


Radiotherapy Dose and Induction Chemotherapy Cycles Are Associated With Prognosis and Toxicity Risk: A Retrospective Study of 227 Patients With Unresectable Stage III Non-Small-Cell Lung Cancer

Technology in Cancer Research & Treatment
Volume 19: 1-8
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1533033820951802
journals.sagepub.com/home/tct


Liyao Chen^{1*}, Yu Hou^{2*}, Yaoxiong Xia^{2*}, Li Chang^{2*}, Xianmin Diao¹, Li Wang², Lan Li², Qing Long², Ying Liu², Yan Liu², and Wenhui Li² 

Abstract

Objective: Concurrent chemoradiation (cCHRT) has been confirmed as the standard treatment for local advanced non-small-cell lung cancer (NSCLC). This study is to assess the appropriate timing of radiotherapy and cycles of induction chemotherapy for those patients. **Methods:** 227 inoperable stage III NSCLC patients were selected, we analyzed the potential prognostic factors and the influence of induction chemotherapy was evaluated. **Results:** The median survival time was 20.7 months; only 25 patients chose chemotherapy alone (11.0%), 137 patients underwent sequential chemoradiation (sCHRT, 60.4%), and 65 patients received cCHRT (28.6%). Multivariate analyses showed radiation therapy ($P = 0.001$), the Eastern Cooperative Oncology Group (ECOG) score ($P = 0.000$) and the lymph node stage ($P = 0.001$) were independent prognostic factors. cCHRT was not found to be superior ($P = 0.330$). We selected patients received 60-66 Gy and found the cCHRT groups achieved a relatively better outcome, with a median Overall Survival (OS) of 25.2 months vs 20.1 months in the sCHRT group ($P = 0.019$). We also found cycles of induction chemotherapy did not compromise survival; however, ≥ 3 cycles resulted in more grade 3-4 hematology toxicities, with a proportion of 18/99 compared with 53/103 among patients who underwent ≤ 3 cycles. In addition, higher grade hematology toxicities and poor ECOG were also the most common reasons for abandoning cCHRT. **Conclusions:** For inoperable stage III NSCLC, cCHRT showed its superiority only when the radiotherapy dose was 60-66 Gy. Cycles of induction chemotherapy did not interfere with survival; however, ≥ 3 cycles resulted in more grade 3-4 hematology toxicities, leading to the cessation of cCHRT.

Keywords

non-small-cell lung cancer, chemoradiation, survival, induction chemotherapy

Received: May 19, 2020; Revised: July 29, 2020; Accepted: July 31, 2020.

Introduction

Lung cancer has become the leading cause of cancer-related death and has been divided into non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC).^{1,2} Approximately 80-85% of lung cancers are pathologically classified as NSCLC, and one-third of these are diagnosed as locally advanced NSCLC.³ A part of stage III NSCLC can be treated by surgery.⁴ For patients with unresectable tumors, concurrent chemoradiation (cCHRT) has been confirmed as the standard treatment, and cCHRT results in better local control and

¹ Department of Radiotherapy Oncology, People's Hospital of Yuxi City, Yuxi, Yunnan, China

² Department of Radiotherapy Oncology, The Third Affiliated Hospital of Kunming Medical University (Tumor Hospital of Yunnan Province), Kunming, Yunnan, China

*These authors contributed equally.

Corresponding Author:

Wenhui Li, Department of Radiotherapy Oncology, The Affiliated Hospital of Kunming Medical University (Tumor Hospital of Yunnan Province), No. 519 Kunzhou Road, Xishan District, Kunming 650118, Yunnan, China.
Email: 2827569600@qq.com



reduces the possibility of distant metastasis compared with sequential chemoradiation (sCHRT).^{5,6} A meta-analysis containing several clinical trials showed a favorable OS and an absolute reduction in the local regional progression rate in the cCHRT group compared to the sCHRT group.⁷

Despite the definite clinical effect of cCHRT, not all patients tolerate it well, and potentially valid alternatives include sCHRT, radiotherapy (RT) alone, chemotherapy (ChT) and other palliative treatments.⁸ Survival is influenced by many factors, such as poor ECOG score, older age and the volume of the primary tumor.⁹ With the enlargement of the primary tumor, the target volume increases, which results in the risk of damaging organs. Therefore, the majority of patients undergo induction chemotherapy before cCHRT. However, few studies have addressed the optimal cycle regimen of induction chemotherapy.

Moreover, some studies have shown a correlation between the outcome and thoracic radiotherapy dose, but the results of these studies are contradictory. Theoretically, the higher the local dose the patients received, the better the local control and the better their survival.¹⁰ However, with an increase in radiation dose, there may be more toxic adverse events.¹¹ Therefore, we conducted the present study to investigate the suitable radiation dose and the optimal cycles of induction chemotherapy in patients with unresectable stage III NSCLC.

Materials and Methods

Patient Demographics and Tumor Characteristics

Following Institutional Review Board approval, we conducted a retrospective analysis of 227 patients who were retrieved from the Tumor Hospital of Yunnan Province, China, between January 1, 2010, and December 31, 2016. The present study was approved by the Ethics Committee of The Third Affiliated Hospital of Kunming Medical University (Tumor Hospital of Yunnan Province). Informed consent was waived by the committee because of the retrospective nature of this study. This trial was conducted in accordance with the Declaration of Helsinki. We confirm that patient data confidentiality was maintained. The main inclusion criteria were histologically/cytologically proven NSCLC stage III (American Joint Committee on Cancer 7th, AJCC). Key exclusion criteria were a prior history of thoracic RT or received surgery and other malignant disease. Additional information on patient characteristics, treatment and survival was retrospectively collected from the electronic medical records. This is a retrospective study; all patients received conventional treatment, and all methods were performed in accordance with the NCCN Clinical Practice Guideline in Oncology.

Chemoradiation

The overwhelming majority of patients underwent induction chemotherapy. Chemotherapy consisted of two-drug cis- or carboplatin-based regimens. The platinum partner number

of cycles depended on the histology and response of the tumor. All patients received computed tomography scans or positron emission tomography computed tomography (PET/CT) scans. For patients who underwent radiation, intensity modulated radiotherapy (IMRT) was used, and the median dose was 60 Gy, delivered in the conventional fraction, 2 Gy/F, 5 F/W. Treatment strategies consisted of cCHRT (patients received cis/carboplatin and etoposide every 21 days during the radiotherapy), sCHRT (thoracic RT alone followed induction chemotherapy) and ChT.

Follow-Up and Endpoints

All patients underwent clinical follow-up examinations including Magnetic Resonance Imaging (MRI) or CT of the head 1 month after the end of radiotherapy and every 3 months thereafter. The primary endpoints of our study were overall survival (OS) and progression-free survival (PFS). OS was calculated from the day of pathologic confirmation to death or the last day of follow-up. PFS was the time from the end of the radiotherapy to the progression of previously treated lung lesions or the last day of follow-up. The secondary endpoints were distant metastasis-free survival (DMFS) which was defined as the time of the completion of thoracic radiation therapy (TRT) to the day of new distant metastasis or the last day of follow-up and hematological toxicity. Acute toxicities were scored according to the CTCAE (version 4.0).

Statistical Analyses

Statistical analyses were performed with IBM SPSS Statistics 22.0. Patient characteristics were described according to treatment strategy (cCHRT, sCHRT), and significant differences between treatment groups were assessed by χ^2 -test and Fisher's exact test. The Kaplan–Meier method was used to perform univariate survival analysis to find the correlation between OS and clinical features, including sex, age, smoking history, ECOG score, tumor location, lymph nodes, cycles of induction ChT, and receipt of radiotherapy. Among cCHRT group, 56 patients received 60–66 Gy of thoracic RT. A Cox proportional hazards algorithm using the backward–forward and stepwise method was used in multivariate analyses. Patients who received 60–66 Gy of thoracic RT in cCHRT and sCHRT groups were compared after propensity score matching (PSM) analysis. We used one to one matching, the Caliper width was 1. A group of 53 patients with cCHRT was matched to 53 patients with sCHRT based on the baseline age, sex, smoking, ECOG score, stage, location of tumor, lymph nodes, and ChT cycle number to find the relationship between RT dose and OS. The comparison of survival curves between different groups was conducted using the log-rank test.

Results

A total of 227 patients were recruited from January 2010 to December 2016 at Yunnan Province Tumor Hospital. In Table

Table 1. Baseline Characteristics of Patients.

Characters	n	%
Sex		
Female, n (%)	27	11.9%
Male, n (%)	200	88.1%
Age		
<60, n (%)	148	65.2%
≥60, n (%)	79	34.8%
Smoking		
Yes, n (%)	150	66.1%
No, n (%)	77	33.9%
ECOG score		
0 -1, n (%)	130	57.3%
≥2, n (%)	97	42.7%
Pathology type		
Squamous cell cancer	167	73.6%
Adenocarcinoma	53	23.3%
Other	7	3.1%
T stage		
1, n (%)	12	5.3%
2, n (%)	81	35.7%
3, n (%)	19	8.4%
4, n (%)	115	50.7%
N stage		
0, n (%)	5	2.2%
1, n (%)	19	8.4%
2, n (%)	139	61.2%
3, n (%)	64	28.2%
Stage		
IIIA, n (%)	95	41.9%
IIIB, n (%)	132	58.1%
Size		
<5 cm, n (%)	95	41.9%
≥5 cm, n (%)	132	58.1%
Location, n (%)		
Center, n (%)	182	80.2%
Peripheral, n (%)	45	19.8%
Induction chemotherapy		
0, n (%)	14	6.9%
1, n (%)	17	8.4%
2, n (%)	39	19.3%
3, n (%)	29	14.4%
4-6, n (%)	103	60.0%
Treatment		
ChT alone, n (%)	25	11.0%
sCHRT, n (%)	137	60.4%
cCHRT, n (%)	65	28.6%

1, patient characteristics according to the administered treatment are shown: 202 received RT (89.0%), and 25 received ChT only (11.0%); 137 patients chose sCHRT, and 65 patients received cCHRT. The proportions of cycles of induction ChT were as follows: 0 (6.9%), 1 (8.4%), 2 (19.3%), 3 (14.4%), and 4-6 (60.0%). Univariate and multivariate analysis were shown in Table 2. Our univariate analysis demonstrated that stage IIIA, lower N stage, TRT, ECOG score (0 -1) and treatment regimens were OS prognostic factors. Multivariate analysis showed that TRT ($P = 0.001$, HR: 0.294, 95% CI: 0.144-0.601), ECOG score (0 -1) ($P = 0.000$, HR: 1.972, 95% CI:

1.457-2.670) and lower N stage ($P = 0.001$, HR: 1.472, 95% CI: 1.169 -1.853) were the independent, favorable prognostic factors for OS. Among all patient characteristics, age, ECOG score, TRT, N stage and treatment regimens influenced the DMFS according to univariate survival analysis. However, multivariate analysis showed that N stage ($P = 0.002$, HR: 1.410, 95% CI: 1.131 -1.754) and ECOG score (0 -1) ($P = 0.021$, HR: 1.409, 95% CI: 1.053 -1.886) were prognostic factors for DMFS. We did not find any factors correlated with PFS.

The median follow-up period was 48.4 months, and the median OS of the cCHRT group was 25.0 months (95% CI 22.5–27.8). For the sCHRT group, the median OS was 20.5 months (95% CI 17.74–20.0). For the ChT group, the median OS was 13.0 months (95% CI 9.9–16.1). However, cCHRT did not result in a significantly superior OS compared to sCHRT (25.0 months vs. 20.5 months) ($P = 0.330$) (Figure 1).

All patients underwent conventional fraction RT (2 Gy/F, 5 F/W); however, the RT dose they finally received was variable. Thirty-eight patients (18.8%) received doses less than 60 Gy, doses ranging from 60 Gy to 66 Gy were administered to 138 patients (68.3%), and 26 patients (12.9%) received doses greater than 66 Gy. It is well known that a lower RT dose may result in poor local control, while a higher dose may result in more side effects. According to the TRT dose, we divided 65 patients who chose cCHRT into two groups: the nonstandard dose group (dose <60 Gy and dose >66 Gy) and the standard dose group (60-66 Gy). Compared with the nonstandard dose group, the OS of the standard dose group was substantially increased (25.2 months vs. 16.8 months, $P = 0.001$) (Figure 2). This superiority was also shown in DMFS (15.0 months vs. 7.8 months, $P = 0.000$). Moreover, 138 patients who received 60-66 Gy were separated into the cCHRT group and sCHRT group and were compared after PSM (Table 3). After PSM, patients who received cCHRT (25.2 months) showed substantially better survival outcomes than patients who underwent sCHRT (20.1 months) ($P = 0.019$) (Figure 3).

We wanted to determine whether induction ChT had any significant impact on patient outcomes, and there were significant differences in OS ($P = 0.141$), PFS ($P = 0.499$) and DMFS ($P = 0.833$). However, we found that 18/99 (18.2%) of the patients who underwent 0-3 cycles of induction chemotherapy developed grade 3-4 acute hematologic toxicities during their treatment. This proportion significantly increased to 53/103 (51.5%) ($P = 0.000$) in patients who received more than 3 cycles of induction chemotherapy. Notably, the occurrence of grade 3-4 acute hematologic toxicities was significantly lower among those receiving fewer cycles than among those receiving more cycles in both the sCHRT group (17.7% vs 53.3%; $P = 0.000$) and the cCHRT group (16.2% vs 50.0%; $P = 0.008$) (Figure 4).

In our study, approximately two-thirds (137) of patients received sCHRT, and only 65 patients received the standard treatment. The following were the reasons for not receiving cCHRT: fifty-one (37.2%) patients suffered grade 3-4 acute hematologic toxicities after induction chemotherapy,

Table 2. Univariate and Multivariate analysis for OS, DMFS and PFS.

Clinical characters	Univariate		Multivariate			Univariate		Multivariate			Univariate	
	mOS	P	HR	95%CI	P	mDMFS	P	HR	95%CI	P	mPFS	P
Sex		0.181					0.713					0.211
Female	27.1					13.0					6.0	
Male	19.7					14.6					8.1	
Age		0.235					0.003	0.817	0.785 -1.011	0.314		0.303
<60	19.7					12.6					8.9	
≥60	21.5					16.0					12.1	
Smoking		0.615					0.140					0.659
Yes	19.2					15.1					8.1	
No	21.6					12.4					7.8	
ECOG score		0.001	1.972	1.457-2.670	0.000		0.004	1.409	1.053 -1.886	0.021		0.950
0-1	22.1					14.1					7.2	
≥2	18.2					10.9					9.7	
Pathology type		0.515					0.324					0.828
Squamouscell cancer	21.0					14.9					7.9	
Adenocarcinoma	19.4					12.1					7.8	
Other	25.4					19.5					12.0	
T stage		0.391					0.201					0.680
1	16.5					10.2					5.8	
2	19.7					13.8					7.5	
3	19.3					12.3					7.8	
4	21.7					15.7					9.2	
N stage		0.001	1.472	1.169 -1.853	0.001		0.002	1.410	1.131 -1.754	0.002		0.082
0	24.2					22.9					16.0	
1	26.7					18.6					10.0	
2	21.5					15.1					8.8	
3	16.5					10.8					6.4	
Stage		0.038	1.011	0.987 -1.036	0.382		0.141					0.828
IIIA	23.1					15.2					7.8	
IIIB	18.5					13.8					8.5	
Size		0.393					0.751					0.415
<5cm	21.1					14.1					7.9	
≥5cm	19.5					14.9					8.1	
Location		0.065					0.140					0.596
Center	21.4					15.1					8.4	
Peripheral	16.8					12.4					6.6	
Treatment		0.002	0.294	0.144-0.601	0.001		0.027	0.899	0.850 -1.015	0.412		0.293
ChT	13.0					7.3					6.9	
sCHRT	25.2					14.0					7.8	
cCHRT	19.3					15.5					9.0	

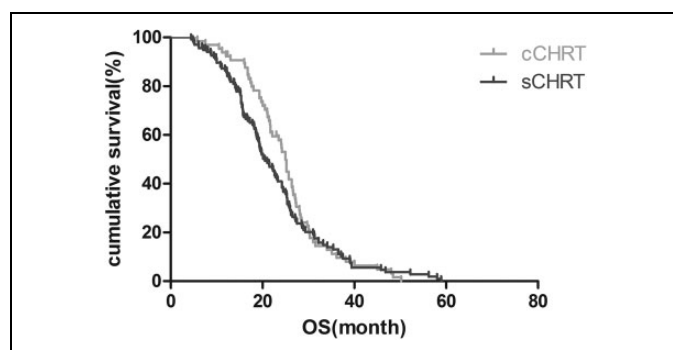


Figure 1. Kaplan-Meier analysis comparing OS in patients treated with cCHRT and sCHRT. Abbreviations: OS, overall survival; cCHRT, concurrent chemoradiation; sCHRT, sequential chemoradiation.

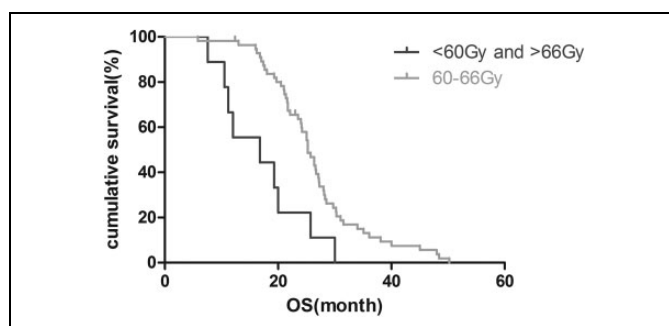
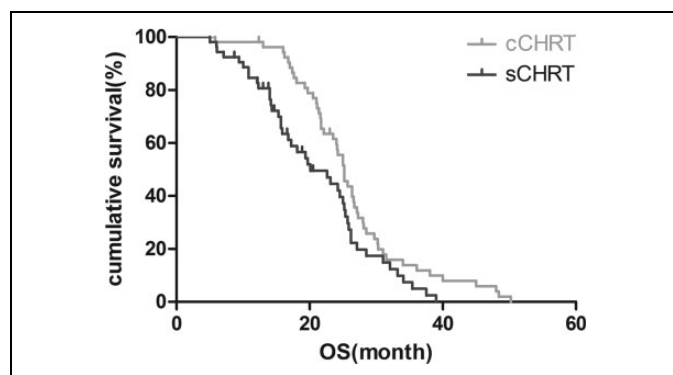


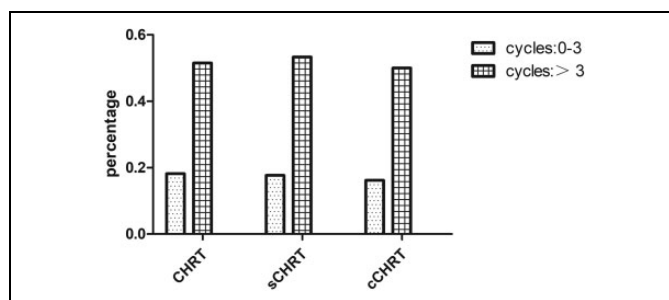
Figure 2. Kaplan-Meier analysis comparing OS in patients treated with cCHRT with different radiation dose. Abbreviations: OS, overall survival; cCHRT, concurrent chemoradiation.

Table 3. Characteristics of Patients With sCHRT vs. cCHRT After Propensity Score Matching.

Characteristics	Before matching			After matching		
	sCHRT (n = 82)	cCHRT (n = 56)	<i>p</i>	sCHRT (n = 53)	cCHRT (n = 53)	<i>p</i>
Age, <60	51	29	0.403	39	37	0.666
Sex, male	74	54	0.298	46	51	0.161
ECOG,0-1	41	34	0.215	37	32	0.308
Smoking, Yes	51	38	0.495	32	37	0.308
Pathology type			0.491			0.586
Squamous cell	60	42		38	39	
Adenocarcinoma	19	14		13	14	
Other	3	0		2	0	
T stage			0.899			0.736
1	3	1		2	0	
2	30	19		17	19	
3	7	6		5	5	
4	42	30		29	29	
N stage			0.076			0.129
0	2	0		1	0	
1	5	8		4	8	
2	49	38		30	35	
3	26	10		18	10	
stage			0.471			1.000
IIIA	33	26		22	23	
IIIB	49	30		31	30	
Size			0.741			0.435
<5cm	46	33		27	31	
≥5cm	36	23		26	22	
Location			0.030			0.104
Center	63	51		42	48	
Peripheral	19	5		11	5	

**Figure 3.** Kaplan-Meier analysis comparing OS in patients treated with cCHRT and sCHRT after PSM. Abbreviations: OS, overall survival; cCHRT, concurrent chemoradiation; sCHRT, sequential chemoradiation; PSM, propensity score matching.

twenty-three (16.8%) patients were more than 70 years old, twenty-seven (19.7%) patients refused cCHRT because of potential side effects, twenty-one (15.3%) patients could not tolerate the treatment due to poor ECOG score or decompensation of organs evaluated by physicians, and the other fifteen (10.9%) patients had unknown reasons. The most common motivations for omitting cCHRT were grade 3-4 hematologic toxicities (37.2%), advanced age (16.8%) and refusal by the

**Figure 4.** Percentage of grade 3-4 acute hematologic toxicities in different treatment group. Abbreviations: ChT, chemoradiation; cCHRT, concurrent chemoradiation; sCHRT, sequential chemoradiation.

patient (19.7%). Among the 51 patients who developed 3-4 hematologic toxicities, 82.4% (42) underwent more than 3 cycles of induction chemotherapy.

Discussion

This study was performed to analyze the correlation between the radiation dose and the survival of unresectable stage III NSCLC and optimal induction chemotherapy. Among patient characteristics, ECOG score, N stage and TRT were independent prognostic factors.

In our research, cCHRT was not superior to sCHRT. This result is quite different from a previous meta-analysis,⁷ which contained several clinical trials and showed a favorable outcome, with 3-year and 5-year OS rates of 23.8% and 15.1% for cCHRT and 18.1% and 10.6% for sCHRT, and an absolute decrease in the 3-year and 5-year local regional progression rates from 34.1% to 28.1% and 35.0% to 28.9% in the sCHRT and cCHRT groups, respectively. However, other studies obtained similar results. Driessen retrospectively investigated 216 inoperable stage III NSCLC patients who were more than 70 years old and found that compared with palliative treatment, cCHRT, sCHRT and RT alone all showed substantial superiority, while they observed no significant differences among the three groups.¹² At the same time, the rate of completed treatment without unplanned hospitalizations was 26% for cCHRT compared to 40% for sCHRT and 59% for RT ($P = 0.000$). They finally concluded that elderly patients often had factors contributing to a poor prognosis, and factors in younger patients related to a better prognosis and treatment tolerance included a better general performance status and fewer complications. cCHRT had a lower treatment completion rate and led to more side effects in the elderly population, and sCHRT and RT alone might be more suitable.

In clinical practice, not all patients are eligible for aggressive or radical treatment, especially elderly patients,^{13,14} and treatment for those patients usually remains conservative.^{8,15} In Driessen's research, all patients received a minimum total tumor dose of 54 Gy. In our study, the dose received was variable: 38 patients (18.8%) received doses less than 60 Gy, 138 patients (68.3%) received doses ranging from 60 Gy to 66 Gy, and 26 patients (12.9%) received doses greater than 66 Gy. Of the thirty-eight patients who received doses less than 60 Gy, most suffered from side effects, 15 patients had ECOG scores ≥ 2 , 8 patients were older than 70 years, and 7 patients withdrew from treatment due to adverse events. After eliminating those receiving doses less than 60 Gy and performing PSM, we compared the survival of the cCHRT groups and sCHRT groups, and patients in the cCHRT group had a substantially higher survival duration than those receiving sCHRT. The median survival time was 25.0 months for the cCHRT group and 20.1 months for the sCHRT group ($P = 0.019$). Here, we further showed that cCHRT is suitable for patients with younger age, better ECOG score, fewer complications and fulfillment of the optimal TRT dose. A lower dose led to poor local control, and a higher dose resulted in more adverse events and more organs at risk, such as the heart, lung and esophagus.¹⁶ RTOG 0617 research showed that there was no survival benefit but more RT side effects obtained by escalating the radiation dose from 60 to 74 Gy.¹⁷ The present study recommends 60-66 Gy as the optimal dose.^{11,17,18} In summary, not all patients diagnosed with unresectable stage III NSCLC are suitable for concurrent chemoradiotherapy. All patient factors must be taken into account before decisions are made. The aim of various treatments, including cCHRT, sCHRT, palliative treatment and emerging treatments, such as immunotherapy and targeted therapy, to prolong patients' lives while maintaining a better

quality of life.^{8,15,19,20} Tanta University Research Project Unit and Tanta University hospitals conducted a study to evaluate the safety and efficacy of immunization with specific anti-hepatocellular carcinoma dendritic cells (DCs) in Egyptian patients with advanced hepatocellular carcinoma (HCC), they found that patients who received DCs vaccine showed mild decrease in Child-Pugh score as well as AFP and PIVKA II levels and developed 20% partial response [PR] 40% stable disease [SD] and 40% progressive disease while all adverse events were grade 1 or 2.²¹

Before RT, most patients underwent induction chemotherapy, but there was no evidence that induction chemotherapy led to a survival benefit. A 7-year follow-up of the CALGB 8433 trial showed that induction chemotherapy extended the duration median survival by 4.1 months.²² However, Everett E. Vokes found that compared to cCHRT, cCHRT after induction ChT did not prolong survival but instead increased the risk of neutropenia, and the rates of radiation pneumonitis and esophagitis were similar.²³ Our results also suggested that there was no overall survival benefit of induction ChT but rather an increased marrow depression rate. On the other hand, induction ChT shrinks tumors before cCHRT, which reduces radiation-related toxicities and improves local control. It is important to clarify the optimal number of cycles of induction chemotherapy. We found that more than 3 cycles of induction ChT resulted in more hematological toxicities, which then led to less cCHRT. Since less induction ChT did not compromise the survival outcome, fewer than 3 cycles of induction ChT is a better strategy for these patients.

It is noteworthy that there are also shortcomings in this study. First, as a retrospective study, a total of 227 patients were selected, which is not a large sample, and there may have been bias. Although we tried to minimize bias by performing PSM, it is possible that factors other than those included in the matching may have influenced the outcomes. Second, the RT parameters have strong relationships with adverse events. We did not record parameters such as V20 that may be related to radiation pneumonitis.¹⁸ These factors may have had an impact on the results. Third, different chemotherapy regimens may have different effects on the hemograms,²⁴⁻²⁶ but more cycles of induction chemotherapy resulted in more hematological toxicities. A large, prospective clinical trial focusing on the TRT dose, cycles of induction ChT and reduction of side effects should be developed to assess the best timing for cCHRT interventions and guide the management of inoperable stage III NSCLC.

Conclusion

In conclusions, for inoperable stage III NSCLC, cCHRT showed its superiority only when patients accomplish treatment with dose at 60-66 Gy, cycles of induction chemotherapy did not interfere the survival, however cycles ≥ 3 result in more 3-4 grade hematology toxicity and become the main factors of quitting cCHRT. A large, prospective clinical trial focus on TRT dose, cycles of induction ChT and reduction of

side effects should be developed to assess the best time for cCHRT.

Authors' Note

Treatment described in this manuscript is a routine modality performed on the base of treatment protocol accepted by radiotherapy board at our institute. Corresponding author gave lectures for Accuray. Liyao Chen, Yu Hou, Yaoxiong Xia, and Li Chang contributed equally. Provided the full name and institution of the review committee but the approved number is waived. The reasons for the waiver of approved number were as follows: 1. Our study did not adversely affect the health and rights of patients because of the retrospective nature of this study; 2. We guarantee that the patients' privacy and personal information are protected. This trial was conducted in accordance with the Declaration of Helsinki. We confirm that patient data confidentiality was maintained.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Natural Science Foundation of China (Nos. 81660504 and 81560488), the Yunnan Provincial Training Special Funds for High-level Health Technical Personnel (No. H-201624), and the Yunnan Health Science Foundation (Nos. 2016NS085, 2016NS08 and 2017NS191).

ORCID iD

Wenhui Li  <https://orcid.org/0000-0001-5283-841X>

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69(1):7-34. doi:10.3322/caac.21551
2. Didkowska J, Wojciechowska U, Manczuk M, Lobaszewski J. Lung cancer epidemiology: contemporary and future challenges worldwide. *Ann Transl Med*. 2016;4(8):150. doi:10.21037/atm.2016.03.11
3. Walters S, Maringe C, Coleman MP, et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007. *Thorax*. 2013;68(6):551-564. doi:10.1136/thoraxjnl-2012-202297
4. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet*. 2009;374(9687):379-386. doi:10.1016/s0140-6736(09)60737-6
5. Bayman N, Blackhall F, McCloskey P, Taylor P, Faivre-Finn C. How can we optimise concurrent chemoradiotherapy for inoperable stage III non-small cell lung cancer? *Lung Cancer*. 2014; 83(2):117-125. doi:10.1016/j.lungcan.2013.11.017
6. Van Schil PE. Optimal treatment of stage IIIA-N2 non-small cell lung cancer: a neverending story? *J Thorac Oncol*. 2017;12(9): 1338-1340. doi:10.1016/j.jtho.2017.07.001
7. Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol*. 2010; 28(13):2181-2190. doi:10.1200/jco.2009.26.2543
8. Kumar SS, Higgins KA, McGarry RC. Emerging therapies for stage III non-small cell lung cancer: stereotactic body radiation therapy and immunotherapy. *Front Oncol*. 2017;7:197. doi:10.3389/fonc.2017.00197
9. Koo TR, Moon SH, Lim YJ, et al. The effect of tumor volume and its change on survival in stage III non-small cell lung cancer treated with definitive concurrent chemoradiotherapy. *Radiat Oncol*. 2014;9:283. doi:10.1186/s13014-014-0283-6
10. Machtay M, Bae K, Movsas B, et al. Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non-small cell lung carcinoma treated with chemoradiation: an analysis of the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys*. 2012;82(1):425-434. doi:10.1016/j.ijrobp.2010.09.004
11. Wang K, Eblan MJ, Deal AM, et al. Cardiac toxicity after radiotherapy for stage III non-small-cell lung cancer: pooled analysis of dose-escalation trials delivering 70 to 90 Gy. *J Clin Oncol*. 2017;35(1):1387-1394. doi:10.1200/jco.2016.70.0229
12. Driessen EJ, Bootsma GP, Hendriks LE, et al. Stage III non-small cell lung cancer in the elderly: patient characteristics predictive for tolerance and survival of chemoradiation in daily clinical practice. *Radiation Oncol*. 2016;121(113):26-31. doi:10.1016/j.radonc.2016.07.025
13. Kale MS, Mhango G, Gomez JE, et al. Treatment toxicity in elderly patients with advanced non-small cell lung cancer. *Am J Clin Oncol*. 2017;40(1):470-476. doi:10.1097/coc.000000000000188
14. Kang KM, Jeong BK, Ha IB, et al. Concurrent chemoradiotherapy for elderly patients with stage III non-small cell lung cancer. *Radiat Oncol J*. 2012;30(5):140-145. doi:10.3857/roj.2012.30.3.140
15. Rizvi NA, Peters S. Immunotherapy for unresectable stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377(3): 1986-1988. doi:10.1056/NEJMe1711430
16. Mellemaard A, Luchtenborg M, Iachina M, et al. Role of comorbidity on survival after radiotherapy and chemotherapy for non-surgically treated lung cancer. *J Thorac Oncol*. 2015;10(20): 272-279. doi:10.1097/jto.0000000000000416
17. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol*. 2015;16(2):187-199. doi:10.1016/s1470-2045(14)71207-0
18. Liu M, Wang Z, Zhou T, et al. Individual isotoxic radiation dose escalation based on V20 and advanced technologies benefits unresectable stage III non-small cell lung cancer patients treated with concurrent chemoradiotherapy: long term follow-up. *Oncotarget*. 2017;8(2):51848-51858. doi:10.18632/oncotarget.16288
19. Katakami N, Hida T, Nokihara H, et al. Phase I/II study of teceotide as immunotherapy in Japanese patients with unresectable stage III non-small cell lung cancer. *Lung Cancer*. 2017;105: 23-30. doi:10.1016/j.lungcan.2017.01.007

20. Oshiro Y, Okumura T, Kurishima K, et al. High-dose concurrent chemo-proton therapy for Stage III NSCLC: preliminary results of a Phase II study. *J Radiat Res.* 2014;55(31):959-965. doi:10.1093/jrr/rru034
21. Ghafara MTA, Morada MA, El-Zamarany EA, et al. Autologous dendritic cells pulsed with lysate from an allogeneic hepatic cancer cell line as a treatment for patients with advanced hepatocellular carcinoma: a pilot study. *Int Immunopharmacol.* 2020;82:106375. doi:10.1016/j.intimp.2020.106375
22. Dillman RO, Herndon J, Seagren SL, Eaton WL Jr, Green MR. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J Natl Cancer Inst.* 1996;88(17):1210-1215. doi:10.1093/jnci/88.17.1210
23. Vokes EE, Herndon JE, Kelley MJ, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. *J Clin Oncol.* 2007; 25(13):1698-1704. doi:10.1200/jco.2006.07.3569
24. Langer CJ, Hirsh V, Ko A, Renschler MF, Socinski MA. Weekly nab-paclitaxel in combination with carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: analysis of safety and efficacy in patients with renal impairment. *Clin Lung Cancer.* 2015;16(2):112-120. doi:10.1016/j.clcc.2014.09.003
25. Wang Z, Cai XJ, Chen LY, et al. Factors potentially associated with gemcitabine-based chemotherapy-induced thrombocytopenia in Chinese patients with nonsmall cell lung cancer. *J Cancer Res Ther.* 2018; 14:S656-s660. doi:10.4103/0973-1482.187338
26. Steuer CE, Behera M, Ernani V, et al. Comparison of concurrent use of thoracic radiation with either carboplatin-paclitaxel or cisplatin-etoposide for patients with stage III non-small-cell lung cancer: a systematic review. *JAMA Oncol.* 2017;3(8):1120-1129. doi:10.1001/jamaoncol.2016.4280