의학 석사학위 논문

Comparison of adjuvant chemotherapy followed by concurrent chemoradiotherapy versus sequential radiochemotherapy in patients with completely resected non-small cell lung cancer

아 주 대 학 교 대 학 원

의학과/의학전공

김 환 익

Comparison of adjuvant chemotherapy followed by concurrent chemoradiotherapy versus sequential radiochemotherapy in patients with completely resected non-small cell lung cancer

지도교수 오 영 택

이 논문을 의학 석사학위 논문으로 제출함.

2017년 8월

아 주 대 학 교 대 학 원

의학과/의학전공

김 환 익

김환익의 의학 석사학위 논문을 인준함.

심사위원장 오 영 택 인

심 사 위 원 전 미 선 인

심 사 위 원 노 오 규 인

아 주 대 학 교 대 학 원

2017년 7월 14일

감사의 글

2012년 가을 무렵, 처음 아주대학교병원 방사선종양학과에 아무 연고도 없이 오로지 인터넷 검색만으로 병원에 대한 정보를 알아보고 전공의에 지원하던 때가 생각납니다. 경희대학교 의대를 졸업하고 경희대학교병원에서 인턴생활을 하면서 방사선종양학과에 지원하기로 마음을 먹고 모병원에는 방사선종양학과 전공의TO가 있지 않아, 외부병원을 알아보고 지원한 저로서는 아주대병원에 아무런 연고가 없었기에 새로운 도전을 시작함에 있어서 두려움과 설렘이 공존할 수 밖에 없었는데, 그 시기에 저를 잘 이끌어주었던 오영택 과장님 덕분에 저는 무사히 전공의생활에 안착하여 적응할 수 있었습니다.

2013년 봄부터 전공의 생활을 시작하면서 초반에 같은 파트에 배정되어 대부분의 일과시간을 함께하며 과생활에 빠른 적응을 할 수 있도록 도움을 주었던 전미선 교수님께도 감사의 말씀을 전합니다. 제일 주니어 교수님으로서 과에 많은 시간을 있으면서 실질적으로 전공의들의 학문활동 및 논문작업에 가장 도움을 많이 주었던 노오규 교수님께도 큰 감사의 말을 전하고 싶습니다. 위 교수님들의 헌신적인 도움이 없었다면 많이 부족한 저로서는 전공의 생활 및 학문활동을 무사히 마치기 힘들었을 것으로 생각됩니다.

그리고 같이 전공의생활을 하면서 실무에 있어서 실제적인 도움과 조언을 많이 해주신 조오연 선생님, 허재성 선생님에게도 감사의 말을 전하고 싶습니다. 지금은 전공의생활을 끝마치고 조교수 및 임상강사의 길을 걷고 있는데 앞으로 나아가는 길에 있어 무궁무진한 영광이 있기를 바랍니다. 대학원 생활과 병원 생활을 병행하는데 있어서 큰 무리가 없도록 지지해준 아주대학교병원 방사선종양학과 식구들에게도 감사의 마음을 전합니다.

마지막으로 자식으로서의 도리를 잘 수행하지 못하고 있지만 부족한 저를 물심양면으로 지지해주는 부모님께도 감사의 마음을 전하며, 고려대학교 진학 후 아직 자리를 제대로 잘 잡지는 못했지만 노력중인 동생에게 이 자리를 빌어 응

원의 말을 전합니다. 결혼한 이후 옆에 붙어 있으면서 조언과 함께 기댈 수 있는 심적인 언덕이 되어주는 아내에게도 감사의 말을 전합니다. 앞으로 더 노력하여 기대에 부응할 수 있는 사람이 되도록 하겠습니다. 다시 한번 인사드리며 글을 마칩니다. 감사합니다 !

김환익 올림.

– 영문초록 –

Comparison of adjuvant chemotherapy followed by concurrent chemoradiotherapy versus sequential radiochemotherapy in patients with completely resected non-small cell lung cancer

Purpose : Our institution has executed two different kinds of adjuvant protocols in treating patients with non-small cell lung cancer (NSCLC): 1) chemotherapy followed by concurrent chemoradiotherapy (CTx-CCRT) and 2) sequential postoperative radiotherapy (PORT) followed by postoperative chemotherapy (POCT) (i.e. RT-CT). This study is targeted to compare the clinical outcomes between the two adjuvant protocols.

Materials and Methods : From March 1997 to October 2012, 68 patients were treated with CTx-CCRT (n = 25) and RT-CT (n = 43). The CTx-CCRT protocol consisted of 2 cycles of cisplatin-based POCT followed by PORT concurrently with 2 cycles of POCT. The RT-CT protocol consisted of PORT followed by 4 cycles of cisplatin-based POCT. PORT was implemented with conventional fractionations of 50.4 - 60 Gy dose. We compared the outcomes between the two adjuvant protocols and studied about the clinical factors affecting survivals.

Results : Median follow-up time was 43.9 months (range 3.2 - 74.0), and the 5-year overall survival (OS), locoregional recurrence-free survival (LRFS), and distant

metastasis-free survival (DMFS) were 53.9%, 68.2%, and 51.0%, respectively. There were no significant differences in OS (p = 0.074), LRFS (p = 0.094), and DMFS (p = 0.490) between the two protocols. In multivariable analyses, adjuvant protocol remained as a significant prognostic factor for LRFS, favouring CTx-CCRT (HR = 3.506, p = 0.046) over RT-CT, not for OS (HR = 0.647, p = 0.229).

Conclusions : CTx-CCRT protocol increased LRFS more than RT-CT protocol in patients with completely resected NSCLC, but not in OS. Further studies are warranted to evaluate the benefit of CTx-CCRT strategy compared with sequential strategy.

핵심어 : Non-small-cell lung carcinoma, Adjuvant chemotherapy, Adjuvant radiotherapy, Sequence of therapies

목 차

그림 목차

표 목차

I. Introduction

Since surgery alone is not a satisfactory strategy for the treatment of non-small cell lung cancer (NSCLC), adjuvant treatment with postoperative chemotherapy (POCT) and postoperative radiotherapy (PORT) is usually recommended to patients. Cisplatin-based POCT is the standard of care for stage II-III NSCLC patients who undergo complete resection [1, 2]. However, the benefit of PORT has been an issue of debate. A meta-analysis showed that while PORT significantly lowered local recurrence, it had a detrimental effect on survival [3]. However, such harmful effect on survival can be attributed to old-fashioned radiotherapy techniques with increased cardiopulmonary toxicity. Modern radiotherapy using linear accelerator can improve local control and survival [4]. A large-scaled retrospective study using data set of Surveillance, Epidemiology, and End Results (SEER) reported a survival benefit of PORT for N2 disease [5]. The Adjuvant Navelbine International Trialist Association (ANITA) trial also showed a potential benefit of PORT for N2 disease in the setting of POCT [6]. Recently, a review of the data from the National Cancer Data Base (NCDB) showed additional survival benefit of PORT in patients with N2 disease who received adjuvant chemotherapy [7-9]. Therefore, PORT can be considered as an adjuvant

therapy after POCT in patients with N2 disease with complete resection as well as those with a close or positive resection margin status.

In October 1996, before POCT became a standard of care for stage II-III NSCLC, adjuvant chemotherapy followed by concurrent chemoradiotherapy (CTx-CCRT) was established as an institutional protocol for patients showing pathologic N1-2 disease (mainly N2) and in patients with close or positive resection margin. After POCT became a standard of care, sequential PORT followed by POCT (RT-CT) has been a routine protocol in our institution with a consensus of a multidisciplinary team [10].

In cases where both POCT and PORT are administered after surgery, the optimal way of combining these two therapies has not been discovered. We aimed to compare the clinical outcomes between our two historical protocols (CTx-CCRT versus RT-CT) in this study.

II. Methods and Materials

By using our institutional tumor registry database, we chose 68 patients who underwent both PORT and POCT after complete surgical resection for NSCLC between 1997 and 2012. Chest computed tomography (CT), bronchoscopy, enhanced brain CT or magnetic resonance imaging (MRI), and bone scan or positron emission tomography (PET) were routinely performed for staging workup. Lobectomy or pneumonectomy with mediastinal lymph node dissection were performed in patients with clinical N0-1 or single-station minimal N2 disease. Pathologic stages were graded according to the 7th edition of AJCC TNM classification.

PORT was administered to patients with pathologic N1-2 disease (mainly N2) and positive or close resection margins. Before year 2002, PORT was performed using the conventional 2-dimensional technique (2D-RT) with megavoltage beams (≥ 6 MV). Initial anterior/posterior – posterior/anterior fields included an ipsilateral hilum and involved lymph nodal stations plus its next close draining stations, and doses of 30.6 – 41.4 Gy using conventional fractionations (1.8 – 2.0 Gy/day) were irradiated. Two off-cord oblique fields were implemented to boost the ipsilateral hilum and involved nodal stations with a dose up

to 50.4 – 60.0 Gy. After 2002, 3-dimensional conformal radiation therapy (3D-CRT) was adopted using mega-voltage photon beam. For 3D-CRT, CT simulation was scanned under the free-breathing condition. The initial clinical target volume (CTV) included a bronchial stump, involved mediastinal lymph nodal stations, and its next draining stations. The boost CTV only included a bronchial stump and involved nodal stations. The planning target volume (PTV) was expanded in all directions from the CTV with a margin of 1.0 – 1.5 cm. Conventional fractionation was used with a dose of 44 – 45 Gy for initial volume, and the boost volume was irradiated up to 50.4 – 60.0 Gy. In case of a close resection margin (less than 5 mm), the region of the close margin was boosted up to doses of 66 Gy.

POCT was administered in patients with pathologic stage II/III according to our institutional protocols. 1) CTx-CCRT protocol (adjuvant chemotherapy followed by concurrent chemoradiotherapy): Two cycles of cisplatin-basted chemotherapy were administered, followed by PORT concurrently with two cycles of chemotherapy [11]. 2) RT-CT protocol (sequential PORT followed by POCT): PORT was administered within 4 – 6 weeks after surgery, followed by 4 cycles of cisplatin-based adjuvant chemotherapy [10].

To analyze comorbidity, we calculated an age-adjusted Charlson comorbidity score by using of previous established International Classification of Disease-10 diagnosis codes from

inpatient and outpatient records - from the time of first visit of each patient to the date of surgical resection [12].

We then assessed the pattern of first failures and clinical parameters influencing locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS) and overall survival (OS). We compared the pattern of first failures and survivals between CTx-CCRT and RT-CT protocols. Comparison between the two protocols was analyzed using a chi-square test or Fisher's Exact Test for categorical variables and the Student's t-test or the Mann-Whitney U test for continuous variables. Survival time was calculated by the interval between the date of the surgery and the date of the last follow-up or events (death event for OS, first loco-regional failure for LRFS, and first distant metastasis for DMFS). Survivals were calculated using the Kaplan-Meier method. The log-rank test and Cox proportional hazards regression model was used for univariate and multivariate analyses, respectively. Factors with a p-value of less than 0.2 by a univariate analysis were used for a multivariate analysis. Two-sided p-values less than 0.05 were regarded as statistically significant. All statistical analyses were performed using R statistical packages [13]. This study was reviewed and approved by the institutional review board of our institution.

III. Results

Among a total of 68 patients, 45 (66.2%) patients were males and the median age was 58 years (range, 30 – 69). The CTx-CCRT and RT-CT protocols were executed in 25 (36.8%) and 43 patients (63.2%), respectively. The types of surgery included lobectomy in 53 patients (77.9%) and pneumonectomy in 15 (22.1%). Squamous cell carcinoma and adenocarcinoma were observed in 36 patients (52.9%) and 24 patients (35.3%), respectively. The pathologic nodal stages were N1 in 15 patients (22.1%) and N2 in 51 patients (75.0%), while 2 patients with pN0 disease showed a close resection margin of less than 5 mm. Median dose of PORT was 54.0 Gy (range, 39.6 – 64.4) and median cycle of POCT was 4 (range, 2 – 6).

Patient characteristics for CTx-CCRT and RT-CT protocols are summarized in Table 1. There were no significant differences in proportions of gender, history of smoking, comorbidity index, tumor histology, type of surgery, T-stage and N-stage between the two protocols. Age of the patients in the CT-CCRT protocol was significantly older than that of patients in the RT-CT protocol (mean age, 58.7 versus 52.9, $p = 0.025$). The proportion of patients showing ECOG PS 2 in the RT-CT protocol was significantly higher than that of patients in the CT-CCRT protocol (0% versus 14.0%, $p = 0.050$). The absolute value of

preoperative FEV1 in the RT-CT protocol was significantly higher than that of the CT-CCRT protocol (mean FEV1, 2.2 L versus 2.7 L, p = 0.002). The postoperative FEV1 was available in 35 patients (51.5%) and there was no significant difference between the two protocols. 21 patients (84.0%) who underwent the CT-CCRT protocol were treated by 2-D RT, while 42 patients (97.7%) who received the RT-CT protocol were treated with 3-D RT. Radiation was delivered with a significantly higher dose in the RT-CT protocol compared to that in the CT-CCRT protocol (mean dose, 52.8 Gy versus 55.8 Gy, p = 0.013). The median POCT cycle was 4 in both protocols. Mild to moderate grade radiation esophagitis was found in 2 patients (8.0%) for the CTx-CCRT protocol, and in 11 patients (25.6%) for the RT-CT protocol (p = 0.145). The rate of symptomatic radiation pneumonitis treated with steroid was not significantly different between the two protocols (24.0% versus 9.3%, p = 0.195). The hematologic toxicities of grade 3 – 4 was also not significantly different between the two protocols (20.0% versus 46.5%, p = 0.054). Comparing the pattern of first failures, there were no significant differences in locoregional recurrence (LR), distant metastasis (DM), and both LR and DM between the two protocols (Table 2).

The median follow-up time of 68 patients was 43.9 months (range 3.2 – 74.0), and the OS was 53.9% at 5 years. The 5-year LRFS and DMFS were 68.2% and 51.0%, respectively.

Patients with CTx-CCRT protocol showed favourable LRFS, but showed unfavourable OS compared to the RT-CT protocol (5-year LRFS, 82.8% versus 60.3%, p = 0.094; 5-year OS, 44.0% versus 61.3%, p = 0.074). The DMFS between the two protocols showed no significant difference (5-year DMFS, 53.3% versus 46.4%, p = 0.490) (Table 3).

Univariate analyses for clinical variables influencing survival are presented in Table 3. There wer no significant factors affecting OS, LRFS, and DMFS. The age at diagnosis (< 58 versus ≥ 58) and comorbidity index (< 2 versus ≥ 2) were found to be marginally significant factors affecting OS (age, p = 0.072; comorbidity index, p = 0.081). Male patients showed favorable trend compared to female patients in LRFS (p = 0.071) and DMFS (p = 0.084).

The results of multivariate analysis are summarized in Table 4. There was no significant variable affecting on DMFS and OS (Fig. 1A and 1C). Adjuvant protocol (CTx-CCRT versus RT-CT) remained as a statistically significant prognostic factor for LRFS (HR = 3.506, p = 0.046) (Fig. 1B).

Table 1. Patient characteristics according to treatment protocols

Characteristic	CT-CCRT (n = 25)	RT-CT (n = 43)	*p-value*
Age (year)			0.025
Mean ± SD	58.7 ± 8.4	52.9 ± 10.7	
Gender			0.106
Male	13	32	
Female	12	11	
Smoking history			0.579
Yes	10	13	
No	15	30	
ECOG PS			0.050
0-1	25	37	
2	0	6	
Comorbidity index			0.206
< 3	13	29	
≥ 3	12	14	
Preoperative FEV1 (L)			0.002
Mean ± SD	2.2 ± 0.5	2.7 ± 0.7	
Postoperative FEV1 (L)*			0.718
Mean ± SD	2.2 ± 0.9	2.0 ± 0.6	
Tumor histology			0.694
Squamous cell	13	23	
Adenocarcinoma	10	14	
Others	2	6	
Type of surgery			0.550
Lobectomy	18	35	
Pneumonectomy	7	8	
Pathologic T stage			0.347
T1	5	4	
T2	13	29	
T3	7	10	
Pathologic N stage			0.095
N0	2	0	
N1	7	8	

N2	16	35	
Radiotherapy Technique			< 0.001
2-dimensional	21	1	
3-dimensional	4	42	
Radiotherapy dose (Gy)			0.013
Mean ± SD	52.8 ± 5.5	55.8 ± 4.3	

CT-CCRT, adjuvant chemotherapy followed by concomitant chemoradiotherapy; RT-CT, sequential postoperative radiotherapy followed by adjuvant chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; FEV1, forced expiratory volume in 1 second.

*Postoperative FEV1 was available in 35 patients (51.5%).

Table 2. Pattern of first failures according to treatment protocols

First failure site	CT-CCRT (n = 25) No. of patients (%)	RT-CT (n = 43) No. of patients (%)	*p-value*
Locoregional (LR)	0 (0.0)	2 (4.7)	0.528
Distant metastasis (DM)	6 (24.0)	7 (16.3)	0.527
Both LR and DM	4 (16.0)	13 (30.2)	0.251

CT-CCRT, adjuvant chemotherapy followed by concomitant chemoradiotherapy; RT-CT, sequential postoperative radiotherapy followed by adjuvant chemotherapy

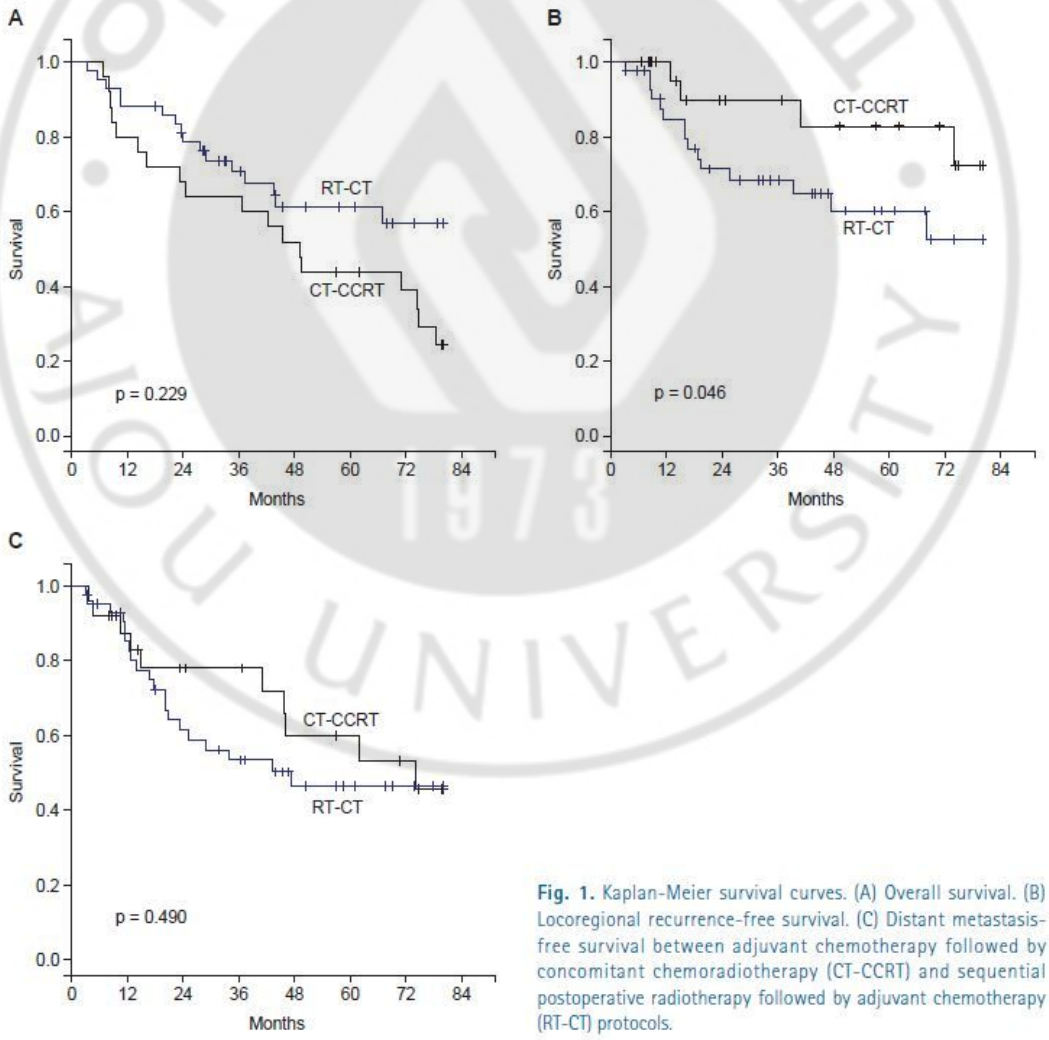

Fig. 1. Kaplan-Meier survival curves. (A) Overall survival. (B) Locoregional recurrence-free survival. (C) Distant metastasis-free survival between adjuvant chemotherapy followed by concomitant chemoradiotherapy (CT-CCRT) and sequential postoperative radiotherapy followed by adjuvant chemotherapy (RT-CT) protocols.

Table 3. Univariable analyses for clinical variables affecting survivals

Variable	5-year LRFS (%)	p-value (log-rank)	5-year DMFS (%)	p-value (log-rank)	5-year OS (%)	p-value (log-rank)
Age (< 58 vs. ≥ 58)	68.6 vs. 67.2	0.632	50.0 vs. 52.0	0.793	65.3 vs. 43.3	0.072
Gender (male vs. female)	73.0 vs. 59.4	0.071	55.3 vs. 42.7	0.084	53.6 vs. 54.6	0.855
Smoking history (no vs. yes)	65.3 vs. 69.5	0.223	48.0 vs. 52.0	0.233	60.8 vs. 50.7	0.472
ECOG PS (0-1 vs. 2)	69.3 vs. 53.3	0.188	54.7 vs. 0.0	0.174	53.4 vs. 62.5	0.955
Comorbidity index (< 2 vs. ≥ 2)	62.8 vs. 70.4	0.873	51.5 vs. 50.6	0.861	66.2 vs.49.4	0.081
Preoperative FEV1 (< 2.5 L vs. ≥ 2.5 L)	64.3 vs. 73.8	0.189	47.5 vs. 57.5	0.407	46.7 vs. 61.9	0.378
Surgery (lobectomy vs. pneumonectomy)	65.3 vs. 82.5	0.375	49.5 vs. 54.5	0.961	56.0 vs. 45.7	0.242
Tumor histology (squamous vs. others)	63.7 vs. 74.1	0.297	42.7 vs. 61.5	0.165	55.3 vs. 51.6	0.786
Pathologic T stage (1-2 vs. 3)	69.4 vs. 63.5	0.747	54.8 vs. 41.7	0.612	55.9 vs. 49.3	0.573
Pathologic N stage (0-1 vs. 2)	67.0 vs. 68.7	0.424	44.7 vs. 52.8	0.835	50.4 vs. 55.2	0.999
Radiation dose (< 54 Gy vs. ≥ 54 Gy)	72.2 vs. 64.4	0.548	59.0 vs. 44.9	0.675	51.2 vs. 56.1	0.885
Protocol (CT-CCRT vs. RT-CT)	82.8 vs. 60.3	0.094	59.9 vs. 46.4	0.490	44.0 vs. 61.3	0.074

LRFS, locoregional recurrence-free survival; DMFS, distant metastasis-free survival; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status; FEV1, forced expiratory volume in 1 second; CT-CCRT, adjuvant chemotherapy followed by concomitant chemoradiotherapy; RT-CT, sequential postoperative radiotherapy followed by adjuvant chemotherapy

Table 4. Multivariable analyses for clinical variables affecting survivals

Variable	*LRFS*			*DMFS*			*OS*		
	HR	*95% CI*	*p-value*	*HR*	*95% CI*	*p-value*	*HR*	*95% CI*	*p-value*
Age (< 58 vs. ≥ 58)							1.284	0.535 – 3.082	0.575
Gender (male vs. female)	2.525	0.827 – 7.712	0.104	1.525	0.647 – 3.592	0.334			
ECOG PS (0-1 vs. 2)	0.754	0.183 – 3.100	0.696	1.567	0.504 – 4.867	0.430			
Comorbidity index (< 2 vs. ≥ 2)							1.594	0.532 – 4.772	0.405
Preoperative FEV1 (< 2.5 L vs. ≥ 2.5 L)	0.581	0.195 – 1.720	0.326						
Tumor histology (squamous vs. others)				0.775	0.315 – 1.909	0.580			
Protocol (CT-CCRT vs. RT-CT)	3.506	1.020 – 12.053	0.046				0.647	0.318 – 1.315	0.229

LRFS = locoregional recurrence-free survival; DMFS = distant metastasis-free survival; OS = overall survival; HR = hazard ratio; CI = confidence interval; POCT = postoperative chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; FEV1, forced expiratory volume in 1 second; CT-CCRT, adjuvant chemotherapy followed by concomitant chemoradiotherapy; RT-CT, sequential postoperative radiotherapy followed by adjuvant chemotherapy

IV. Discussion

In this study, we compared the outcomes of two historic institutional protocols (CTx-CCRT versus RT-CT) in patients with completely resected NSCLC, and our results showed that the CTx-CCRT protocol has statistically significant favorable prognostic value in LRFS compared with the RT-CT protocol, while there were no significant differences in OS or DMFS. Patient characteristics were not different between two protocols except age, ECOG PS, preoperative FEV1, radiotherapy technique and radiation dose (Table 1). Although preoperative FEV1 was significantly different (mean, 2.2 L versus 2.7 L, $p = 0.002$), postoperative FEV1, which could have a significant effect on OS [14], was not different between the two protocols. The age of patients in the CT-CCRT protocol was older than that of RT-CT protocol (mean, 58.7 versus 52.9, $p = 0.025$) and this may have negatively affected the outcomes in patients treated with the CT-CCRT protocol. However, age was not a prognostic factor for survivals in both univariate and multivariate analyses. The higher proportion of ECOG PS 2 may have influenced the poorer outcome of the RT-CT protocol, but it also did not show prognostic values (Table 3, 4). Radiation was more irradiated in RT-CT protocol than CTx-CCRT protocol, due to the different proportion of RT-techniques used in the protocols. In the clinical setting, the dose difference of 3 Gy did not seem to be

significant (mean, 52.8 Gy versus 55.8 Gy, p = 0.013).

Our CTx-CCRT protocol had been adopted during a time before POCT became a standard of care (from October 1996 to mid-2005). But, the RT-CT protocol, which was established in mid-2005, has been implemented as a current active protocol in our institution. Considering the variety of developments in chemotherapy and radiotherapy over time, the recent RT-CT protocol should have showed superior outcomes compared to that of the old CTx-CCRT protocol. However, the two protocols did not show significant differences in OS and DMFS. Rather, the CTx-CCRT protocol showed superior outcomes compared to the RT-CT protocol in controlling locoregional disease, despite CCRT protocol having mainly adopted 2D-RT (Fig 1B) (Table 4). These results suggest that the CT-CCRT protocol can be effective in controlling locoregional disease, which may lead to a potential OS benefit.

Although its use has been an issue of debate, PORT can be administered in patients with N2 disease based on several large-scale population-based studies which favored the use of PORT even in the era of POCT [5, 8, 9]. When PORT is determined to be implemented in the clinical setting, the way of combining PORT with POCT can become an important issue in order to maximize the effect of adjuvant therapies. Currently, POCT followed by PORT is generally accepted when combining two adjuvant therapies due to concrete evidence in

supporting the survival benefit of POCT. However, the POCT-first strategy may delay the start of PORT by more than 4-5 months after surgery. Considering the relatively high locoregional tumor burden compared to that of systemic metastasis and the better response rate of radiation therapy than chemotherapy, delaying PORT may lead to the loss of opportune timing in controlling locoregional residual tumors. In the strategy of PORT-first, POCT can be started within 3 months after surgery due to the shorter treatment time of PORT (5-6 weeks) compared to that of POCT (12-16 weeks). Our RT-CT protocol reflected such rationales, and we reported that the outcomes of PORT-first strategy were comparable to those of the POCT-first strategy, while also preserving the survival benefit of POCT [10]. In this context, concurrent execution of PORT and POCT (CCRT) can be an ideal way to combine two adjuvant therapies and it can also minimize the delay time of both PORT and POCT. Locoregional control can be achieved more effectively by radio-sensitization. This benefit, however, can be offset by increases in treatment-related complications. The results of this study show the improved LRFS of the CTx-CCRT protocol compared to the RT-CT protocol without any apparent increases in complications. Although these results may not represent all complications, several other studies adopting the CCRT protocol report its comparable outcomes and acceptable complication profiles [15-19]. Shen et al. reported an

early closed randomized trial comparing POCT versus POCRT (postoperative concurrent chemoradiotherapy) [20]. This trial showed that POCRT increased both locoregional and distant disease free survival rate compared with POCT alone in patients with IIIA-N2 NSCLC. However, there was no increase of OS rate in POCRT. Although there have been no definite studies supporting the benefit of adjuvant CCRT, the tendency of increased LRFS or DFS suggests the need of a large-scaled randomized trial evaluating the OS benefit comparing CCRT with POCT alone or sequential RT-CT/CT-RT strategies in patients with IIIA-N2 disease.

The results of this study are limited because of the comparisons between two protocols were performed consecutively in our institution. This study is also limited by a small sample size, heterogeneous study population (including pN1 disease), and single-institutional retrospective study design. However, despite these limitations, the results of this study suggest again the potential role of adjuvant CCRT in locoregional tumor control.

In conclusion, CTx-CCRT protocol increased LRFS compared to RT-CT protocol in patients with completely resected NSCLC, but not in OS and DMFS. Further large-scaled randomized studies are warranted to evaluate the benefit of CCRT strategy compared with sequential CT-RT or RT-CT strategy.

V. References

[1] Douillard JY, Rosell R, De Lena M, Carpagnano F, Ramlau R, Gonzales-Larriba JL, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol. 2006;7:719-27.

[2] Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008;26:3552-9.

[3] Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group. Lancet. 1998;352:257-63.

[4] Billiet C, Decaluwe H, Peeters S, Vansteenkiste J, Dooms C, Haustermans K, et al. Modern post-operative radiotherapy for stage III non-small cell lung cancer may improve local control and survival: a meta-analysis. Radiother Oncol. 2014;110:3-8.

[5] Lally BE, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. J Clin Oncol. 2006;24:2998-3006.

[6] Douillard JY, Rosell R, De Lena M, Riggi M, Hurteloup P, Mahe MA, et al. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. Int J Radiat Oncol Biol Phys. 2008;72:695-701.

[7] Corso CD, Rutter CE, Wilson LD, Kim AW, Decker RH, Husain ZA. Re-evaluation of the role of postoperative radiotherapy and the impact of radiation dose for non-small-cell lung cancer using the National Cancer Database. J Thorac Oncol. 2015;10:148-55.

[8] Mikell JL, Gillespie TW, Hall WA, Nickleach DC, Liu Y, Lipscomb J, et al. Postoperative radiotherapy is associated with better survival in non-small cell lung cancer with involved N2 lymph nodes: results of an analysis of the National Cancer Data Base. J Thorac Oncol. 2015;10:462-71.

[9] Robinson CG, Patel AP, Bradley JD, DeWees T, Waqar SN, Morgensztern D, et al. Postoperative radiotherapy for pathologic N2 non-small-cell lung cancer treated with adjuvant chemotherapy: a review of the National Cancer Data Base. J Clin Oncol. 2015;33:870-6.

[10] Lee HW, Noh OK, Oh YT, Choi JH, Chun M, Kim HI, et al. Radiation Therapy-First

Strategy After Surgery With or Without Adjuvant Chemotherapy in Stage IIIA-N2 Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2016;94:621-7.

[11] Jeong SH, Lee HW, Han JH, Kang SY, Choi JH, Jung YM, et al. Low expression of Bax predicts poor prognosis in resected non-small cell lung cancer patients with non-squamous histology. Jpn J Clin Oncol. 2008;38:661-9.

[12] Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol. 2004;57:1288-94.

[13] R Development Core Team. R: A language and environment for the statistical computing, R Foundation for Statistical Computing, Vienna, Austria. URL https://www.r-project.org/. 2016.

[14] Kim H, Lussier YA, Noh OK, Li H, Oh YT, Heo J. Prognostic implication of pulmonary function at the beginning of postoperative radiotherapy in non-small cell lung cancer. Radiother Oncol. 2014;113:374-8.

[15] Keller SM, Adak S, Wagner H, Herskovic A, Komaki R, Brooks BJ, et al. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung cancer. Eastern Cooperative Oncology Group. N Engl J Med.

2000;343:1217-22.

[16] Bradley JD, Paulus R, Graham MV, Ettinger DS, Johnstone DW, Pilepich MV, et al. Phase II trial of postoperative adjuvant paclitaxel/carboplatin and thoracic radiotherapy in resected stage II and IIIA non-small-cell lung cancer: promising long-term results of the Radiation Therapy Oncology Group--RTOG 9705. J Clin Oncol. 2005;23:3480-7.

[17] Wakelee HA, Stephenson P, Keller SM, Wagner H, Herskovic A, Komaki R, et al. Post-operative radiotherapy (PORT) or chemoradiotherapy (CPORT) following resection of stages II and IIIA non-small cell lung cancer (NSCLC) does not increase the expected risk of death from intercurrent disease (DID) in Eastern Cooperative Oncology Group (ECOG) trial E3590. Lung Cancer. 2005;48:389-97.

[18] Feigenberg SJ, Hanlon AL, Langer C, Goldberg M, Nicolaou N, Millenson M, et al. A phase II study of concurrent carboplatin and paclitaxel and thoracic radiotherapy for completely resected stage II and IIIA non-small cell lung cancer. J Thorac Oncol. 2007;2:287-92.

[19] Lee HC, Kim YS, Oh SJ, Lee YH, Lee DS, Song JH, et al. The single institutional outcome of postoperative radiotherapy and concurrent chemoradiotherapy in resected non-small cell lung cancer. Radiat Oncol J. 2014;32:147-55.

[20] Shen WY, Ji J, Zuo YS, Pu J, Xu YM, Zong CD, et al. Comparison of efficacy for postoperative chemotherapy and concurrent radiochemotherapy in patients with IIIA-pN2 non-small cell lung cancer: an early closed randomized controlled trial. Radiother Oncol. 2014;110:120-5.

- 국문초록 -

비소세포폐암 환자에서 수술 후 동시항암화학요법과 순차적 방사선화학요법의 비교연구

목적 : 우리 병원에서는 비소세포폐암 환자들을 대상으로 2 가지의 다른 보조치료 프로토콜을 시행하였다 : 1)항암제 이후 동시항암방사선요법 시행 (CTx-CCRT) 그리고 2)순차적으로 수술 후 방사선치료 시행 이후 항암치료 시행 (i.e. RT-CT). 이 연구는 이 2 가지 보조치료 프로토콜의 임상 결과를 분석비교하는 것이다.

연구대상 및 방법 : 1997 년 3 월부터 2012 년 10 월까지 25 명의 CTx-CCRT 치료 환자와 43 명의 RT-CT 환자 그룹을 선정하였다. CTx-CCRT 프로토콜에서는 2 사이클의 시스플라틴 기반의 항암치료 시행 이후 방사선치료와 함께 동시항암화학요법 2 사이클을 시행하였다. RT-CT 프로토콜에서는 수술 후 방사선치료 이후 4 사이클의 시스플라틴 기반의 항암치료를 시행하였다. 수술 후 방사선치료는 통상분할조사 방법으로 50.4 - 60 Gy 의 선량을 시행하였다. 우리는 2 가지 프로토콜 그룹의 결과를 비교하며 생존율에 영향을 미치는 임상적 인자에 대해 분석해보았다.

결과 : 중앙 추적기간은 43.9 개월이었고 (범위 3.2 - 74.0), 5 년 전체 생존율, 무국소재발생존율, 무원격전이생존율은 각각 53.9%, 68.2%, 51.0% 였다. 2 가지

프로토콜간에 전체생존율 (p = 0.0.74), 무국소재발생존율 (p = 0.094), 무원격전이생존율 (p = 0.490) 에서의 유의미한 차이는 없었다. 다변수 분석에서 CTx-CCRT 프로토콜 시행군이 RT-CT 군에 비해서 무국소재발생존율 (위험비 = 3.506, p = 0.046) 향상에 유의미한 좋은 예후 인자가 되는 것을 확인할 수 있었지만, 전체생존율 (위험비 = 0.647, p = 0.229)에는 유의미한 차이를 보이지 못했다.

결론 : 완전절제된 비소세포폐암환자들에서 CTx-CCRT 프로토콜은 RT-CT 프로토콜에 비해 무국소재발생존율을 향상시켰지만 전체생존율에서는 유의미한 차이가 없었다. 여기에서 확인된 순차적 치료군에 비한 CTx-CCRT 치료군의 이득을 확인하기 위해 추가적인 연구가 더 진행되어야할 것이다.

핵심어 : 비소세포폐암, 보조항암화학요법, 보조방사선요법, 치료순서 비교