The survival impact of concurrent chemotherapy and primary tumor radiotherapy on stage IV squamous non-small-cell lung cancer

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Abstract

Objective: To analyse the impact of survival with three-dimensional radiotherapy for stage IV squamous non-small cell lung cancer (NSCLC). **Methods:** Data for 629 eligible patients who received three-dimensional radiotherapy between 2002 and 2016 were retrospectively analyzed. 161 of 183 cases were included pre-protocol. Patients received platinum-doublet chemotherapy with concurrent irradiation of the primary tumour. Primary endpoints were overall survival (OS) and progress-free survival (PFS). **Results:** Of 161 patients, the 1-, 2-, 3- and 5-year OS rates and median survival time (MST) were 45.7%, 14.1%, 11.2%, 2.2% and 11 months, respectively. Using contrastive analysis PTV dose ≥ 63 Gy and < 63 Gy, the 1-, 2-, 3- and 5-year overall survival (OS) rates and median survival time (MST) were 48.9% vs 43.3%, 21.8% vs 8.2%, 18.4% vs 4.4%, 5.1% vs 0%, and 12 months vs 11 months ($\chi^2 = 7.222$, $P=0.007$). Contrastive analysis patients received radical concurrent chemoradiation therapy, and the 1-, 2-, 3- and 5-year overall survival (OS) rates and median survival time (MST) were 54.3% vs. 37.2%, 27.2% vs. 7.5%, 24.9% vs. 4.8%, 8.3% vs. 0%, and 14 months vs. 10 months ($\chi^2 = 13.180$, $P=0.000$). Multivariate analysis showed that PTV ≥ 63 Gy was an independent favourable factor for survival. **Conclusion:** Concurrent chemotherapy and three-dimensional radiotherapy to the primary tumour in stage IV squamous NSCLC could prolong survival, and with increasing intensity of comprehensive treatment, OS gradually improved. PTV ≥ 63 Gy is the independent prognostic factors for OS. **[Key Words]** Stage IV; Squamous non-small cell lung cancer (NSCLC); Concurrent chemoradiotherapy; Overall survival

Background

At present, lung cancer is still the leading cause of cancer deaths worldwide[1]. Non-small cell lung cancer (NSCLC) accounts for approximately 75% of the cancers and consists of squamous cell, adenocarcinoma and other cell types. Squamous cell carcinomas account for 30% of NSCLC worldwide[2]. The majority of lung cancers (57%) are diagnosed at a distant stage, and the 5-year survival rate is approximately 4% for distant stage disease. In recent years, first-line chemotherapy, including third-generation agents (including gemcitabine, paclitaxel, and pemetrexed), molecular targeted therapies or immunotherapy drugs, has improved overall survival (OS) of patients with advanced NSCLC[1, 3, 4].

For patients with non-squamous NSCLC without identified oncogenic drivers, bevacizumab, a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF), in combination with platinum-based chemotherapy, remains a valid first-line treatment option[5-8]. Cisplatin or carboplatin combined with pemetrexed and concurrent radiation therapy may also associated with more clinical benefits[9, 10]. However, none of the above treatments are suitable for patients with squamous NSCLC. The discovery of activating mutations of the epidermal growth factor receptor (*EGFR*) and the echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase (*EML4-ALK*) fusion has led to changing treatments for patients with NSCLC who harbour these drivers. Agents that inhibit the tyrosine kinase binding sites of these molecules have demonstrated improved PFS versus chemotherapy [11-13]. However, these mutations are very rare in squamous NSCLC [2, 14].

For patients with squamous NSCLC, although some potentially targetable molecular lesions have been identified in tumours[2], including PIK3CA amplification, FGFR1 amplification, MET amplification, and DDR2 mutation, none of these biomarkers have yet been validated in this setting as predictive for targeted therapies, and available first-line regimens have remained essentially unchanged for the past two decades. In general, such regimens comprise a platinum-based doublet of cisplatin or carboplatin combined with gemcitabine, vinorelbine, or a taxane [2, 15]. ECOG1594 study shows that the third-generation agents combined with platinum had similar efficacy in the treatment of advanced NSCLC. The median survival about 8 months, 1-year OS ~ 30%[4]. The treatment with chemotherapy alone entered a plateau. Thus, new strategies involving combinations of chemotherapy with other treatment modalities should be explored.

Some studies have shown that controlling the primary tumour may be important in prolonging survival among patients with advanced NSCLC. Local control of the primary tumour has not only reduced symptoms but also improved overall survival (OS) [16, 17]. More evidence suggests that some patients with stage IV disease could benefit from aggressive thoracic radiation therapy beyond palliative irradiation [18-20]. Moreover, the role of concurrent chemotherapy with thoracic radiation therapy for advanced NSCLC is not well-defined [19, 21].

Our previous study showed that treatment of IV NSCLC with joint administration of four to five cycles of chemotherapy and three-dimensional radiotherapy may prolong survival especially for patients with single metastatic sites [22-24]. However, the role of chemotherapy given concurrently with primary tumor radiotherapy for stage IV squamous NSCLC patients is not well-defined, and the independent prognostic factors for OS in stage IV squamous NSCLC patients treated with concurrent chemoradiotherapy remains to be answered. Therefore, 164 eligible stage IV squamous NSCLC patients come from multiple cancer centers and tumor hospitals who received three-dimensional radiotherapy between 2002 and 2016 were retrospectively analyzed—we assessed the impact of survival with primary tumour radiotherapy and concurrent chemotherapy for stage IV squamous NSCLC patients.

Methods

Patient selection

Inclusion criteria of patients are as follows: (1) Histologically or cytologically confirmed Squamous Carcinoma; (2) Newly diagnosed stage IV disease (staged according to the 2002 system of the American Joint Committee on Cancer); (3) No previous anticancer treatment; (4) 18 to 80 years of age; (5) Karnofsky performance status (KPS) score ≥ 70 ; (6) No contraindications to radiation therapy or chemotherapy; (7) Metastatic disease limited to ≤ 3 organs; and (8) Presumed ability to tolerate thoracic radiation therapy at a dose of ≥ 36 Gy in 20 fractions. Exclusion criteria were (1) a history of thoracic surgery, radiation therapy, or chemotherapy; (2) pregnancy or lactation at the time of enrolment; (3) previous malignancy or other concomitant malignant diseases.

Pre-treatment evaluations

All patients underwent fibrotic bronchoscopy and contrast-enhanced computed tomography (CT) of the chest to evaluate the extent of the primary tumour and regional lymph node status. All patients also underwent bone scintigraphy, contrast-enhanced CT of the abdominal region, and magnetic resonance imaging (MRI) of the head to detect distant metastases. Positive findings on positron emission tomography (PET)/CT or bone scintigraphy required additional radiologic confirmation (e.g., MRI or CT of the bone). Pre-treatment evaluations were completed within 2 weeks before treatment started.

Thoracic radiotherapy protocol

All patients were immobilized in the supine position using a T bar, wing board, and Vac-lock cradle. Images with contrast were obtained from the CT simulator for treatment planning purposes. All patients were scanned using serial 5-mm slices from the hyoid bone through the third lumbar vertebra. All patient 3D-CRT or IMRT treatment plans were performed using the ADAC pinnacle planning system (version 7.4f), and dose distribution was computed with a tissue heterogeneity correction.

Chemotherapy protocol

Platinum-based doublets chemotherapy (cisplatin in combination with docetaxel, paclitaxel or vinorelbine) was used for all patients, and concurrent thoracic radiation was given within 1 week following the start of chemotherapy. The commonly used regimens were as follows: 140 mg/m² of paclitaxel (P) or 75 mg/m² of docetaxel (D) on day 1, followed by 80 mg of cisplatin (C) per square metre of body-surface area (mg/m²) or carboplatin (Cb) at a dose calculated to produce an area under the concentration-time curve of 6.0 mg/ml/min were administered on day 2; gemcitabine was not given because of the risk of its increasing radiation-related toxicity. After completion of thoracic radiotherapy, patients demonstrating a response or stable disease continued chemotherapy up to 4–6 cycles, whereas patients who experienced progressive disease or unacceptable toxicity were transferred to second-line therapy. No maintenance therapy was given.

Patients who received at least 2 cycles of chemotherapy and thoracic radiation doses of ≥ 36 Gy were considered to have completed treatment according to the protocol.

Evaluation of treatment-related toxicity and response

Treatment-related acute toxicity was scored according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. During treatment, a routine blood test was

performed at least once per week; and routine blood, liver function, renal function tests and electrocardiograms were examined prior to chemotherapy. If necessary, a chest X-ray or CT examination and barium meal radiography were used to evaluate radiation pneumonitis and oesophagitis. Treatment response was assessed by extramural reviewers using the Response Evaluation Criteria in Solid Tumours (RECIST).

Patients were also classified as having a response if they had CR or PR and no response if they had SD or PD. The conventional response criteria were measured at each individual institution and verified by the central principal investigator (PI). Disease-free survival and OS were calculated from the time of registration.

Follow-up

After the completion of treatment, an intravenous contrast CT scan of the chest and upper abdomen was obtained, and tumour response was assessed at 1 month after the completion of treatment. Patients were followed monthly for the first 3 months, every 3 months for 2 years, and then every 6 months thereafter.

Statistical analyses

Intent-to-treat analyses were performed on data from all patients who entered the study. The endpoints of this study included overall survival (OS) and progress-free survival (PFS). The overall survival time was measured from the first day of concurrent chemoradiotherapy to the date of death or the last follow-up. The progress-free survival time was measured from the first day of concurrent chemoradiotherapy to the date on which the tumour progressed or the date on which the patient died from any cause.

Treatment response was assessed by extramural reviewers using the Response Evaluation Criteria in Solid Tumours (RECIST)(18). According to the RECIST evaluation, comprehensive treatment response was defined as primary and metastatic tumour treatment response evaluation. Effective (Objective Response Rate, ORR) included complete response and partial response and invalid (No Response Rate, NRR) included stability and progressing disease.

The Statistical Package for Social Sciences, version 13.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. The Kaplan-Meier method was used to calculate the OS. The log-rank test was used to compare the survival curves. Multivariate Cox regression analysis was used to test independent significant prognostic factors for OS. All statistical tests were two-sided, and a P-value <0.05 was considered statistically significant.

Results

Patient Clinical characteristics

In total, 629 patients were enrolled in this study. The last follow-up was in January 2019. The follow-up period ranged from 1.0 to 84.0 months; among the patients, 183 had squamous cancer, the male/female ratio was nearly 7.3:1.0 and the patient median age was 60 years (range from 36 to 80 years). The T and N stages were as follows: 5, 53, 34, and 91 cases were T1, T2, T3 and T4, respectively, and 68.3% were T3-4; 6, 20, 56, and 101 cases were N0, N1, N2 and N3, respectively, and 85.8% were N2-3. Approximately 60.1% of patients had metastasis to only one site, and 39.9% patients had metastasis in ≥ 2 sites. Approximately 57.9% and 42.1% patients had 1-5 or ≥ 5 metastasis lesions, and the median primary tumour dose was 57.6 Gy (12, 24, 73, and 74 patients received 36 Gy, 36-44.9 Gy, 45-62.9 Gy and ≥ 63 Gy, respectively). The type of chemotherapy received was as follows: 168 patients received platinum with a taxane (docetaxel or paclitaxel), the median chemotherapy cycle was 3 cycles (10, 83, and 88 patients completed 1, 2-3 and 4-6 cycles, respectively). Of the 183 patients, 177 (96.7%) could be used to evaluate the effect of comprehensive treatment (CR 8, PR 106, SD 23, PD 30), 161 (88%) completed treatment in accordance with the protocol (i.e., received at least 2 chemotherapy cycles and a thoracic radiation dose of at least 36 Gy). The clinical characteristics of patients are listed in Table 1.

Clinical factors associated with survival outcomes

Of the 563 patients who completed treatment in accordance with the protocol (i.e., received at least 2 chemotherapy cycles and a thoracic radiation dose of at least 36 Gy), 161 had squamous cancer, and they had no significant difference in OS and PFS compared with non-squamous NSCLC ($\chi^2=0.417$, $P=0.519$ and PFS $\chi^2=0.024$, $P=0.877$). Stratified analysis results of squamous cancer showed that there was no significant difference between T1-2 and T3-4 staging or N0-1 and N2-3 staging. There was a trend of OS in single organ compared with multi-organ metastasis ($\chi^2=3.053$, $P=0.081$). The 1-, 2-, 3-, and 5-year OS rates and MST of 1-5 metastatic lesions were 50.2%, 20.7%, 16.1%, 1.9% and 13 months, respectively, which was significantly better than >5 metastatic lesions ($\chi^2=6.069$, $P=0.014$), but the PFS was not significantly different (Table 2).

Survival outcomes of different primary tumour radiation doses and comprehensive treatments

The 1, 2, 3 and 5 year OS of different primary tumour doses (<36 Gy, 36-44.9 Gy, 45-62.9 Gy and ≥ 63 Gy) of 183 cases of squamous stage IV NSCLC were significantly different ($\chi^2= 31.028$, $P = 0.000$) and showed that the survival rate was prolonged with radiation dose escalation. For the 161 squamous stage IV NSCLC of the study, the 1-, 2-, 3-, and 5-year OS rates of different primary tumour doses between 36-44.9 Gy, 45-62.9 Gy and ≥ 63 Gy were also significantly different ($\chi^2= 7.231$, $P = 0.027$). Patients with a radiation dose ≥ 63 Gy had a trend towards a better OS, and there were significant differences in OS

between stratification analysis of ≥ 63 Gy and <63 Gy ($\chi^2=7.222$, $P=0.007$). However, for patients receiving 4 chemotherapy cycles, there was trend to increase OS ($\chi^2=3.357$, $P=0.067$).

Compared with 2-3 cycles of chemotherapy, the OS and PFS were prolonged after 4 cycles of chemotherapy ($\chi^2 = 12.433$, $P = 0.000$ and $\chi^2 = 8.909$, $P = 0.003$). Combined with different chemotherapy and radiation doses, the OS survival results of different treatment intensities (dose <36 Gy with 1 cycle, dose <63 Gy with 2-3 cycles, dose ≥ 63 Gy with 2-3 cycles and dose ≥ 63 Gy with more than 4 cycles) were significantly different ($\chi^2=24.497$, $P=0.000$). In addition, the 1-, 2-, 3-, and 5-year OS rates of patients who received radical treatment (4-5 cycles with doses ≥ 63 Gy) were better than those who had non-radical treatment regimens (including 2-3 cycles with doses ≥ 63 Gy, 2-3 cycles with doses <63 Gy, and 4-5 cycles with doses <63 Gy) ($\chi^2 = 13.180$, $P = 0.000$) (Table 3). There are no significant difference in LRPFS with increased dose in squamous NSCLC but in overall patients and non-squamous NSCLC patients are significant difference.

Cox regression analyses for overall survival

According to multivariate analyses, patient age, metastatic lesions and treatment response were not related to survival, but the primary tumour radiation dose the patient received was an independent predictor of survival (HR, 0.703; 95% CI, 0.498–0.991; $P=0.044$). (Table 4)

Discussion

In the present series, squamous cell carcinomas accounted for 30% of patients, and in this study, squamous cell carcinomas accounted for approximately 29% of patients. The ratio of males to females in squamous cell carcinoma was 7.3: 1, which is higher than that for non-squamous cell carcinoma (2.1: 1), and the incidence of squamous cell carcinoma was higher in men [3]. The incidence of squamous cell carcinoma was 46% in patients ≥ 65 years of age. In the entire group, T3-4 squamous cell carcinoma accounted for approximately 68.9% of patients, which is slightly higher than 62.3% being adenocarcinoma. This may be because squamous cell carcinomas easily infiltrate the surrounding large blood vessels, similar to the epidemiological characteristics of NSCLC. Regarding the lymph node metastasis rate, the N2-3 stage accounted for approximately 85.8%, with adenocarcinoma being 85.7%. Regarding the organ metastatic rate, 60.1% had single organ metastasis, which was lower than the IV NSCLC metastatic rate of 69.5% [25], but when it was defined by metastatic lesions, for less than 5 lesions, 57.9% of squamous cell carcinoma was oligometastatic, and the non-squamous cell carcinoma rate was 50.2%. This may show that the metastasis of squamous cell carcinoma was later and more limited than adenocarcinoma[26].

After three-dimensional radiation therapy of the primary tumour, the OS of single organ metastasis was trend of improved, especially for the patients with 1-5 metastatic lesions. The OS was significantly

prolonged, showing that 75% of squamous lung cell carcinoma patients died of primary tumour progression[27]. Local treatment may be more important for squamous carcinoma, and more oligometastatic patients would have survival benefits from local treatment. However, there was no difference in PFS between single organ metastasis and 2-3 organ metastasis—also no difference in 1-5 metastatic lesions and >5 lesions. The reason may be due to insufficient follow-up time. There was no difference in OS and PFS in the T and N stages between squamous cell carcinoma and non-squamous cell carcinoma[28].

Platinum-based two-dose chemotherapy is still the standard treatment of squamous IV NSCLC [15]. In this study, the results of three-dimensional radiotherapy with concurrent chemotherapy of the primary tumour showed that the 1-year OS, MST and PFS were 45.7% and 13.8% and 11 months and 6 months, respectively, similar to the standard treatment of 33% and 11% and 8 months and 4 months (part of the case IIIB period) [29], indicating that radiotherapy for stage IV squamous cell carcinoma will result in PFS extension. However, recent retrospective and prospective clinical studies of IV NSCLC in patients with squamous cell carcinoma have shown a significantly longer survival period than with chemotherapy alone, particularly for the patients who received 4 cycles of chemotherapy and a concurrent dose of ≥ 63 Gy radiotherapy. The 1 year OS rate, MST and PFS were 59%, 16 months and 9 months [23, 24], respectively, for patients who had 5 or fewer oligometastatic lesions, and the OS, PFS and local control were improved when the primary tumour received a high dose of radiation, ≥ 63 Gy[21, 22]. Therefore, in stage I-III NSCLC, a primary tumour irradiation dose from 40 Gy to 60 Gy gradually extended the OS, and local recurrence of squamous cell carcinoma after treatment was the main failure [30-32]. Large data results of IV NSCLC radiotherapy alone showed that the OS after a dose lower than 36 Gy was significantly lower than 36-50 Gy and did not further improve at doses higher than 50 Gy [33]. According to the primary tumour dose stratification analysis in 183 patients of this study (Table 3), the 1 year OS and PFS were 8.3% and 0 for <36 Gy, but for 36-44.9 Gy and 45-62.9 Gy patients, the 1 and 2-year OS rates were 31.7% and 45.5% and 5.3% and 7.1%, respectively. The median PFS was 8 and 11 months, and for ≥ 63 Gy patients, the 1, 2, 3 and 5-year OS rates were 46.1%, 21.3%, 17.9% and 5.0%, respectively, and the median PFS was 5 months. Further analysis of the 161 cases that completed the study programme showed that the OS was significantly prolonged with increased dose, suggesting that for squamous IV NSCLC, the OS gradually extended with increases in the primary tumour dose. With a dose ≥ 63 Gy, the extension OS were more pronounced than at <63 Gy, indicating that higher dose improves local control, which was the main failure pattern in squamous NSCLC [32]. These results were similar to a previous report of primary tumour radical dose three-dimensional radiotherapy with IV NSCLC (including squamous cell carcinoma and non-squamous cell carcinoma) [23]. In our study there are no significant difference in PFS and LRPFS with increased dose in squamous NSCLC. However, there are significant differences in the overall patients and non-squamous NSCLC patients, which may be due to radiosensitivity and the need for radiation therapy doses vary between pathological types of tumors. Adenocarcinoma may require higher local control dose.

It is commonly agreed that a primary treatment of stage IV NSCLC with systemic chemotherapy will improve OS and PFS for stage IV NSCLS patients. In this study, concurrent chemo-radiotherapy was the

main treatment mode, and the OS and PFS after 4 cycles of chemotherapy for stage IV squamous NSCLC were significantly longer than after 2-3 cycles. This was similar to IV NSCLC patients receiving chemotherapy [34], indicating that chemotherapy and its intensity can interfere with the results of comprehensive treatment. Thus, for the patients who received 4-6 cycle chemotherapy, the OS of the primary tumour at ≥ 63 Gy trend to longer than at <63 Gy, but the PFS was not statistically different ($P = 0.356$). Radiotherapy as a local treatment would treat the primary tumour, and chemotherapy would control not only primary tumours but also metastases. New metastases or small metastases can reduce PFS, but patients can survive with the tumour. Three-dimensional radiotherapy to the primary tumour may affect the OS, and the emergence of new metastatic lesions is not a direct death factor for patients [25]. Systemic and local treatment may be more important for squamous stage IV NSCLC. Therefore, different intensities of combined chemotherapy and radiotherapy were analysed (Table 3). Four cycles of chemotherapy with a primary tumour dose ≥ 63 Gy were defined as radical treatment. The results showed with intense chemo-radiotherapy, the MST were 3, 8, 10, and 14 months, the OS gradually increased, and the PFS was no significant difference ($P = 0.377$). For radical treatment, the 1-, 2-, 3-, and 5-year OS rates were 54.3%, 27.2%, 24.9%, and 8.3%, respectively, and the PFS was 5 months. These results demonstrated that the increase in the chemotherapy cycle and radiotherapy dose may prolong OS and PFS in IV NSCLC. If the patients tolerate the radio-chemotherapy toxicity, adequate chemotherapy and radical radiation therapy will control not only the metastatic disease but also the primary tumour. The combined treatment contribution to improved survival may be important [24].

Compared to patient age and number of metastatic lesions, the response after comprehensive treatment multivariate analysis showed that primary tumour radiation dose was an independent prognostic factor, and ≥ 63 Gy provided better OS and LRPFS. This was similar to the results from previous studies with IV NSCLC [23].

We acknowledge several limitations to the current study. Although we found that a dose of 63 Gy was associated with better OS, the range of doses for the thoracic lesions was broad, from 36 to 72 Gy, and the choice of dose depended on factors such as PS and tumour burden, leading to possible selection bias. Moreover, we found that radiation dose remained a predictor of improved survival outcomes even when patient and treatment factors were considered in the multivariate analyses. Finally, we recognize that the limited number of patients means that additional studies and patients will be needed in the future.

Conclusions

In summary, chemotherapy given concurrently with 3D-RT to the primary tumour may improve survival in stage IV squamous NSCLC. The radiation dose to the primary tumour was the main contributor to OS. Consistent with conclusions from previous studies we reported [22-24], we found that aggressive radiation to the primary tumour improved survival outcomes for a subset of patients with metastatic NSCLC. Further randomized trials and more patients are warranted to evaluate the optimal thoracic radiation dose (palliative or aggressive) in combination with chemotherapy. Additional trials are

necessary to investigate the value of thoracic radiation in combination with targeted therapy or immunotherapy for patients with advanced NSCLC.

List Of Abbreviations

NSCLC: Non-small cell lung cancer; LRPFS: Local-regional progression-free survival; OS: Overall survival; PFS: Progression-free survival; MRI: Magnetic resonance imaging; CT: Computed tomography; 2D: Two-dimensional; 3D: Three-dimensional; KPS: Karnofsky Performance Status; GTV: Gross tumour volume; C: Cisplatin; Cb: Carboplatin; P: Paclitaxel; D: Docetaxel; V: Vinorelbine; MST: Median survival time.

Declarations

Ethics approval and consent to participate

This retrospective study was reviewed by the ethical review boards in China (Ethics Committee of the Affiliated Hospital of Guiyang Medical University, Guiyang, China), and all patients' data were obtained by reviewing the medical records.

Consent for publication

Not applicable

Availability of data and material

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XH W,B L designed the study. YC G,QN Z, Z M, YX H, WW O, SF S,QS L, HQ L, RF L,HT L,SH W and LN W collected the data. YC G,QN Z, SF S, B L, and XH W undertook the data analyses and interpretation, performed the statistical analyses and wrote the report.

All authors have read and approved the final manuscript.

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Tables

Table 1 Clinical characteristics

Characteristic		Squamous carcinoma n=183	Squamous carcinoma Δ n=161	Non-squamous carcinoma n=446	Non-squamous carcinoma Δ n=402
Gender	Male	161	142	304	269
	Female	22	19	142	133
Age (years)	≤ 65	130	116	159	318
	≥ 65	53	45	62	84
T stage	T1-2	58	53	166	148
	T3-4	125	108	278	252
N stage				Unknown=2*	Unknown=2*
	N0-1	26	23	64	58
	N2-3	157	138	382	344
PTV dose[Gy]	Median	57.6	59.4	60.3	63
	dose				
	≤ 63	109	90	235	205
Chemotherapy cycle	≥ 63	74	71	211	197
	Median	3	4	4	4
	0	2	0	7	0
	1	10	0	23	0
	2	48	41	76	72
	3	35	35	89	85
	4	83	80	223	217
	5	3	3	19	19
	6	2	2	9	9
Metastasis lesions	1-5	106	93	224	211
	≥ 5	77	68	222	191

△at least 2 chemotherapy cycles and a thoracic radiation dose of at least 36 Gy

*T stage could not be measured due to pleural effusion

Table 2. Clinical factors associated with survival outcomes

MST95% CImonths	OS %				N	MST95% CImonths	PFS %				χ^2	P
	1	2	3	5			1	2	3	5		
											0.417	0.519
119.493-12.507	45.7	14.1	11.2	2.2	101	64.997-7.003	13.8	5.7	0	0	0.024	0.877
1211.143-12.857	49.5	15.9	6.8	4.2	276	53.927-6.073	17.3	5.2	3.0	0		
											0.652	0.419
118.325-13.675	43.4	13.8	9.9	2.0	35	61.290-10.710	6.1	3.0	0	0		
119.269-12.731	46.9	14.2	10.7	2.3	66	84.873-11.127	18.0	5.4	2.7	0	1.838	0.175
											1.836	0.175
1410.654-17.346	60.1	23.1	23.1	0	12	74.737-9.263	25.0	8.3	0	0		
119.222-12.778	43.3	12.6	9.1	2.3	89	53.879-6.121	12.2	4.1	0	0	2.625	0.103
											3.053	0.081
118.971-13.029	47.6	18.3	17.1	3.9	48	62.605-9.395	15.3	10.9	2.7	0		
129.235-14.765	43.6	9.0	4.0	0	53	54.029-5.971	12.2	0	0	0	0.939	0.332
											6.069	0.014
1311.007-14.993	50.2	20.7	16.1	1.9	62	64.464-7.536	15.2	8.4	2.1	0		
106.724-13.276	39.5	3.7	3.7	1.8	39	53.103-6.897	11.4	0	0	0		

Table 3. Effects of different doses and comprehensive treatments on OS and PFS

MST95% CI months	OS%				χ^2	P	N	MST95% CI months	PFS%				χ^2	P
	1	2	3	5					1	2	3	5		
43.200-4.800	8.3	0	0	0	31.028	0.000	3	50.000-13.002	0	0	0	0	1.775	0.620
84.727-11.273	31.7	5.3	0	0			13	84.562-11.438	15.4	0	0	0		
119.250-12.750	45.5	7.1	3.8	0			47	63.521-8.479	15.3	4.4	0	0		
129.277-14.723	46.1	21.3	17.9	5.0			44	54.241-5.759	10.7	10.7	3.6	0		
905.519-12.481	36.7	10.5	5.2	0	7.231	0.027	13	84.562-11.438	7.7	0	0	0	0.192	0.909
119.171-12.829	45.2	7.5	4.0	0			46	63.546-8.454	15.6	4.5	0	0		
129.072-14.928	48.9	21.8	18.4	5.1			42	54.252-5.748	11.2	11.2	3.7	0		
1108.765-13.235	43.3	8.2	4.4	0	7.222	0.007	59	74.768-9.232	15.6	3.5	0	0	0.188	0.665
129.072-14.928	48.9	21.8	18.4	5.1			42	54.252-5.748	11.2	11.2	3.7	0		
1311.244-14.756	57.9	10.1	3.8	0	3.357	0.067	28	107.500-12.500	26.0	7.4	0	0	0.853	0.356
149.174-18.826	54.3	27.2	24.9	8.3			23	53.514-6.486	16.3	16.3	8.2	0		
906.780-11.220	30.1	5.7	4.3	0	12.433	0.000	51	53.967-6.033	6.0	2.0	0	0	8.909	0.003
1310.680-15.320	54.3	19.2	15.4	4.1			51	85.947-10.053	21.6	9.6	3.2	0		
300.000-6.601	0	0	0	0	24.497	0.000	2	—	0	0	0	0	3.378	0.337
84.597-11.403	28.9	5.8	2.9	0			21	51.636-8.364	9.5	0	0	0		
105.868-14.132	30.0	0.0	0	0			8	54.219-5.781	0	0	0	0		
149.174-18.826	54.3	27.2	24.9	8.3			23	53.514-6.486	16.3	16.3	8.2	0		
1008.377-11.623	37.2	7.5	4.8	0	13.180	0.000	84	53.822-6.178	12.2	3.7	0	0	0.656	0.418
149.174-18.826	54.3	27.2	24.9	8.3			23	53.514-6.486	16.3	16.3	8.2	0		

Table 4 Multivariate analysis for overall survival

	HR	95.0% confidence interval		χ^2	P value
		Lower	Upper		
Age	0.788	0.541	1.149	1.536	0.215
65 Gy vs. ≥65 Gy					
Metastatic lesions	1.324	0.939	1.867	2.562	0.109
1-5 vs. ≥5					
Primary tumour	0.703	0.498	0.991	4.051	0.044
radiation dose					
63 Gy vs. ≥63 Gy					
Response	1.347	0.933	1.947	2.521	0.112
ORR vs. NRR					

ORR:CR+PR; NRR:SD+PD