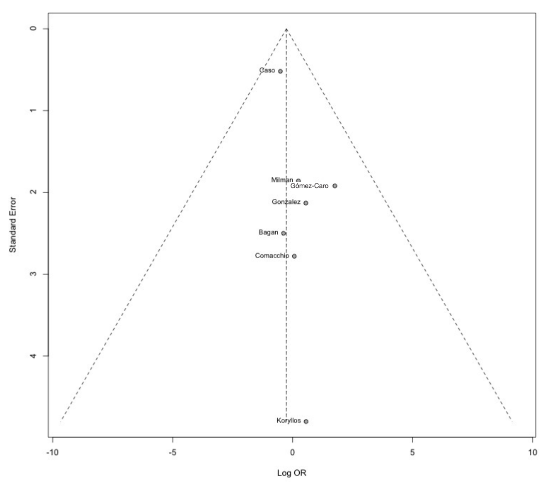

Figure S4 Funnel plots for the 5-year survival outcome. Individual circles indicate studies included in the aggregated pool. The position of these circles along the horizontal axis represents the effect-estimate in log of the OR. This is plotted against the inverse of the SE of the log-OR which is an estimate of study precision. Asymmetry is suggestive of small study or publication bias causing overestimation of the effect size in a meta-analysis. OR, odds ratio; SE, standard error.

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Appendix 1

Search strategy: for EMBASE (all field)

#1. lobectomy
#2. 'sleeve lobectomy'
#3. 'sleeve resection'
#4. 'bronchial resection'
#5. 'bronchial anastomosis'
#6. 'bronchial suture'
#7. 'pulmonary suture'
#8. 'pulmonary anastomosis'
#9. 'lung anastomosis'
#10. 'lung suture'
#11. 'lung resection'
#12. bronchoplasty
#13. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#14. 'pre-operative treatment'
#15. 'induction treatment'
#16. 'neoadjuvant treatment'
#17. 'pre-surgery therapy'
#18. 'pre-operative therapy'
#19. 'induction therapy'
#20. 'neoadjuvant therapy'
#21 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
#22. #13 AND #21
#23. #22 AND (2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py)

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