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Adjuvant platinum-based chemotherapy in non-small cell lung cancer: The role of relative dose-intensity and treatment delay

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ABSTRACT

Background: The study investigated the association of the relative dose-intensity (RDI) of cisplatin and timing of adjuvant platinum-based chemotherapy (APC) with survival for stage I-III non-small cell lung cancer (NSCLC) patients.

Material and Methods: Real-life data of patients treated with APC (four cycles of cisplatin and vinorelbine) between 2007 and 2014 was included to analyse the association between disease-free survival (DFS) and overall survival (OS) with RDI (ratio of received to planned dose-intensity). High RDI was defined as cisplatin RDI of > 75% and low RDI ≤ 75%.

Results: Out of 198 patients, 166 were eligible. Low RDI was administered to 72 (43%) patients. In multivariate analysis, those patients had a significantly higher risk of recurrence (HR: 1.87, 95%CI 1.13–3.09, $p = 0.01$) and death (HR: 1.91, 95%CI 1.32–3.23, $p = 0.01$) versus patients in the high RDI group. The risk of death was significantly higher in patients with PS 1 treated with low versus high RDI (HR: 2.72, 95%CI: 1.22–6.09, $p = 0.014$). The risk of recurrence was higher for patients with squamous cell carcinoma of low versus high RDI (HR: 3.82, 95%CI: 1.01–14.4, $p = 0.048$). No impact of delayed APC beyond six weeks from surgery on neither DFS (HR: 0.78, 95%CI: 0.46–1.33, $p = 0.36$) nor OS (HR 0.67, 95%CI: 0.40–1.15, $p = 0.15$) was observed.

Conclusion: Low cisplatin RDI ≤ 75% of APC, but not extended time from surgery to APC onset > six weeks, was associated with significantly shorter survival in NSCLC patients.

1. Introduction

Adjuvant platinum-based chemotherapy (APC) is a standard post-operative treatment for radically operated patients with I-III stage non-small cell lung cancer (NSCLC) [1]. The reduction of recurrence risk and increased survival has been shown for patients with tumour greater than 4 cm and / or lymph node metastases [2, 3] but according to the most current meta-analysis, there is only 4% absolute increase in 5-year survival [1]. Many patients are not able to complete the four recommended cycles of APC due to toxicity [4-6]. The suggested timing of APC is 4–6 weeks after NSCLC surgery [7], but delays due to post-operative complications and reduced performance status (PS) are commonly observed [8-11]. The impact of time interval between surgery and APC is uncertain and the results, based on observational studies, are inconclusive [8-11].

The most frequent reason for APC discontinuation or reduction is cisplatin-related toxicity [12] resulting in lower cisplatin dose intensity. The dose per square metre differs within the randomized studies [12]. The dose intensity of APC is rarely reported in the literature and therefore, its impact on survival is difficult to assess [13-14]. The most accurate description of the dose intensity resulting from treatment delay, dose reduction, discontinuation or combination of those, is the relative dose intensity (RDI) [15]. The RDI is the ratio of received to planned dose intensity [15]. The positive impact of high RDI of adjuvant

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chemotherapy on survival was first presented in breast cancer and later across several solid tumours [16,17]. The results showed a significant clinical benefit of adjuvant chemotherapy only if full or nearly full doses were administered. In one study of adjuvant chemotherapy for stage II NSCLC, administration of less than 80% of the planned platinum dose along with high Charlson comorbidity index (CCI) and age $\geq$ 70 were associated with shorter OS [8]. Currently, there is no consensus on which RDI threshold may have impact on survival in NSCLC treatment [8,18-20].

The aim of this retrospective real-life registry study was to investigate the association of cisplatin RDI and timing of APC after surgery and survival in patients radically operated for stage I-III NSCLC.

2. Materials and methods

The study included real-life data of patients that received APC at the Department of Oncology, Aalborg University Hospital following radical surgery for stage I-III NSCLC between July 2007 and December 2014. All patients were followed by clinical and radiological assessment for at least 60 months from APC. The primary NSCLC diagnosis was established by biopsy and confirmed histopathologically in the surgical specimens. Pathological tumour, lymph node, metastasis (pTNM) staging was established according to the current guidelines of TNM staging system (the 6th and 7th TNM edition) [21,22] and retrieved from the medical records. Patients operated for oligometastatic disease prior to NSCLC surgery, non-radically operated patients, or diagnosed with synchronous cancer other than non-melanoma skin cancer within two years before and after the lung cancer diagnosis were excluded from the study. Chemotherapy-related data (date of the treatment, dose in mg/m^2 per treatment, cumulative dose and treatment delay) were retrieved from the chemotherapy prescription programme (ARIA for Medical Oncology v10, Varian Medical Systems, California, USA). The clinical characteristics including PS and CCI estimated before the chemotherapy administration, were retrieved from patients' medical files. The study was approved by the Danish Health Authority (3–3013–2051/1) and the Danish Data Protection Authority (2008–58–0028).

The APC regime contained four cycles of cisplatin 75 mg/m^2 (maximum dose 150 mg) intravenously administered (i.v.) at day 1 and vinorelbine 25 mg/m^2 i.v. at day 1 and 8 scheduled every three weeks. Only patients with PS 0–1 were considered eligible for APC according to the study institution guidelines. The standard delay schedule was 7 days in case of any grade 3 or 4 toxicity or haematological toxicity in form of neutrophil count $< 1.5 \times 10^9$/l or platelets $< 100 \times 10^9$/l. No granulocyte colony-stimulating factor was administered. Switching to carboplatin was allowed in exceptional cases of toxicity to cisplatin. In case of persistent haematological toxicity or further treatment after neutropenic infection, the dose was reduced to 75% at the subsequent cycle. The treatment was discontinued if a 75% dose was not tolerated.

The disease-free survival (DFS) was defined as time from surgery to radiological signs of recurrence on computed tomography scan or magnetic resonance imaging and was censored at the last follow-up date or at non-lung cancer death. The OS was measured as time from surgery to the date of death. To investigate the potential bias arising from comparing time-to-event outcome between RDI groups, the results of survival analyses were repeated using a landmark method [23] (Supplementary material). Body surface area (BSA) was calculated using the Mosteller formula [24]. The RDI was calculated according to the Hryniuk's model [15] as a ratio of received DI to planned DI.

$$\mathrm{DI} = \frac{total\ dose(mg/m2)}{total\ time(weeks)}$$

$$\mathrm{RDI}(\%) = \frac{given\ DI}{planned\ DI} \times 100$$

The given DI was calculated as the total given dose divided by the total time of completed APC. The planned DI was calculated as the planned dose of APC in the scheduled time of 12 weeks. When the treatment was discontinued before the planned duration, missing weeks of the planned treatment time were added to the treatment duration with dose null. The days of delay between the cycles were expressed as a cumulative delay over the duration of APC. The time interval between surgery and APC was defined as number of days from the operation date to the first day of APC.

The cohort was divided into low and high RDI groups according to the RDI of cisplatin. A threshold of 75% was chosen as it reflects the common practice of dose reduction at the study hospital and represents three out of four recommended cycles of APC. Cisplatin RDI $\leq$ 75% was defined as low RDI group and cisplatin RDI $>$ 75% as high RDI group. Clinical variables contrasting the low versus the high RDI groups were analysed using the Fisher's exact test, the chi-squared test or the *t*-test depending on the variable type. Kaplan-Meier estimation was used to construct the DFS and OS curves. Log-rank test was used to analyse the differences in survival between the low and high RDI groups. Univariate Cox regression analyses were performed to estimate the association of RDI groups with DFS and OS. Multivariate Cox regression analyses were performed to investigate the co-variation of significant variables influencing the DFS and OS. P-values < 0.05 were considered significant and 95% confidence intervals (CI) were used. All statistical analyses were performed using Stata version 15 (StataCorp LLC, College Station, TX, USA).

3. Results

3.1. Patient characteristics

During the study period, 198 patients were treated with APC. Thirty-two patients were excluded from the analyses due to synchronous cancer ($n = 13$), palliative chemotherapy ($n = 8$), non-radical NSCLC surgery ($n = 5$), APC after surgery for oligometastatic NSCLC ($n = 4$) and registered but never administered APC ($n = 2$). Thus, the final study cohort consisted of 166 patients. The majority of patients had PS 0 ($n = 105$, 63%) and CCI 0 ($n = 116$, 70%) (Table 1). There were no patients with PS > 1 in the cohort.

With a median follow-up time of 82 months, the 5-year DFS and OS was 59% and 73%, respectively (Table 2). The 10-year OS was 53% for patients operated before 2010. The TNM staging was prognostic for DFS (log-rank test, $p < 0.01$) and OS (log-rank test, $p = 0.03$). The lymph node status was prognostic for DFS (log-rank test, $p = 0.02$) but not OS (log-rank test, $p = 0.1$). Patients with squamous cell carcinoma (SCC) had longer DFS than patients with adenocarcinoma (AC) (log-rank test, $p = 0.01$). The 0S was longer for patients with PS 0 compared to patients with PS 1 (log-rank test, $p < 0.01$).

More than one third of patients ($n = 59$, 35%) received cisplatin RDI $>$ 90%, whereof 12 patients (7%) received 100% cisplatin RDI without dose reductions or treatment delay. The median cumulative cisplatin dose was 480 mg (range, 83–600 mg). Two patients were switched to carboplatin after one ($n = 1$) and two ($n = 1$) cycles of APC. The mean RDI of cisplatin for all patients was 73.4%. The low RDI of $\leq$ 75% was administered in 72 (43%) patients and high RDI $>$ 75% in 94 (57%) patients. Significantly more patients in the high RDI group had PS 0 compared to patients in the low RDI group ($p < 0.01$). There was no statistically significant difference between the RDI groups regarding the age, sex, CCI, histopathological characteristics, TNM stage, type of NSCLC surgery and time interval from thoracic surgery to APC (Table 1).

3.2. The cisplatin RDI and survival

The 3–5 year DFS and OS were significantly longer in the high RDI compared to the low RDI group (Table 2). The recurrence rate was significantly higher in the low RDI group compared to the high RDI group (50% versus 34%, $p = 0.02$) (Table 2). The survival estimates of DFS (Fig. 1A), OS (Fig. 1B), and univariate Cox regression analyses

Table 1
Characteristics of the patients.

Characteristics	All (n = 166)	RDI ≤ 75% (n = 72)	RDI > 75% (n = 94)	p - value
Age, years median (range)	65 (43–76)	65 (44–75)	65 (43–76)	0.78
Sex				
Female	81	35	46	0.55
Male	85	37	48	
Charlson comorbidity index				
0	116	46	70	0.52
1	33	17	16	
2	9	5	4	
3	2 (*6 N/A)	1 (*3 N/A)	1 (*3 N/A)	
ECOG PS				
0	105	37	68	< 0.01
1	56 (*5 N/A)	33 (*2 N/A)	23 (*3 N/A)	
TNM stage **				
IB	38	15	23	0.67
IIA	44	20	24	
IIB	38	15	23	
IIIA	44	22	22	
IIIB	2	0	2	
Lymph nodes				
Negative (N0)	78	33	45	0.45
Positive (N+)	88	39	49	
Histopathology				
AC	101	42	59	0.72
SCC	51	23	28	
NSCLC, NOS	14	7	7	
NSCLC surgery				
Lobectomy	140	62	78	0.55
Pneumonectomy	22	10	12 (*4 N/A)	
CHT timing				
From surgery (days, median)	39	37	40.5	0.52
Received ≤ 6 weeks	106	48	58	
Received > 6 weeks	60	24	36	
CHT administration				
Cisplatin reduction No of received cycles	17	9	8	0.27
1	23	23	0	< 0.01
2	17	17	0	
3	23	23	0	
4	103	9	94	
CHT delay				
Days - mean (range)	6.1 (0–38)	4.1 (0–38)	7.6 (0–28)	< 0.01
Delay of ≤ 7 days	114	58	56	
Delay of > 7 days	52	14	38	
Cisplatin				
RDI ≤ 50%	41	41	0	< 0.01
RDI > 50–75%	31	31	0	
RDI > 75–90%	35	0	35	
RDI > 90%	59	0	59	< 0.01
Median total dose (mg)	480	288	539	
Median RDI	80.6%	50%	92.3%	

RDI, relative dose intensity for cisplatin; PS, performance status; TNM-tumour nodes metastasis; AC, adenocarcinoma; SCC, squamous cell carcinoma; NSCLC, non-small cell lung cancer; NOS, non-other specified; CHT, chemotherapy (Cisplatin/Vinorelbine); *data of patients were not available; ** based on the 6th and 7th edition of TNM staging system.

showed that patients who received RDI of ≤ 75% had a significantly higher risk of recurrence (HR: 1.85, 95%CI 1.12–3.06, p = 0.016) and death (HR: 2.12, 95%CI 1.30–3.48, p < 0.01) compared to patients in the high RDI group (Table 3). In the multivariate Cox regression analyses, adjusted for the significant variables of the univariate analyses, the risk of recurrence (HR: 1.87, 95%CI 1.13–3.09, p = 0.015) and death (HR: 1.91, 95%CI 1.32–3.23, p = 0.015) remained significantly higher in the low compared to the high RDI group (Table 3).

Table 2
Disease-free survival and overall survival in patients treated with low and high cisplatin RDI.

Survival	All (n = 166)	RDI ≤ 75% (n = 72)	RDI > 75% (n = 94)	p-value
25th percentile DFS	23 months (95%CI 12–35)	15 months (95%CI 7–25)	40 months (95%CI 13-NA)	p = 0.01
Median DFS	N/A	107 months (95%CI 29-NA)	N/A	
1-year DFS	134/166 (80.7%)	54/72 (75.0%)	80/94 (85.1%)	p = 0.08
2-year DFS	119/166 (71.7%)	45/72 (62.5%)	74/94 (78.7%)	p = 0.03
3-year DFS	108/166 (65.0%)	39/72 (54.2%)	69/94 (73.4%)	p = 0.01
4-year DFS	105/166 (63.2%)	38/72 (52.7%)	67/94 (71.3%)	p = 0.02
5-year DFS	98/166 (59.0%)	36/72 (50.0%)	62/94 (65.9%)	p = 0.04
25th percentile OS	54 months (95%CI 35–76)	32 months (95%CI 20–55)	78 months (95%CI 45-NA)	p<0.01
Median OS	145 months (95%CI 113-NA)	103 months (95%CI 69-NA)	N/A	
1-year OS	157/166 (94.6%)	66/72 (91.7%)	91/94 (96.8%)	p = 0.13
2-year OS	143/166 (86.1%)	58/72 (80.5%)	85/94 (90.4%)	p = 0.06
3-year OS	135/166 (81.3%)	53/72 (73.6%)	82/94 (87.2%)	p = 0.02
4-year OS	128/166 (77.1%)	49/72 (68.0%)	79/94 (84.0%)	p = 0.01
5-year OS	121/166 (72.8%)	45/72 (62.5%)	76/94 (80.1%)	p<0.01
Recurrence rate	68/166 (40.1%)	36/72 (50.0%)	32/94 (34.0%)	p = 0.02

RDI, relative dose intensity; DFS, disease-free survival; OS, overall survival;. N/A, not applicable (the median survival was not reached).

In the subgroup analyses, the risk of death was significantly higher in patients with PS 1 treated with low RDI versus high RDI (HR: 2.72, 95% CI: 1.22–6.09, p = 0.014) but not in patients with PS 0 (HR: 1.50, 95%CI: 0.71–3.15, p = 0.28) (Fig. 2). The CCI was not significantly different between patients with PS 0 and 1 (p = 0.14). The risk of death was significantly higher in patients with stage I-II who received low RDI compared to patients treated with high RDI (HR: 2.18, 95%CI: 1.18–4.01, p = 0.013) but not in patients with stage III (HR: 1.75, 95% CI: 0.74–4.11, p = 0.199). The risk of recurrence was significantly higher in patients with SCC that received low RDI compared to high RDI (HR: 3.82, 95%CI: 1.01–14.4, p = 0.048) but not in patients with AC (HR: 1.47, 95%CI: 0.79–2.68, p = 0.3) (Fig. 2). The risk of recurrence was significantly higher in patients with stage I-II that received low RDI versus high RDI (HR: 2.34, 95%CI: 1.20–4.54, p = 0.012) but not in patients with stage III (HR: 1.17, 95%CI: 0.54–2.53, p = 0.685). There was no significant difference in the risk of recurrence in patients with positive (HR: 1.85, 95%CI: 0.99–3.46, p = 0.053) or negative lymph node status (HR: 1.84, 95%CI: 0.79–4.27, p = 0.154) treated with high versus low RDI. The survival analyses repeated by the landmark analysis method showed similar results (Appendix A.1, Table A.1).

3.3. Treatment delay and survival

The median number of cumulative days of delayed APC over the treatment duration was six (range 0–38). The total delay of APC more than seven days had no significant impact on DFS (HR: 0.62, 95%CI: 0.34–1.10, p = 0.10) or OS (HR: 0.59, 95%CI: 0.34–1.04, p = 0.07)

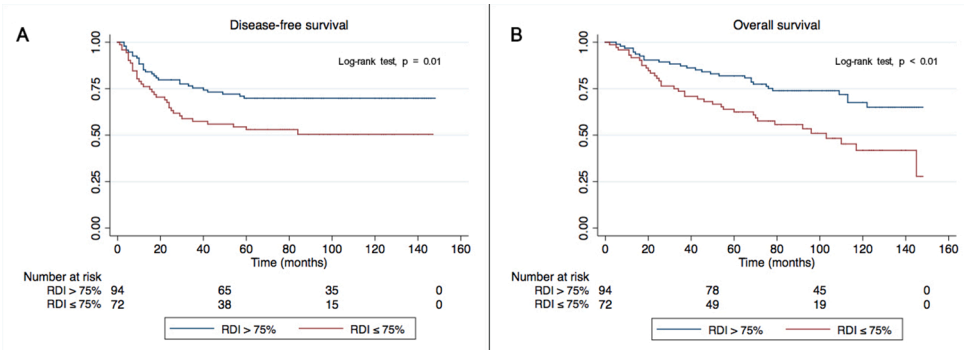

Fig. 1. Kaplan-Meier estimates of disease-free survival (1A) and overall survival (1B) in the low and high RDI groups.

Table 3
Factors affecting the disease-free survival and overall survival.

Variable	Disease-free survival Univariate analysis HR (95%CI)	p-value	Multivariate analysis HR (95%CI)	p-value	Overall survival Univariate analysis HR (95%CI)	p-value	Multivariate analysis HR (95%CI)	p-value
Age								
≤ 70	1				1			
> 70	1.18 (0.67–2.07)	0.551			0.91 (0.50–1.4)	0.747		
Sex								
Male	1				1			
Female	0.76 (0.46–1.26)	0.290			0.71 (0.43–1.16)	0.173		
Performance status								
PS 0	1				1		1	
PS 1	1.61 (0.96–2.70)	0.070			2.55 (1.54–4.22)	0.0003	2.32 (1.39–3.90)	0.001
Charlson comorbidity index								
CCI 0–1	1				1			
CCI ≥ 2	1.11 (0.40–3.07)	0.840			2.02 (0.87–4.71)	0.103		
Histopathology								
AC	1		1		1			
SCC	0.44 (0.23–0.85)	0.016	0.43 (0.22–0.83)	0.012	0.86 (0.50–1.49)	0.594		
NSCLC, other	1.83 (0.86–3.90)	0.116	1.61 (0.75–3.44)	0.222	1.50 (0.67–3.36)	0.324		
Stage								
I-II	1		1		1		1	
III	2.3 (1.40–3.86)	0.001	1.84 (1.05–3.23)	0.032	1.77 (1.06–2.94)	0.029	1.84 (1.08–3.11)	0.024
Lymph node status								
neg.	1		1		1			
pos.	1.8 (1.07–3.04)	0.026	1.42 (0.80–2.53)	0.230	1.47 (0.89–2.40)	0.131		
APC dose								
RDI > 75%	1		1		1		1	
RDI ≤ 75%	1.85 (1.12–3.06)	0.016	1.87 (1.13–3.09)	0.015	2.12 (1.30–3.48)	0.003	1.91 (1.32–3.23)	0.015
Delayed days between APC cycles								
≤ 7 days	1				1			
> 7 days	0.62 (0.34–1.10)	0.104			0.59 (0.34–1.04)	0.071		
Weeks from surgery to APC								
≤ 6 weeks	1				1			
> 6 weeks	0.78 (0.46–1.33)	0.359			0.67 (0.40–1.15)	0.146		

RDI, relative dose intensity; CCI, Charlson comorbidity index; PS, performance status; AC, adenocarcinoma; SCC, squamous cell carcinoma; NSCLC, non-small cell lung cancer; APC, adjuvant platinum-based chemotherapy; HR, hazard ratio; CI, confidence intervals; *data show results of the univariate and multivariate Cox regression analyses.*

(Table 3). There was no correlation between number of cumulative delayed days in APC and CCI ($p = 0.68$). Significantly more patients experienced delay between APC cycles of more than seven days in the high RDI group compared to the low RDI group ($p < 0.01$) (Table 1). The median time interval between surgery and onset of APC was 39 days (range 11–137). There was no impact of delayed onset of APC > six weeks from surgery on neither DFS (HR: 0.78, 95%CI: 0.46–1.33, $p = 0.36$) nor OS (HR: 0.67, 95%CI: 0.40–1.15, $p = 0.15$) (Table 3). Likewise, there was no correlation between later onset of APC and RDI ($p = 0.52$) or CCI ($p = 0.36$) (Table 1). The survival analyses repeated by the landmark analysis method showed similar results (Appendix A.1, Table A.1).

4. Discussion

The role of RDI and timing of adjuvant chemotherapy after NSCLC surgery on survival is uncertain. The current study showed a significant association between low cisplatin RDI ≤ 75% and decreased DFS and OS, while chemotherapy onset beyond six weeks after surgery had no impact on survival.

Currently, there is no international consensus on the association between cisplatin dose, number of cycles, delays, dose reductions and the effect of APC on survival [8,17 25]. Moreover, there are conflicting reports regarding the optimal time to start chemotherapy after surgery [7-11]. The toxicity of APC is high, leading to frequent treatment discontinuation before the recommended four cycles and resulting in decreased RDI [4-6]. Our findings underscore this, as only one third of patients could receive > 90% of the recommended cisplatin RDI and less

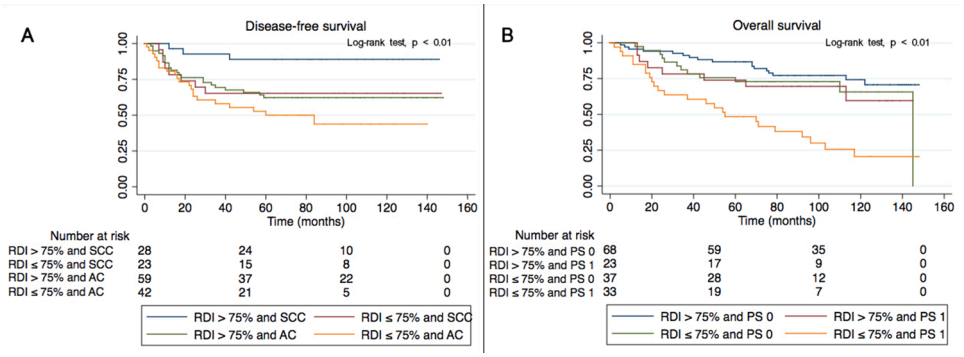

Fig. 2. Kaplan-Meier estimates of disease-free survival (2A) and overall survival (2B) in relation to relative dose-intensity and histopathological subtype (2A) and performance status (2B).

than one in ten were able to complete all four courses without treatment delay. A single study was published concerning dose levels of adjuvant chemotherapy in NSCLC, but only in stage II. The study showed improved OS in patients receiving more than 80% of the planned platinum dose, interpreted as four completed cycles [8]. Similarly, in the current study, patients that received cisplatin RDI $\leq$ 75% reflecting less than four recommended cycles, had an almost double risk of recurrence and death. It seems that completion of four APC cycles is crucial for long-term effect on survival. The comorbidity was comparable between the RDI groups and had no association with worse survival in the current cohort. This contradicts the previously mentioned study, where low CCI was related to improved OS after adjuvant chemotherapy [8]. However, our study concerns a broader population of NSCLC patients including stage I-III, but is limited to PS 0–1 with a relatively low comorbidity burden compared to the cited study [8]. Therefore, the results do not seem to be directly comparable.

The other important finding was the role of PS related to RDI and survival. A meta-analysis of recent APC studies showed a 5.4% improvement in 5-year survival [12], but was detrimental for PS $>$ 1 patients. Therefore, it is recommended, that APC should be reserved to patients with good PS [7, 12]. As expected, the current study showed that patients with PS 0 had a significantly longer OS compared to patients with PS 1. However, high RDI had no influence on survival of patients with PS 0. Interestingly, patients with baseline PS 1 did significantly worse when receiving less than the four recommended courses, while those who were able to complete four cycles of APC, had comparable OS with PS 0 patients (Fig. 2B). It can be speculated that some PS 1 patients may have more aggressive or even microscopic disease compared with PS 0 patients and therefore gain survival benefit by higher cisplatin RDI [26].

The DFS was longer in SCC compared to AC in line with other studies of APC in NSCLC [4,27]. Notably, the risk of recurrence was significantly lower in SCC subgroup treated with high versus low RDI. This was not observed in AC subgroup, possibly suggesting a higher sensitivity of SCC to APC. Study of biomarkers identifying a subgroup of patients that could benefit from adjuvant chemotherapy showed that the excision repair cross-complementation group 1 (ERCC1) protein could have a role in sensitivity to APC [28]. Patients with ERCC1-negative tumours had survival benefit from APC [29], mainly in relation to DFS [30]. However, conflicting results from other studies could not confirm the ERCC1 as a clinically useful biomarker [28]. The biological mechanisms behind the effect of APC are still obscure and further studies concerning the sensitivity to APC in histopathological subgroups of NSCLC are warranted.

The 5-year DFS and OS of all patients in the current study was 59% and 73%, similar to other randomised trials using APC in comparable patient population [4,5]. In other reports, the survival was shorter [6, 31], possibly due to variations in inclusion criteria, patient population, APC adjustment in case of toxicities and follow-up strategy. Interestingly, there was a decrease in 10-year OS reflecting the persistent risk of death from lung cancer beyond five years after the diagnosis [32]. As expected, TNM stage was an independent prognostic factor influencing the DFS and OS [21].

Delay of subsequent cycles due to toxicity impacts the calculation of RDI and could affect the survival of patients receiving APC. However, there are no studies available on this particular point concerning NSCLC. According to the Norton–Simon hypothesis [33], the rate of death of cancer cells responding to treatment is directly proportional to the rate of growth of tumour cells during the treatment. Based on this theory, a mathematical model for the effect of cytotoxic chemotherapy was proposed, determined on dose and treatment time. In theory, treatment delay may be detrimental for the effect of chemotherapy as well as the effect of chemotherapy may also be reduced after dose reduction. The current study shows that cumulative delay of more than seven days between APC cycles did not seem to have a negative impact on survival, while a lower RDI had. There was a significantly higher number of delayed days between the APC cycles in the high RDI compared to low RDI group. However, the higher number of received cycles was not accompanied by dose reductions. These findings suggest that in case of toxicity, one should consider a few days of delay between the APC cycles rather than dose reduction of chemotherapy. Continuing the treatment without dose reduction after a short delay would not significantly influence the RDI and still maintain the survival benefit of APC.

The median time between surgery and APC was 39 days which is comparable to other reports [12-14]. The European Society for Medical Oncology (ESMO) guidelines recommend start of APC within 42 days after surgery [7]. However, there are several studies with conflicting results. One study showed that there was no survival benefit in stage II NSCLC patients receiving APC earlier than 42 days [8], while another study failed to show any significant association between time to APC and survival [10]. A retrospective study based on 12.473 patients concerning mainly stage II NSCLC, found no impact of delayed APC given 57–127 days after surgery [9]. In contrast, another study showed that delay of more than 60 days from surgery to APC was associated with significantly worse 5-year OS [11]. Interestingly, it seems that too early administration of APC is not beneficial. The same study showed increased survival in a group of patients receiving adjuvant chemotherapy 30–45 days after surgery compared to $<$ 30 days [11]. These analyses of survival differences did not include PS and comorbidity of the treated population and none of the mentioned studies involved RDI calculations. The results of our study showed no influence of delayed APC onset on survival. Patients treated within six weeks received a similar RDI compared to patients that started APC later than six weeks from NSCLC surgery.

The strengths of this study are the detailed data of the NSCLC population of one institution treating patients in a homogenous approach, with well-defined criteria concerning the required PS and CCI for the APC treatment. Furthermore, the detailed information of chemotherapy dose and timing from the real-time registry allowed to collect

scrutinized APC-related information. The long observation time of more than 5 years for all patients, and no patients lost to follow-up, reflected the real-life population of radically operated NSCLC patients treated with APC. The associations between survival and treatment delay of APC as well as RDI were investigated using both the standard survival analyses and the landmark method [23]. This allowed to exclude a possible bias and confirmed the survival benefit analysed by the standard method. The limitations of the study are the retrospective design, the relatively small cohort, and insufficient follow-up toxicity data, mainly regarding non-haematological adverse events, that caused cisplatin RDI modifications. The role of vinorelbine RDI was not analysed in this study.

5. Conclusions

Low cisplatin RDI ($\leq$ 75%) was associated with significantly shorter DFS and OS in NSCLC patients treated with APC. There was a significant association between low cisplatin RDI and inferior DFS in patients operated for SCC. Low cisplatin RDI was associated with shorter OS in patients with PS 1. Neither extended time from surgery to APC initiation beyond six weeks nor the number of delayed days between the APC cycles were associated to survival.

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2021.100318.

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