Original Article

Adjuvant chemotherapy for completely resected IIA–IIIA non-small cell lung cancer: compliance to guidelines, safety and efficacy in real-life practice

Anne-Laure Désage[1], Claire Tissot[2], Sophie Bayle-Bleuez[1], Thierry Muron[2,3], Nadine Deygas[4], Valérie Grangeon-Vincent[5], Brigitte Monange[6], Fatah Torche[3], Paul Vercherin[7], David Kaczmarek[8], Olivier Tiffet[9], Fabien Forest[10], Jean-Michel Vergnon[1], Wafa Bouleftour[3]^, Pierre Fournel[3]

[1]Department of Pulmonology and Thoracic Oncology, North Hospital, University Hospital of Saint-Etienne, Saint-Etienne, France; [2]Oncology Department, Private Loire Hospital (HPL), Saint-Etienne, France; [3]Department of Medical Oncology, North Hospital, University Hospital of Saint-Etienne, Saint-Etienne, France; [4]Department of Pulmonology, Gier Hospital, Saint-Chamond, France; [5]Department of Pulmonology, Roanne Hospital, Roanne, France; [6]Department of Medical Oncology, Emile Roux Hospital, Le Puy-en-Velay, France; [7]Public Health and Medical Informatics Department, North Hospital, University Hospital of Saint-Etienne, Saint-Etienne, France; [8]Thoracic and Digestive Surgery Department, Private Loire Hospital (HPL), Saint-Etienne, France; [9]Department of Thoracic Surgery, North Hospital, University Hospital of Saint-Etienne, Saint-Etienne, France; [10]Pathology Department, North Hospital, University Hospital of Saint-Etienne, Saint-Etienne, France

Contributions: (I) Conception and design: AL Désage, C Tissot, W Bouleftour, P Fournel; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: AL Désage, F Torche, W Bouleftour; (V) Data analysis and interpretation: AL Désage, C Tissot, P Fournel, P Vercherin, W Bouleftour; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Wafa Bouleftour. Department of Medical Oncology, Cancerology and Hematology Institute, University Hospital of Saint-Etienne, 42055 Saint-Etienne, France. Email: wafa.esquis@chu-st-etienne.fr.

Background: Since randomised clinical trials demonstrated a survival benefit of adjuvant chemotherapy (AC) following curative-intent lung surgery, AC has been implemented as a standard therapeutic strategy for patients with a completely resected IIA–IIIA non-small cell lung cancer (NSCLC). Regarding the moderate benefit of AC and the lack of literature on AC use in real-life practice, we aimed to evaluate compliance to guidelines, AC safety and efficacy in a less selected population.

Methods: Between January 2009 and December 2014, we retrospectively analysed 210 patients with theoretical indication of AC following curative-intent lung surgery for a completely resected IIA–IIIA NSCLC. The primary objective of this retrospective study was to evaluate compliance to AC guidelines. Secondary objectives included safety and efficacy of AC in real-life practice.

Results: Among 210 patients with a theoretical indication of AC, chemotherapy administration was validated in multidisciplinary team (MDT) for 62.4% of them and 117 patients (55.7%) finally received AC. Patient's clinical conditions were the main reasons advanced in MDT for no respect to AC guidelines. Most of the patients received cisplatin-vinorelbine (86.3%) and AC was initiated within 8 weeks following lung surgery for 73.5% of patients. One-half of patients who received AC experienced side effects leading to either dose-intensity modification or treatment interruption. In real-life practice, AC was found to provide a survival benefit over surgery alone. Factors related to daily-life practice such as delayed AC initiation or incomplete AC planned dose received were not associated with an inferior survival.

Conclusions: Although AC use might differ from guidelines in real-life practice, this retrospective study highlights that AC can be used safely and remains efficient among a less selected population. In the context of immunotherapy and targeted therapies development in peri-operative treatment strategies, the place of AC has to be precised in the future.

Keywords: Adjuvant chemotherapy (AC); non-small cell lung cancer (NSCLC); real-life practice

^ ORCID: 0000-0002-8485-9386.

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Introduction

According to 2020 Global Cancer Observatory, lung cancer represents 11.4% of new cancer cases around the world (1). Lung cancer is also considered as the leading cause of cancer death, as it is involved in 18% of cancer deaths (1). In particular, approximately one-half of non-small cell lung cancer (NSCLC) patients are diagnosed at a metastatic stage disease while locally (i.e., stage I and II) and advanced (i.e., stage III) NSCLC represent respectively 25.2% and 18.7% of NSCLC patients at diagnosis (2).

For the approximately one third of patients who present early-stage disease, complete lung resection provides the best chance of cure. Nonetheless, patients still have a substantial risk of recurrence and death (3). Therefore, adjuvant chemotherapy (AC) has been a rational approach developed to decrease the risk of recurrence and improve patient outcomes by eliminating residual disease (4). AC has been implemented as part of the multimodal treatment strategy since three main randomised clinical trials on AC for completely resected NSCLC (i.e., IALT, ANITA and JBR.10) demonstrated a significant survival benefit of AC from 4.1% to 15% over surgery alone (5-7). These results were confirmed in large meta-analysis as AC was demonstrated to provide a significant increase of disease-free survival (DFS) [hazard ratio (HR) =0.8; 95% confidence interval (CI): 0.78–0.9; P<0.0001] (8) and an absolute improvement in overall survival (OS) of 4% (9) and 5.4% (8) at 5 years. Consequently, since 2004, adjuvant cisplatin-based chemotherapy is recommended following curative-intent lung surgery for IIA–IIIA completely resected NSCLC (10-12). According to guidelines, cisplatin-vinorelbine regimen must be preferred and has to be initiated within 4 to 8 weeks following lung surgery. Indeed, the vinorelbine sub-group analysis of LACE meta-analysis which included 1,888 patients, showed a 8.9% survival improvement at 5 years with cisplatin-vinorelbine compared to observation (HR =0.8; 95% CI: 0.70–0.91; P<0.001) (13). The survival benefit of cisplatin-vinorelbine was also significantly higher (P=0.04) compared to other studies randomising patients with other chemotherapy regimen or observation (13). Notably, the survival benefit of cisplatin-vinorelbine regimen significantly increased with stage disease (13).

However, given the potential toxicity of cisplatin-based chemotherapy, the benefit of AC for completely resected IIA–IIIA NSCLC is considered as limited. Moreover, good functional status, low comorbidities and the limited number of elderly patients enrolled in these large randomised clinical trials as well as the lack of predictive biomarkers, might counterbalanced these results in a less fit and more heterogenous population. Herein, we aim to evaluate the compliance to AC guidelines as well as AC efficacy and toxicity profile in real-life practice. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-345/rc).

Methods

Study population and data sources

We retrospectively reviewed all patients presented in OncoLoire multidisciplinary team (MDT) who underwent lung surgery between January 2009 and December 2014. The selection steps are summarized in *Figure 1*. Hospital information system and medical records were used to collect patient data information. Based on AC guidelines during the study period (14), patients were included if they have a theoretical indication of AC following curative-intent lung surgery for a completely resected IIA–IIIA NSCLC according to the 7th tumour, node, metastasis (TNM) classification (15,16). Patients were successively included from source population if they completed inclusion criteria in order to address selection bias.

Patients for whose medical records were not available or who underwent thoracic surgery for either benign lung lesion, thymoma or solitary pleural fibroma were not included in the selection process. Patients were excluded in case of other histologic types, non-anatomical sub-lobar resection or incomplete postoperative resection (i.e., R1). Patients were also excluded if they received preoperative treatment or diagnosed with IA, IB, IIIB postoperative stage disease according to the 7th TNM classification.

Study variables

Demographic and clinical patient characteristics were collected.

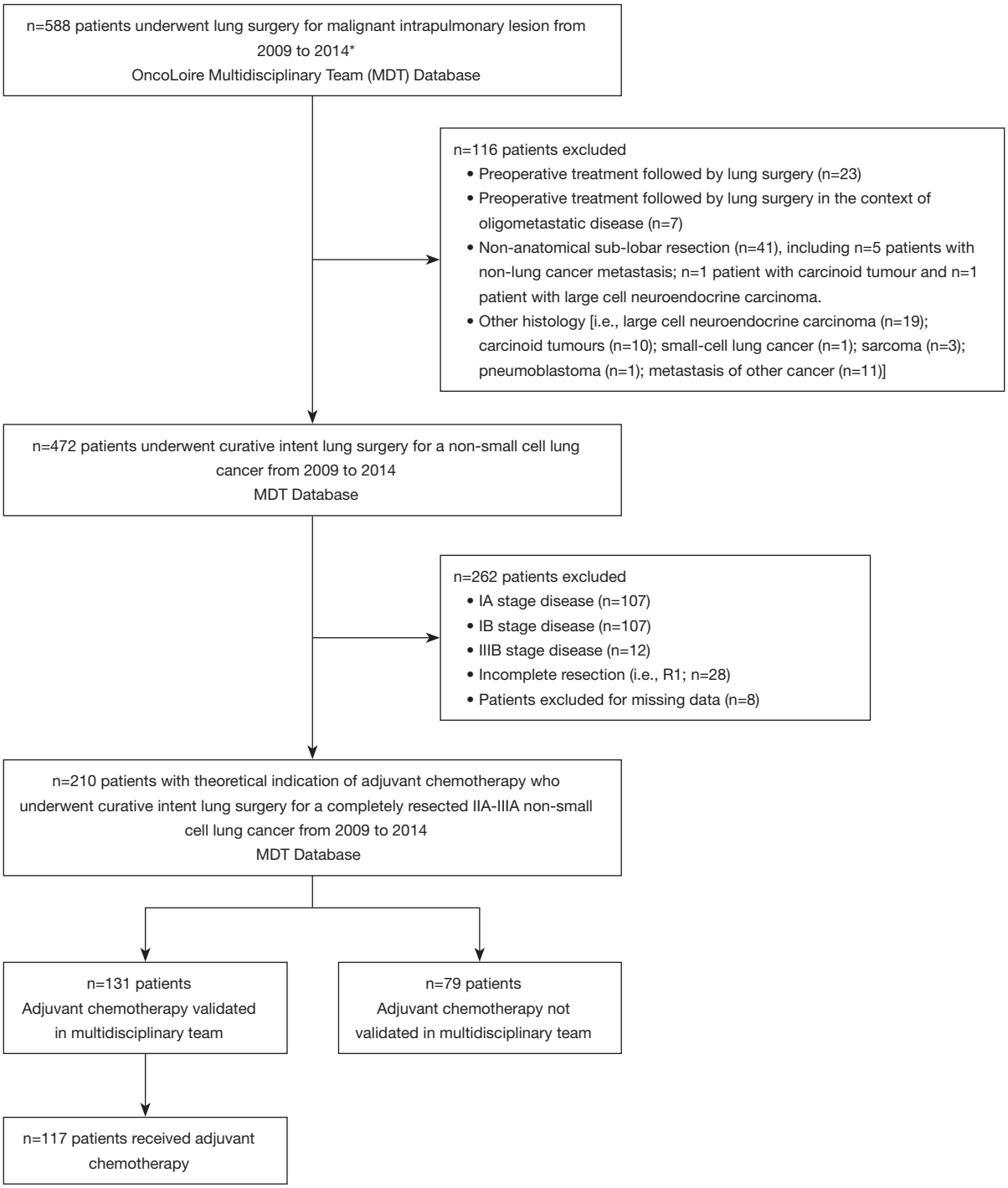

Figure 1 Flow chart presenting the selection process of the cohort study. *, patients whose medical record was not available were not included in the selection process. Patients who underwent thoracic surgery for either benign lung lesion, thymoma resection or solitary pleural fibroma were also excluded from the selection process. MDT, multidisciplinary team.

Histopathologic type was determined as defined by the 2004 World Health Organisation classification, Pathology and genetics of tumours of the lung, pleura, thymus and heart (17). Postoperative stage disease was defined according to the 7th TNM classification (15,16). The quality of lung resection was defined according to French guidelines of Société Française de Chirurgie Thoracique et Cardio-Vasculaire (18). All study variables were collected from hospital information system and medical records using standardized questionnaires to limit information bias.

AC compliance

The primary objective was to evaluate compliance to AC guidelines in real-life practice. Compliance was determined as patient management in accordance with AC guidelines during the study period (14) following curative-intent lung surgery for a completely resected IIA–IIIA NSCLC.

Type of AC regimen, delay of AC initiation following lung surgery and the number of AC cycles received were collected from MDT and medical records.

Efficacy and safety profile of AC

The secondary objectives included efficacy and tolerance of AC in real-life practice.

AC tolerance variables included dose reduction or omission, AC treatment discontinuation and AC adverse events. The number of complete AC cycles was defined as the number of AC cycles received without dose reduction or omission. AC toxicities were compared according to AC regimen prescribed and age groups (i.e., <70 or ≥70 years old).

To determine AC efficacy, data regarding DFS and OS were collected continuously within 5 years following lung surgery. For each patient, the cut-off date was defined as 5 years following the date of curative-intent lung surgery. DFS was defined as the time elapsed between curative-intent lung surgery to locoregional or distant recurrences. Patients without tumour relapse at cut-off date were censored at the date of last contact. OS was defined as the time elapsed between curative-intent lung surgery to death from any cause or to last follow-up at the time of data cut-off. Patients who were still alive at the time of cut-off date or lost to follow-up were censored.

Statistical analyses

Statistical analyses were carried out using the SAS package 9.4.

Patients' characteristics were described using median and (25th–75th) interquartile range for quantitative variables except for loss of weight. Categorical variables were described by absolute frequencies and percentages.

For categorical variables, bivariate analysis was conducted using the Chi-squared test. In case of low frequencies where Chi-squared test could not be used, a Fischer exact test was performed. The Student *t*-test was used for continuous variables. All statistical tests were two-sided; a P value less than 0.05 was considered as statistically significant.

A logistic regression model with a stepwise selection was performed in order to identify the independent predictive factors associated with AC compliance, AC use according to age and delay of AC initiation. Missing variables were coded as unknown for multivariable modelling and were excluded from the analysis.

DFS and OS were determined using the Kaplan-Meier method. DFS and OS of patients with and without AC following curative-intent lung surgery were compared using the log-rank test. Univariate and multivariate Cox proportional hazard models were performed to identify potential prognostic factors on OS among the whole cohort. Exploratory analyses using the Kaplan-Meier method were conducted to evaluate the impact of AC real-life practice on OS.

Ethical consideration

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Collection and analysis of medical data were approved by the French data protection authority (CNIL) and the Research Ethics Board of the University Hospital of Saint-Etienne (IRBN992019/CHUSTE). All alive patients were sent an informed consent approved by the Research Ethics Board of the University Hospital of Saint-Etienne and subsequently approved the use of their medical data.

Results

Patient characteristics

Among 472 patients who underwent curative-intent

Table 1 Baseline characteristics of the patients

Characteristics	Values
Age (years)	
Median (IQR)	65 (58–73)
Sex, n (%)	
Male	175 (83.3)
Female	35 (16.7)
ECOG performance status*, n (%)	
0–1	188 (91.3)
≥2	18 (8.7)
Smoking status**, n (%)	
Current smoker	81 (38.8)
Former smoker	113 (54.0)
Non smoker	15 (7.2)
Professional exposure, n (%)	28 (13.3)
Charlson index, n (%)	
0–1	22 (10.5)
≥2	188 (89.5)
Cardiovascular comorbidities, n (%)	123 (58.6)
Pulmonary comorbidities, n (%)	140 (66.7)
Previous cancer, n (%)	61 (29.0)
Tobacco-related cancer†	39 (63.9)
Non-tobacco-related cancer‡	22 (36.1)
Medical cancer center, n (%)	
University hospital and cancer center	130 (61.9)
General hospital	46 (21.9)
Private hospital	34 (16.2)

IIA–IIIA NSCLC patients with theoretical indication of AC (n=210). *, four missing data; **, one missing data; †, tobacco-related cancer included: lung cancer, oral cavity and pharynx-larynx cancer, bladder cancer, kidney cancer, oesophagus cancer, stomach cancer, colon and rectum cancer, pancreas cancer and cervix cancer; ‡, non-tobacco related cancer included: prostate cancer, breast cancer, carcinoid tumour of the appendix, basal cell carcinoma and hematologic malignancies. IQR, interquartile range (25^{th}–75^{th}); ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; AC, adjuvant chemotherapy.

lung surgery for a NSCLC between January 2009 and December 2014, 210 patients had a theoretical indication of AC following lung surgery and were included in this retrospective study (*Figure 1*). The median follow-up of the whole cohort was 3.85 years. Patient baseline characteristics are shown in *Table 1*. The median age was 65 years (58–73 years); 35.2% patients were 70 years or older. Most of patients were men (83.3%) and had a tobacco history (92.8%). Notably, 18.6% of patients had a previous tobacco-related cancer and either pulmonary or cardiovascular comorbidities were reported in respectively 66.7% and 58.6% cases.

The characteristics of curative-intent lung surgery are reported in *Table 2*. Among the whole cohort, 70.5% patients underwent a lobectomy whereas 25.2% had a pneumonectomy. Histologic types were predominantly adenocarcinoma or squamous-cell carcinoma. A postoperative lymph node invasion was confirmed for 65.7% of patients; among them 31.2% had a capsular effraction. Likewise, most of patients (42.4%) were diagnosed with IIIA postoperative stage disease. Among all patients, the median length of stay in hospital after curative-intent lung surgery was 12 days (10–16.5 days) and 41.1% experienced postoperative complications. The most frequent postoperative complications reported were as follows: infectious (46.5%), cardiac (22.1%) and atelectasis (14%). Besides postoperative complications, an altered recovery following lung surgery was reported for 13.8% of patients. After lung surgery, most of patients were referred to rehabilitation care unit (58.2%).

Compliance to AC guidelines in real-life practice

Despite theoretical indication, AC was validated in MDT for only 131 patients (*Figure 1*). Thereby, the compliance to AC guidelines was 62.4% in this cohort. Notably, age (27.8%), age and comorbidities (27.8%) and altered recovery or postoperative complications (24.1%) were the main reasons for the non-compliance to AC guidelines in MDT (*Figure 2A*).

Predictive factors for the no respect to AC guidelines in MDT were analysed (*Table 3*). In multivariate analysis, age [i.e., ≥70 years old; odd ratio (OR) =0.045; 95% CI: 0.016–0.12; P<0.0001] and altered recovery after lung surgery (OR

Table 2 Characteristics of curative-intent lung surgery

Characteristics	Values
Type of surgery, n (%)	
Lobectomy	148 (70.5)
Pneumonectomy	53 (25.2)
Bilobectomy	7 (3.3)
Segmentectomy	2 (1.0)
Histology[#], n (%)	
Adenocarcinoma	95 (45.2)
Squamous-cell carcinoma	91 (43.3)
Mixed	4 (2.0)
Other histologic subtypes	20 (9.5)
Postoperative stage[¶], n (%)	
IIA	74 (35.2)
IIB	47 (22.4)
IIIA	89 (42.4)
Lymph nodal status[¶], n (%)	
N0	72 (34.3)
N1	67 (31.9)
N2	71 (33.8)
Capsular effraction	43 (31.2)
Tumour size (cm)	
Median (IQR)	5.0 (2.8–6.4)
Number of pulmonary lesions, n (%)	
1	187 (89.0)
≥2	23 (11.0)
Length of stay in hospital after lung surgery* (days)	
Median (IQR)	12 (10–16.5)
Post-operative complications*, n (%)	86 (41.1)
Altered recovery after lung surgery (PS ≥2), n (%)	29 (13.8)
Referral to rehabilitation care unit after lung surgery**, n (%)	121 (58.2)

IIA–IIIA NSCLC patients with theoretical indication of AC (n=210). [#], according to World Health Organisation classification, Pathology and genetics of tumours of the lung, pleura, thymus and heart, 2004. Mixed indicated the coexistence of one lesion of adenocarcinoma and one lesion of squamous-cell carcinoma. Other histologic subtypes included adenosquamous carcinoma, large cell carcinoma and sarcomatoid carcinoma; [¶], according to 7th TNM classification; *, one missing data; **, two missing data. IQR, interquartile range (25th–75th); PS, performance status; NSCLC, non-small cell lung cancer; AC, adjuvant chemotherapy.

=0.08; 95% CI: 0.02–0.25; P<0.0001) were significantly associated with a less likely to receive AC based on MDT decision. On the contrary, lymph node invasion remained an independent predictive factor associated with a higher probability to receive AC based on MDT decision (OR =2.64; 95% CI: 1.21–5.76; P=0.0151).

Among 131 patients for whose AC was validated in MDT, 117 patients had finally received AC (55.7%). Indeed, 3 patients refused AC while others did not receive AC because of tumour progression (n=5), readmission within thoracic unit surgery for collection drainage (n=1), patient lost to follow-up (n=1) and death (n=4). As a result, patient death attributed to curative-intent lung surgery in our study is estimated at 1.9%. Cisplatin-vinorelbine was the most frequently regimen prescribed (86.3%) (*Figure 2B*) and median delay of AC initiation was 49 days (43–57 days). AC was initiated within 8 weeks following lung surgery for 73.5% of patients (*Figure 2C*). The median number of AC cycles received was 4 for both cisplatin-vinorelbine and carboplatin-paclitaxel regimen (*Figure 2D*) while the median number of AC cycles without dose reduction or omission was 3 [1–4] and 4 [3–4] for cisplatin-vinorelbine and carboplatin-paclitaxel regimen respectively (*Figure 2E*).

AC use in real-life practice

As previously underlined, cisplatin-vinorelbine (i.e., cisplatin 80 mg/m^2 day 1 and vinorelbine 30 mg/m^2 day 1 and 8, every 3 weeks) was the most frequent AC regimen prescribed (86.3%). Other initial AC regimens prescribed were as follows: carboplatin-paclitaxel (12.8%) and carboplatin-pemetrexed (0.9%). Among 74 patients aged 70 years or older included in this study, 21.6% finally received AC including cisplatin-vinorelbine (56.3%), carboplatin-paclitaxel (37.5%) and carboplatin-pemetrexed (6.2%) as initial regimen prescribed. Although elderly patients (i.e., ≥70 years old) received significantly less AC (OR =16.9; 95% CI: 7.6–37.8; P<0.0001), no significant difference was observed regarding AC regimen prescribed between younger and elderly patients (*Table 4*). Among patients who received cisplatin-vinorelbine or carboplatin-paclitaxel as initial AC regimen, 88.8% of them achieved at least 3 AC cycles or more independently of dose reduction or omission. Notably, the total number of AC cycles completed was not significantly different between younger and elderly patients (*Table 4*).

AC initiation exceeded 8 weeks for 31 patients (26.5%). Predictive factors associated with a delayed AC

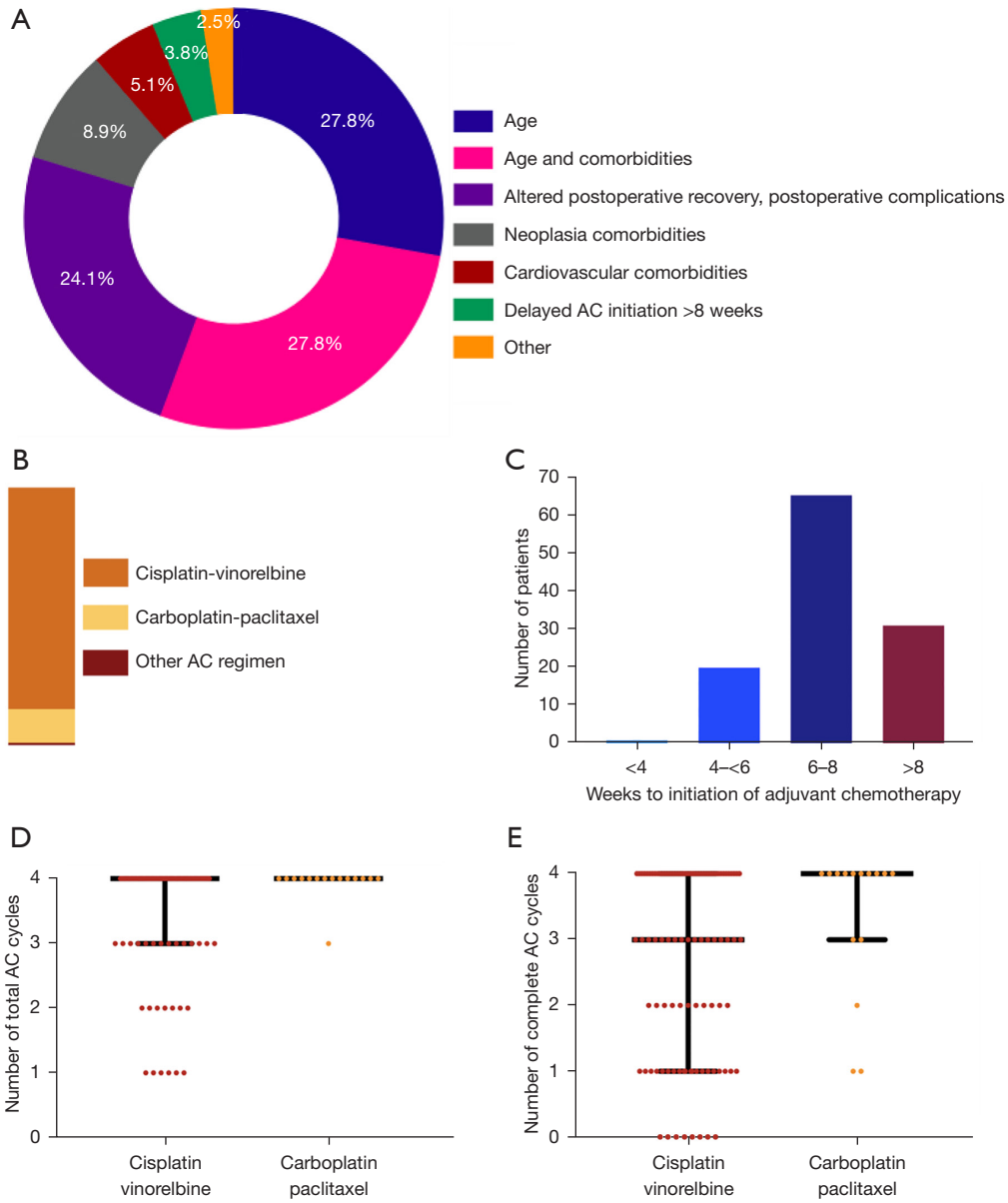

Figure 2 Compliance to AC guidelines. (A) Main reasons for no AC validation in MDT. (B) AC regimen prescribed. (C) Delay of initiation of AC. (D) Total number of AC cycles received. Median and interquartile range (25^{th}–75^{th}) are represented by the black line. Dots represent patients who received AC. Patients for whose cisplatin-vinorelbine was switched for other chemotherapy regimen (n=3) were not included in this analysis. (E) Number of AC cycles received without dose reduction or omission. Median and interquartile range (25^{th}–75^{th}) are represented by the black line. Dots represent patients who received AC. Patients for whose cisplatin-vinorelbine was switched for other chemotherapy regimen (n=3) were not included in this analysis. AC, adjuvant chemotherapy; MDT, multidisciplinary team.

Table 3 Predictive factors affecting compliance to AC guidelines in MDT

Variables	Univariate analysis			Multivariate analysis		
	AC group (n=131)	No AC group (n=79)	P	OR	95% CI	P
Age (years), n (%)			<0.0001			
<60	56 (42.7)	8 (10.1)		1		
60–69	55 (42.0)	17 (21.5)		0.46	(0.17–1.28)	NS
≥70	20 (15.3)	54 (68.4)		0.045	(0.016–0.12)	<0.0001
Sex, n (%)			NS	–	–	–
Male	107 (81.7)	68 (86.1)				
Female	24 (18.3)	11 (13.9)				
Charlson index, n (%)			0.0007	–	–	–
0–1	21 (16.0)	1 (1.3)				
≥2	110 (84.0)	78 (98.7)				
Previous cancer, n (%)	34 (26.0)	27 (34.2)	NS	–	–	–
Cardiovascular comorbidities, n (%)	67 (51.1)	56 (70.9)	0.0049	–	–	–
Type of surgery, n (%)			NS	–	–	–
Lobectomy or other	95 (72.5)	62 (78.5)				
Pneumonectomy	36 (27.5)	17 (21.5)				
Histologic sub type, n (%)			NS	–	–	–
Adenocarcinoma	60 (45.8)	35 (44.3)				
Squamous-cell carcinoma	54 (41.2)	37 (46.8)				
Other	17 (13.0)	7 (8.9)				
Postoperative stage, n (%)			NS	–	–	–
IIA–IIB	70 (53.4)	51 (64.6)				
IIIA	61 (46.6)	28 (35.4)				
Tumour size (≥5 cm), n (%)	62 (47.3)	45 (56.9)	NS	–	–	–
Lymph nodal status, n (%)			0.0175			
N0	37 (28.2)	35 (44.3)		1		
N1–N2	94 (71.8)	44 (55.7)		2.64	(1.21–5.76)	0.0151
Node capsular effraction, n (%)	32 (24.4)	11 (13.9)	NS	–	–	–
Length of stay in hospital after lung surgery* (days), n (%)			0.0049	–	–	–
<14 days	85 (65.4)	36 (45.6)				
≥14 days	45 (34.6)	43 (54.4)				
Postoperative complications*, n (%)	49 (37.7)	37 (46.8)	NS			
Altered recovery after lung surgery; PS ≥2, n (%)	5 (3.8)	24 (30.4)	<0.0001	0.08	(0.02–0.25)	<0.0001
Referral to rehabilitation care unit after lung surgery**, n (%)	70 (54.3)	51 (64.6)	NS	–	–	–
Medical cancer center, n (%)			NS	–	–	–
University hospital and cancer center	82 (62.6)	48 (60.8)				
General hospital	31 (23.7)	15 (19.0)				
Private hospital	18 (13.7)	16 (20.2)				

Two patients were excluded from multivariate regression analysis due to missing data. *, one missing data; **, two missing data. AC, adjuvant chemotherapy; MDT, multidisciplinary team; OR, odd ratio; CI, confidence interval; NS, non significant; PS, performance status.

Table 4 AC use according to age

Variables	Univariate analysis			Multivariate analysis		
	<70 years (n=136)	≥70 years (n=74)	P	OR	95% CI	P
Charlson index, n (%)			0.0003	–	–	–
0–1	22 (16.2)	0 (0.0)				
≥2	114 (83.8)	74 (100.0)				
Postoperative stage, n (%)			NS	–	–	–
IIA–IIB	82 (60.3)	39 (52.7)				
IIIA	54 (39.7)	35 (47.3)				
Postoperative complications, n (%)	56 (41.2)	31 (41.9)	NS	–	–	–
Length of stay in hospital after lung surgery* (days), n (%)			NS	–	–	–
<14 days	84 (62.2)	37 (50.0)				
≥14 days	51 (37.8)	37 (50.0)				
Referral to rehabilitation care unit after lung surgery**, n (%)	72 (53.7)	49 (66.2)	NS	–	–	–
Adjuvant treatment[#], n (%)			<0.0001			
Cisplatin-vinorelbine	92 (67.7)	9 (12.3)		1		
Carboplatin-paclitaxel	9 (6.6)	6 (8.2)		6.8	(1.97–23.5)	NS
No AC	35 (25.7)	58 (79.5)		16.9	(7.6–37.8)	<0.0001
Total number of AC cycles received[¶], n (%)			NS	–	–	–
<3	10 (9.9)	3 (20.0)				
≥3	91 (90.1)	12 (80.0)				
Number of complete AC cycles received[¶], n (%)			NS	–	–	–
<3	37 (36.6)	7 (47.0)				
≥3	64 (63.4)	8 (53.0)				
4	48 (47.5)	5 (33.3)				
AC dose reduction or treatment arrest[¶†], n (%)			NS	–	–	–
No dose reduction or omission	48 (49.0)	5 (38.5)				
Dose reduction or omission	30 (30.6)	3 (23.0)				
AC treatment arrest	20 (20.4)	5 (38.5)				
Loss of weight[§] (kg), mean ± SD	0.13±5.6	0.91±3.6	NS	–	–	–

One patient was excluded from multivariate regression analysis due to missing data. *, one missing data; **, two missing data; [#], one patient excluded from the analysis (other AC regimen prescribed); [¶], the analysis was conducted on patients who received cisplatin-vinorelbine or carboplatin-paclitaxel AC (n=116); [†], patients whose AC was stopped because of patient's refusal and intercurrent disease or death (n=5) were excluded from this analysis; [§], the analysis was conducted for patients who received at least 3 cycles of either cisplatin-vinorelbine or carboplatin-paclitaxel AC (n=103). AC, adjuvant chemotherapy; OR, odd ratio; CI, confidence interval; NS, non significant; SD, standard deviation.

Table 5 Predictive factors associated with a delayed initiation of AC

Variables	Univariate analysis			Multivariate analysis		
	AC received ≤8 weeks (n=86)	AC received >8 weeks (n=31)	P	OR	95% CI	P
Age (years), n (%)			NS	–	–	–
<60	41 (47.7)	11 (35.5)				
60–69	33 (38.4)	16 (51.6)				
≥70	12 (13.9)	4 (12.9)				
Smoking status*, n (%)			NS	–	–	–
Current smoker	40 (46.5)	17 (56.7)				
Former smoker or non smoker	46 (53.5)	13 (43.3)				
Charlson index, n (%)			NS	–	–	–
0–1	15 (17.4)	5 (16.1)				
≥2	71 (82.6)	26 (83.9)				
Histology, n (%)			NS	–	–	–
Adenocarcinoma	39 (45.4)	15 (48.4)				
Squamous-cell carcinoma	34 (39.5)	13 (41.9)				
Other	13 (15.1)	3 (9.7)				
Stage disease, n (%)			NS	–	–	–
IIA–IIB	48 (55.8)	16 (51.6)				
IIIA	38 (44.2)	15 (48.4)				
Type of surgery, n (%)			NS	–	–	–
Lobectomy or other	60 (69.8)	25 (80.6)				
Pneumonectomy	26 (30.2)	6 (19.4)				
Post-operative complications, n (%)	20 (23.3)	19 (61.3)	0.0001	3.48	(1.29–9.4)	0.0138
Altered recovery after lung surgery; PS ≥2, n (%)	2 (2.3)	1 (3.2)	NS	–	–	–
Length of stay in hospital* (days), n (%)			<0.0001			
<14 days	67 (77.9)	11 (36.7)		1		
≥14 days	19 (22.1)	19 (63.3)		4.01	(1.48–10.87)	0.0064
Referral to rehabilitation care unit after lung surgery**, n (%)	42 (49.4)	25 (83.3)	0.0012	4.03	(1.19–13.6)	0.0249

Two patients were excluded from multivariate regression analysis due to missing data. *, one missing data; **, two missing data. AC, adjuvant chemotherapy; OR, odd ratio; CI, confidence interval; NS, non significant; PS, performance status.

initiation were analysed (*Table 5*). In multivariate analysis, independent predictive factors associated with a delayed AC initiation were postoperative complications (OR =3.48; 95% CI: 1.29–9.4; P=0.0138), a length of stay in hospital following lung surgery exceeding 14 days (OR =4.01; 95% CI: 1.48–10.87; P=0.0064) and referral to rehabilitation care unit after lung surgery (OR =4.03; 95% CI: 1.19–13.6; P=0.0249). In particular, we observed that these predictive factors of delayed AC initiation were not significantly different between younger and elderly patients (*Table 4*).

Table 6 Toxicities of AC according to the initial regimen prescribed

Variables	Cisplatin-vinorelbine (n=97)			Carboplatin-paclitaxel (n=14)			P#
	Toxicity, n (%)	Dose reduction or omission	Treatment discontinuation due to toxicity	Toxicity, n (%)	Dose reduction or omission	Treatment discontinuation due to toxicity	
Febrile neutropenia	15 (15.5)	3	12*	1 (6.7)	1	0	NS
Hematologic toxicities	13 (13.4)	11	2	2 (13.3)	1	1	NS
Renal failure	5 (5.2)	2	3	–	–	–	–
Hematologic toxicities and renal failure	6 (6.2)	3	3	–	–	–	–
Neurologic toxicity	2 (2.1)	2	0	1 (6.7)	1	0	NS
Asthenia, altered performance status	9 (9.3)	3	6**	–	–	–	–
Nausea and vomiting	4 (4.1)	3	1	–	–	–	–

Patients who received either cisplatin-vinorelbine or carboplatin-paclitaxel as initial AC regimen were included in the analysis (n=116). One patient who received carboplatin-pemetrexed as initial regimen was excluded from this analysis. Patients for whose AC was stopped because of patient's refusal, intercurrent disease or death (n=5) were excluded from this analysis. *, for two patients, cisplatin-vinorelbine was switched for carboplatin-paclitaxel because of febrile neutropenia; **, for one patient, cisplatin-vinorelbine was switched for carboplatin-gemcitabine because of altered performance status; #, indicates the P value obtained with contingency Chi-square analysis for the comparison of cisplatin-vinorelbine and carboplatin-paclitaxel toxicities. AC, adjuvant chemotherapy; NS, non significant.

Among whole patients who received AC, treatment was discontinued for 5 patients because of patients' refusal to continue AC (n=1), tumour progression (n=1) and death (n=2) whereas one patient underwent a dose reduction because of intercurrent disease. For one patient, death was considered as not related to chemotherapy toxicity whereas for another patient the exact information was missing. Notably, a dose reduction or omission due to AC toxicities (i.e., cisplatin-vinorelbine or carboplatin-paclitaxel AC regimen) was reported for 33 patients (28.4%) whereas 25 patients (21.6%) had a treatment discontinuation because of AC toxicities.

AC toxicity in real-life practice

AC toxicities leading to treatment modification were reported for 58 patients (50%). Febrile neutropenia (14.4%), hematologic toxicities including non-febrile neutropenia (13.5%) and altered performance status (8.1%) were the most frequent AC toxicities reported leading to either dose-intensity modification or treatment interruption. Although non-significant, febrile neutropenia, renal failure, altered performance status and nausea-vomiting were more frequently reported in case of cisplatin-vinorelbine compared to carboplatin-paclitaxel AC regimen (*Table 6*). In particular, febrile neutropenia and altered performance status led to treatment discontinuation for respectively 12 (12.4%) and 6 (6.2%) patients who received cisplatin-vinorelbine as AC initial regimen (*Table 6*). Among them, cisplatin-vinorelbine was discontinued for three patients and switched for either carboplatin-paclitaxel or carboplatin-gemcitabine because of febrile neutropenia (n=2) or altered performance status (n=1). On the contrary, hematologic toxicities including non-febrile neutropenia resulted more frequently in either cisplatin-vinorelbine dose reduction or omission (11.3%) rather than treatment discontinuation (2.1%) (*Table 6*).

Besides AC toxicities regarding AC regimen prescribed, AC specific side effects among younger and elderly patients were also analysed (*Tables 4*,7). Although small sample size, elderly patients who received either cisplatin-vinorelbine or carboplatin-paclitaxel experienced toxicities leading to dose-intensity modification or treatment interruption in 61.5% of cases (*Table* 7). Interestingly, no significant differences were reported regarding AC toxicities between younger (51%) and elderly patients (61.5%) (*Table* 7). Likewise, for patients who completed at least 3 AC cycles, loss of weight was not significantly different between younger (0.13±5.6 kg) and elderly patients (0.91±3.6 kg) (*Table 4*). As for youngers, febrile neutropenia was the most frequent adverse event reported among elderly patients (*Table* 7). However, elderly patients experienced more frequently asthenia and altered performance status (15.4%) when they received AC compared to younger patients (7.1%) (*Table* 7).

Table 7 Toxicities of AC according to age

Toxicities	<70 years old (n=98)	≥70 years old (n=13)	P
Febrile neutropenia, n (%)	14 (14.3)	2 (15.4)	NS
Hematologic toxicities, n (%)	14 (14.3)	1 (7.7)	NS
Renal failure, n (%)	4 (4.1)	1 (7.7)	NS
Hematologic toxicities and renal failure, n (%)	6 (6.1)	0 (0)	–
Neurologic toxicity, n (%)	2 (2)	1 (7.7)	NS
Asthenia, altered performance status, n (%)	7 (7.1)	2 (15.4)	NS
Nausea and vomiting, n (%)	3 (3.1)	1 (7.7)	NS

The analysis was conducted on n=116 patients who received cisplatin-vinorelbine or carboplatin-paclitaxel as initial AC regimen. One patient who received carboplatin-pemetrexed as initial regimen was excluded from this analysis. Patients whose AC was stopped because of patient's refusal and intercurrent disease or death (n=5) were excluded from this analysis. AC, adjuvant chemotherapy; NS, non significant.

Among patients who received cisplatin-vinorelbine or carboplatin-paclitaxel as initial regimen prescribed, 72 patients (62%) completed at least 3 AC cycles without dose reduction or omission (*Table 4*). Of note, 53.3% elderly patients completed at least 3 AC cycles without dose reduction or omission (*Table 4*). Although 4 AC cycles are recommended according to guidelines, only 53 patients (45.7%) completed 4 AC cycles without dose-intensity modification. Consistently with results on AC toxicity, no significant differences were reported between younger and elderly patients regarding either the total number or the number of complete AC cycles received (*Table 4*).

AC efficacy in real-life practice

Among the whole cohort, recurrence within 5 years following curative-intent lung surgery was documented in 98 patients (46.7%). In both groups, although non-significant, thoracic relapse was the most frequent type of disease recurrence as compared with extra-thoracic or brain recurrences, occurring in 21 (17.9%) and 15 (16.1%) patients in AC and no-AC group respectively. Distant recurrence defined by extra-thoracic recurrence or brain recurrence occurred either alone in 16 patients (13.7%) or associated with thoracic recurrence in 19 patients (16.2%) who underwent AC. Corresponding numbers for patients who did not receive AC after curative-intent lung surgery were 11 (11.8%) and 16 (17.2%) respectively. Notably, brain was the only metastatic site involved in 8 (6.8%) patients who received AC and in 4 (4.3%) patients who underwent curative-intent lung surgery alone. The 5-year DFS rates were respectively of 49.2% for patients who received AC and 43.4% for those who underwent curative-intent lung surgery alone. Median DFS was 48.7 months for patients who received AC and 31.7 months for patients who did not receive AC after curative-intent lung surgery (*Figure 3A*; P=0.2169).

Among the whole cohort, 110 patients (52.4%) died within 5 years following curative-intent lung surgery. Of note, 31 patients (28.2%) died without tumour recurrence documented (i.e., 10 patients in AC group and 21 patients in no-AC group respectively). The 5-year OS rates were respectively of 58.6% for patients who received AC and 30.5% for those who underwent curative-intent lung surgery alone. Median OS was 30.8 months for patients who did not receive AC whereas median OS has not been reached for patients who received AC at the time the database was locked (*Figure 3B*; P<0.0001). In multivariate Cox analyses, tumour size <5 cm [hazard ratio (HR) =0.61; 95% CI: 0.42–0.80; P=0.0125] and AC (HR =0.46; 95% CI: 0.29–0.72; P=0.0007) were significantly associated with improved OS at 5 years independently of age and Charlson index (*Table 8*).

Finally, we conducted exploratory analyses using the Kaplan-Meier method to evaluate whether confounding factors associated with daily-life practice might impact the benefit effect of AC on OS. Interestingly, we found that delayed AC (i.e., >8 weeks) was not associated with inferior OS as compared with AC administration within 8 weeks following curative-intent lung surgery (*Figure 4A*). As well, OS was not inferior whether patients received less than 3

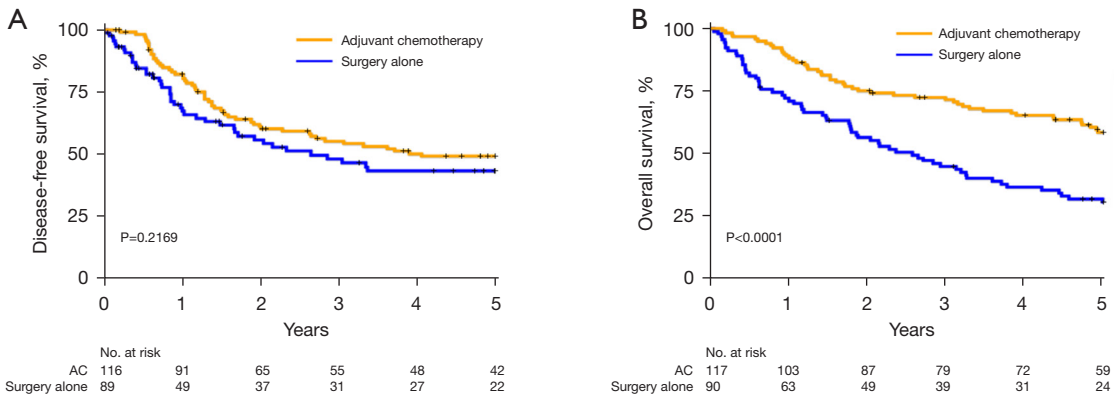

Figure 3 DFS (A) and OS (B) of AC in real-life practice. DFS, disease-free survival; OS, overall survival; AC, adjuvant chemotherapy.

Table 8 Univariate and multivariate Cox analyses of prognostic factors on OS

Variables	Univariate analysis			Multivariate analysis		
	HR for death	95% CI	P	HR for death	95% CI	P
Age (years)			0.0399			NS
<70 *vs.* ≥70	0.67	(0.46–0.98)		1.16	(0.74–1.82)	
Sex			0.25			–
Male *vs.* female	1.38	(0.80–2.38)		–	–	
Charlson index			0.03			NS
0–1 *vs.* ≥2	0.40	(0.18–0.92)		0.51	(0.22–1.21)	
Smoking status			0.19			–
Former or current smoker *vs.* non smoker	0.55	(0.23–1.36)		–	–	
Type of surgery			0.23			–
Lobectomy or other *vs.* pneumonectomy	0.78	(0.51–1.18)		–	–	
Histologic sub type			0.78			–
Non-squamous *vs.* squamous or other	0.95	(0.65–1.38)		–	–	
Lymph node status			0.19			–
N0 *vs.* N1–N2	1.29	(0.88–1.91)		–	–	
Tumour size (cm)			0.01			0.0125
<5 *vs.* ≥5	0.61	(0.41–0.89)		0.61	(0.42–0.8)	
Postoperative stage disease			0.54			–
IIA–IIB *vs.* IIIA	0.88	(0.61–1.30)		–	–	
Treatment			<0.0001			0.0007
AC *vs.* surgery alone	0.44	(0.30–0.65)		0.46	(0.29–0.72)	
Adjuvant radiotherapy			0.45			–
No *vs.* yes	1.33	(0.58–3.02)		–	–	

OS, overall survival; HR, hazard ratio; CI, confidence interval; NS, non significant; AC, adjuvant chemotherapy.

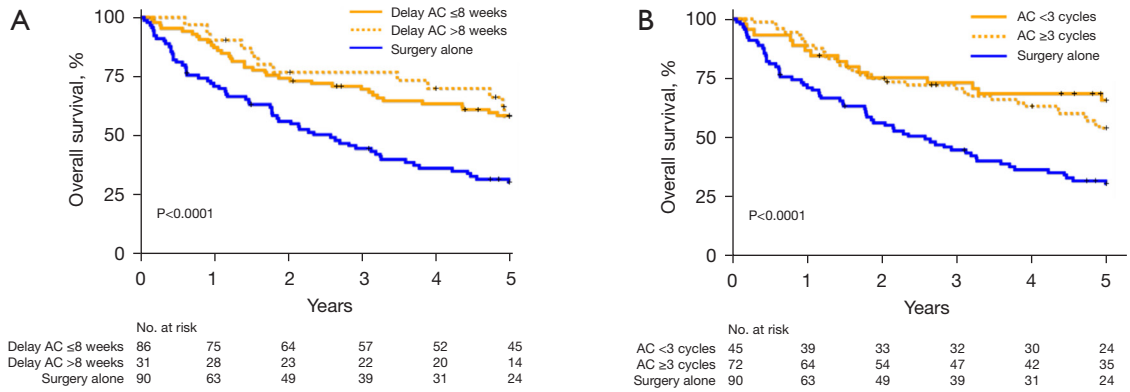

Figure 4 Impact of delayed AC (A) and the number of complete AC cycles received without dose reduction or omission (B) on OS. AC, adjuvant chemotherapy; OS, overall survival.

AC cycles without dose reduction or omission (*Figure 4B*). Finally, the benefit of AC on survival was not significantly different according to postoperative stage disease (i.e., IIA–IIB *vs.* IIIA; P=0.82).

Discussion

Since randomised clinical trials were published at the beginning of 2000 and demonstrated a significant benefit of AC over surgery alone (5-8), AC has been implemented as a standard therapeutic strategy following curative-intent lung surgery for a completely resected IIA–IIIA NSCLC. Otherwise, the absolute improvement of AC estimated at 5.4% of 5-year OS (8) might appear as limited especially regarding the potential toxic side effects of cisplatin-based AC regimen and the expected benefit in a less selected population. In this retrospective study, we reported that although AC use differs from guidelines in real-life practice, AC remains safe and efficient in non-trial setting.

To assess compliance and AC use in real-life practice, we conducted a retrospective study and included 210 patients who presented a theoretical indication of AC according to guidelines (14) following curative-intent lung surgery. Contrary to randomised clinical trials which excluded most of patients with previous cancers (5-7), our study cohort is more representative of daily-life practice as 29% of the patients included had a previous cancer. Then, the median age in our study is 65 years old which is older than the median age reported in randomised clinical trials [i.e., 59 years old for IALT (5) and ANITA (6) trials respectively; 61 years old for JBR.10 trial (7)]. Of note, 35.2% of included patients were 70 years or older. Other baseline population characteristics are in accordance with expected characteristics of patients diagnosed with early-stage NSCLC disease and described in randomised clinical trials (5-7). Indeed, most of the patients included were men with good functional status, tobacco history and were diagnosed with adenocarcinoma or squamous-cell carcinoma. Likewise, most of them underwent a lobectomy rather than a pneumonectomy. We reported postoperative complications and a curative-intent lung surgery mortality rate of 41.1% and 1.9% respectively, which is in accordance with literature (19-21).

In our study, MDT decision is in accordance with AC guidelines in 62.4% cases. After randomised clinical trials were published and demonstrated a survival benefit of AC, AC uptake was estimated at 31% in a study population of 3,354 patients who underwent surgical resection for a NSCLC between 2004 and 2006 (22). Other retrospective studies reported AC compliance to guidelines in a range of 54.1% (23) to 59% (24) among 14,892 patients who underwent surgical resection for pN1 disease and 99 patients who underwent curative-intent lung surgery for stage II–III NSCLC respectively. More recently, post hoc exploratory analyses of AC use before randomisation in ADAURA trial revealed that 60% of IB–IIIA resected NSCLC received AC (25). We identified age, age and comorbidities and altered post-operative recovery or post-operative complications as main reasons advanced in MDT for no respect to AC guidelines. Consistently with these observations, Barni *et al.* also identified patient's clinical conditions as the main reason for no respect to AC guidelines in 43% cases (24). In line with previous observations (23,26-30), we found that older patients (i.e.,

≥70 years old) received significantly less AC based on MDT decision. In our study, altered recovery after lung surgery was significantly associated with a less likelihood to receive AC based on MDT decision whereas patients with postoperative lymph node invasion have a significantly higher probability to receive AC. As described in literature (23,26,28-32), we did not find comorbidities according to Charlson index, pneumonectomy, squamous cell histologic sub-type, postoperative stage disease, length of inpatient stay after lung surgery and postoperative complications to significantly impact the probability to receive AC. In this retrospective study, we were not able to analyse referral to medical oncologist. However, we recently outlined (33) that referral to medical oncologist might impact the likelihood to receive AC as patients were referred to medical oncologist in a range of 44% to 73% in real life-practice (34-36). Interestingly, medical cancer center and referral to rehabilitation care unit after surgery were not considered as predictive factors of AC compliance in our study. Since postoperative radiation therapy was still debated at the time of our study period, we noticed that only 16.9% of pN2 patients underwent adjuvant radiotherapy. Based on recent results of LUNG-ART phase 3 randomised trial (37), it would be interesting to evaluate in the next future whether postoperative radiotherapy is still validated in MDT.

In line with AC guidelines (14) and other retrospective studies published on AC in real-life practice (33), 86.3% of patients received cisplatin-vinorelbine AC regimen. Notably, 62% of patients completed at least 3 AC cycles without dose reduction or omission and 45.7% of patients achieved 4 complete AC cycles. Thus, in real-life practice, AC dose-intensity received remains high. Indeed, 59% and 73.8% patients received at least 240 mg/m^2 of cisplatin in the LACE meta-analysis (8) and IALT trial (5) respectively. In ANITA trial, 38% and 63% patients received more than 66% of the total planned dose of vinorelbine and cisplatin respectively (6). In non-trial setting, the percentage of patients who received platinum-vinorelbine and completed 4 AC cycles ranged from approximately 45% to 66% (32,38-40). Consistently with IALT trial (5), we found that the main factor associated with incomplete planned AC were adverse events. Indeed, 50% of patients experienced AC-related side effect leading to either dose-intensity modification or treatment interruption. As a comparison, the rate of overall grade 3–4 toxicity was estimated at 66% in main randomised clinical trials (8) whereas previous reports in real-life practice estimated that patients experienced a dose reduction or omission between 40% (41) to 64% (22). Otherwise, incomplete planned dose received was not associated with inferior survival in our study. In literature, conflicting results are available as Kenmotsu *et al.* found that the total dose of cisplatin received was not a prognostic factor (42) contrary to other studies which demonstrated that either a delivery of <80% of total planned platinum dose (43) or the number of AC cycles received (44) were significantly associated with survival. Although cisplatin-vinorelbine was associated with higher frequency of either dose-intensity modification or treatment interruption in comparison with carboplatin-paclitaxel regimen, we did not find a statistically significance as it was previously reported in literature (45). Consistently with randomised clinical trials (5-8) and retrospective studies (33), neutropenia was the most frequent adverse event reported in our study with up to 14.4% patients experienced febrile neutropenia. Otherwise, the occurrence of neutropenia is no more frequent in non-trial setting compared to randomised clinical trials. Regarding AC toxicities, a potential limit of this retrospective study is the absence of quality-of-life data as they were not specifically available.

Recurrence was documented for 46.7% of patients, which is in accordance with previous studies in non-trial setting which reported a recurrence rate of 43% (32) and 49.6% (43) among 251 patients with stage IB–IIIA resected NSCLC and 258 patients with stage II resected NSCLC respectively. We found that 5-year DFS rate for AC-group was 49.2% with a median DFS of 48.7 months, highlighting that AC remains an interesting treatment to prevent from tumour relapse in real-life practice. Indeed, the 5-year DFS rates reported in IALT (5) and JBR.10 (7) trials were respectively of 39.4% and 61% for patients assigned to AC group whereas median DFS of AC group was 36.3 months in ANITA trial (6). Our results are also consistent with those observed in real-life practice as the 5-year DFS rate was previously estimated at 46% with a median DFS of 50.4 months among 66 patients who received AC for IB–IIIB resected NSCLC (39). As described in ANITA trial (6), we found that thoracic site was the most common site of tumour relapse. Consistently with our results, a review on stage I–IIIA resected NSCLC outlined that 13% to 24% patients recur locally following lung cancer surgery (46). Likewise, Varlotto *et al.* reported a local failure rate of 32% among 373 patients with IB–III NSCLC stage disease (47).

In our analysis, 5-year OS rates with and without AC were respectively of 58.6% and 30.5%. Median OS was estimated at 30.8 months for patients who underwent

surgery alone whereas median OS was not reached for patients who received AC. As a comparison, the 5-year OS of AC was estimated at 44.5% in IALT trial (5) whereas the median OS in AC group was respectively of 65.7 months (6) and 94 months (7) in ANITA and JBR.10 trials. Outcomes of patients who underwent surgery alone were inferior than those reported in randomised clinical trials as 5-year OS rates were of 40.4% (5) and 54% (7) and median OS of 43.7 months (6) and 73 months (7). Taken together, the survival benefit of AC in our study remains unclear and might be biased by the patient population for whose AC was not validated in MDT. Nonetheless, survival of patients who did not receive AC in our analysis tended to be longer than previous reports in non-trial setting (26,43). Indeed, retrospective studies reported a median survival of 23.2 months (43) and 19 months with a 5-year OS rate of 24% (26) for respectively stage II and pT3N0 NSCLC patients who underwent lung surgery alone. In these retrospective studies, median OS and 5-year OS rate were respectively of 65.1 months (43) and 44% (26) for stage II and pT3N0 NSCLC patients who received AC following lung surgery. Other studies reported AC 5-year OS rates of 66% (39) and 73% (42) for respectively 66 patients with IB–IIIB NSCLC and 100 patients with IIA–IIIA NSCLC who received cisplatin-vinorelbine AC regimen. Overall, although the benefit effect of AC on OS might be overstated in our analysis, our results support AC use in a less selected population.

Contrary to ANITA (6) and JBR.10 (7) trials, we only found tumour size and AC to significantly affect OS. In line with our results, several studies showed that AC improved OS in multivariate analyses (26,43,48). In this setting, HR for death in case of AC received were of 0.61 (95% CI: 0.39–0.94) for stage II disease and 0.71 (95% CI: 0.52–0.96) for stage III disease (48). Based on the 7th TNM classification (15,16), we choose 5 cm as cut-off tumour size to evaluate impact on survival while previous studies found tumour size >4 cm to significantly impact OS in non-trial setting (23,26). However, as described in randomised clinical trials (6,7) and some retrospective studies in real-life practice (26,43); age, sex, comorbidity according to Charlson index, type of surgery resection, length of inpatient stay, postoperative stage disease, lymph node status and histologic sub-type were not identified as independent predictive factors of OS in our multivariate Cox analyses model.

Finally, we aimed to analyse confounding factors related to AC use in real-life practice. The median time between surgery and AC administration was 49 days. Thus, in real-life practice, median time between surgery and AC initiation did not differ significantly compared to randomised clinical trials (i.e., 40 and 39 days for IALT trial and LACE meta-analysis respectively) (5,8). Our results are consistent with retrospective studies which highlighted that the median time between surgery and AC administration was approximately comprised between 5 to 8 weeks (33). In line with previous observations, we found prolonged length of stay in hospital after surgery (49,50) and postoperative complications (43) as significant predictive factors of delayed AC initiation. In accordance with literature, we found that delayed AC was not associated with an increased mortality risk (49-51) and was associated with a significant lower mortality risk compared to patients treated with surgery alone (49). Contrary to Wang *et al.* (52), delayed AC after lung surgery was not associated with a shorter OS compared to patients who received AC within 8 weeks following lung resection. Finally, as previously outlined, we found that elderly patients received significantly less AC based on MDT decision. However, our results showed that AC remains safe among this sub-group population. Such results are in accordance with sub-group analysis of JBR.10 trial (53) and LACE meta-analysis (54) which revealed no significant differences on AC related toxicities regarding age groups. AC use among patients aged 70 years or older was estimated at 21.6% in our study which is consistent with previous retrospective studies reporting AC use from 10% to 25% in this specific population (48,55-59). As previously reported (44,57,60,61), we did not find a significant difference in AC regimen received between younger and elderly patients. Contrary to the sub-group analysis of LACE meta-analysis (54), dose-intensity of AC was not significantly different between younger and elderly patients. In line with our results, no significant differences in either the number of AC cycles or AC dose-intensity received were previously reported in real-life practice between elderly and their younger counterparts (44,60,61).

Conclusions

In summary, this study reports that although AC use in real-life practice might differ from guidelines, AC administration remains efficient and well-tolerated in most patients. Our results highlighted that decision of AC administration is mainly influenced by patient's clinical conditions, thereby suggesting that AC warrants a global evaluation to make decision due to differences between daily-life practice

and guidelines. Despite retrospective data collection associated with potential bias and the limited number of patients included, our study confirmed that AC could be considered as a standard therapeutic treatment in real-life practice. Future perspectives to increase the number of patients that would benefit from adjuvant treatment might include predictive biomarkers as well as immune checkpoint inhibitors and targeted therapies.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-345/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-345/coif). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Collection and analysis of medical data were approved by the French data protection authority (CNIL) and the Research Ethics Board of the University Hospital of Saint-Etienne (IRBN992019/CHUSTE). All alive patients were sent an informed consent approved by the Research Ethics Board of the University Hospital of Saint-Etienne and subsequently approved the use of their medical data.

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