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Prospective study of icotinib concurrent IMRT in patients with inoperable stage Ⅲ non-small cell lung cancer

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Abstract

To evaluate the safety profile and efficacy of icotinib concurrent with intensity modulated conformal radiotherapy (IMRT) in previously untreated patients with inoperable Stage Ⅲ non-small cell lung cancer (NSCLC). 90 patients were enrolled in this prospective study. All patients were assessed for toxicity, and 78 patients were available for efficacy. 24 patients were treated with icotinib concurrent IMRT with curative intent. The primary endpoints were overall survival (OS). The secondary endpoints included progression free survival (PFS), local control rate and acute toxicity. Loss of appetite, leucopenia, rash, pulmonary toxicities were acceptable and manageable. Severe adverse events included pain (Grade 4, 12.5%) and leucopenia (Grade 4, 4.17%), rash (Grade 4, 4.17%). With a median follow-up of 321 days, a local control rate of 95.8% was achieved for thoracic tumor. Overall survival and median PFS were 377 days, 289 days. The current experimental data suggested that icotinib concomitant IMRT was effective and safe for patients with advanced NSCLC as first-line regimen.

1. Background

Non small cell lung cancer (NSCLC) is the leading cause of cancer-related death worldwide [1]. Cure rates remain low for those diagnosed with stage III non small cell lung cancer (NSCLC), and modest progress has been seen over the last 25 years. Traditionally, platinum-based combination chemotherapy represents the standard first-line treatment [2]. Despite this progress, no single chemoradiotherapy regimen can be considered

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standard of care, but both local and distant control remain suboptimal, and the majority of patients continue to die from distant metastases.

Multiple clinical trials have shown Asian patient with NSCLC has more mutations in the EGFR gene [3-4]. These patients are extremely sensitive to treatment with EGFR-specific tyrosine kinase inhibitors (TKIs). EGFR mutation-positive patients with EGFR-TKI treatment efficiency can reach as high as 70-80%,and compared to chemotherapy, oral EGFR-TKI therapy can significantly extend progression-free survival phase and improve the quality of life［5-8］. Patients with advanced EGFR-mutant non-small cell lung cancer (NSCLC) typically respond well to treatment with an EGFR tyrosine kinase inhibitor (TKI).

At present, the basic and pre-clinical studies have confirmed that EGFR-TKI therapy combined with radiation have a synergistic effect [9-10]. In 2011, investigators from the ICOGEN reported their initial results from a randomised, double-blind phase 3 non-inferiority trial [11]，395 patients were treated with icotinib and gefitinib. Icotinib was non-inferior to gefitinib in terms of progression free survival (HR 0•84, 95% CI 0•67–1•05; median progression-free survival 4•6 months [95% CI 3•5–6•3] vs 3•4months [2•3–3•8]; p=0•13). On the basis of the promising survival results reported on the ICOGEN, we designed a retrospective study to assess whether icotinib concurrent IMRT was responsible for the improved progression-free survival (PFS), overall survival (OS) and local control rate.

2. Materials and methods

2.1 Samples

There were ninety patients in this prospective study patients with histologic or cytologic confirmation of NSCLC with unresectable stage IIIA or IIIB disease were assessed for eligibility. Unresectable stage IIIA disease has been defined by multiple and/or bulky N2 mediastinal lymph nodes on computed tomography (CT) scan such that, in the opinion of the treating investigator, the patient was not a candidate for surgical resection. N2 disease had been documented by biopsy, fluorodeoxyglucose positron emission tomography (PET), or CT if nodes were more than 2 cm. Stage IIIB patients must have had N3 or T4 status. N3 status must have been documented by the presence of a contralateral (to the primary tumor) mediastinal lymph node or supraclavicular or scalene lymph node proven by biopsy, fluorodeoxyglucose PET, or more than 2 cm on CT scan. Patients with disease extending into the cervical region were not eligible. Eligible patients for initial TP/IMRT also met the following criteria: measurable or assessable disease; no prior chemotherapy or IMRT; preregistration forced expiratory volume in 1 second (FEV1) ≥ 1 L by spirometry within 42 days of study treatment; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1 at baseline; unintended weight loss of less than 5% in the 3 months preceding study treatment; EGFR gene mutations were detected, 18, 19, 20, 21 target gene at least one locus mutations; and adequate bone marrow (absolute neutrophil count ≥ 1,500/μL, platelets ≥ 100,000/μL, and hemoglobin ≥ 8 g/dL), renal (serum creatinine ≤ 2 mg/dL or calculated creatinine clearance ≥ 50 mL/min), and hepatic function (bilirubin ≤ institutional upper limit of normal [ULN], AST ≤ 2.5×ULN if alkaline phosphatase is ≤ ULN, or alkaline phosphatase ≤ 4× ULN if AST is ≤ ULN). Patients were excluded if they had symptomatic peripheral neuropathy (must be ≤ grade 1) at baseline, malignant effusions (pleural or pericardial), superior sulcus (Pancoast) tumors, or significant cardiac disease (uncontrolled hypertension, unstable angina, congestive heart failure, myocardial infarction in prior year, or ventricular arrhythmias requiring medication). Eligibility for consolidation therapy required completion of initial chemoradiotherapy within 4 to 8 weeks of random assignment without local progression or distant metastases, ECOG PS of 0 to 2 at random assignment, adequate bone marrow and hepatic function (same as baseline requirements), and

absence of symptomatic peripheral neuropathy before random assignment. All patients provided written informed consent before treatment.

2.2 Procedures

Radiotherapy or chemotherapy treatment was taken according to RTOG or NCCN guidelines [12]. Gene mutations were investigated retrospectively (before unblinding of this study) with an EGFR PCR kit (Scorpions amplification refractory mutation system, Qiagen, Germany) to analyse exons 18–21 when paraffin-embedded tissues were available. Patients received docetaxel 20mg/㎡ intravenously (IV) on days 1，and cisplatin 30mg/㎡ IV on days 1，1 time / week, 8 times. Icotinib was given orally in as dose of 125mg 8-hourly. IMRT was administered as 2.0 Gy daily treatments 5 days a week for a total of 30 fractions. The total dose of IMRT was 60 Gy in 30 fractions. IMRT planning underwent central review. Radiotherapy target definition follows the International Commission on Radiation Units and measurement (ICRU) 62-document defines. Gross target volumes included the primary tumor and abnormally enlarged regional lymph nodes more than 1 cm in short axis. The primary and secondary target volumes included a minimum of a 2-cm margin. Elective treatment of supraclavicular lymph nodes was not allowed. Two-centimeter margins were required for IMRT to the ipsilateral hilar lymph nodes and superior mediastinal lymph nodes, and at least 3-cm margins were required below the carina for subcarinal lymph nodes. Treatment interruptions of IMRT were discouraged unless grade 3 or greater non hematologic toxicity or grade 4 hematologic toxicity necessitated disruptions. Patients underwent repeat tumor measurements within 4 to 8 weeks of completing TP/IMRT. Patient assignment was stratified by PS (0 to 1 v 2), stage (IIIA v IIIB), EGFR status Mutant（18，9，20，21）and Smoking status (Smokers v no Smokers). Patients were allowed to receive prophylactic granulocyte colony-stimulating factor support during consolidation docetaxel treatment.

2.3 Study Evaluation and Follow-Up

The evaluation included a complete medical history and physical examination including performance status, laboratory analysis, pulmonary function tests, ECG, and a brain scan. Baseline history and physical examination, assessment of ECOG PS, FEV1, Complete Blood Count(CBC) with platelet count, serum chemistries (repeated on days 8, 29, and 36), and disease evaluation (CT of chest through the upper abdomen) were obtained on all patients. Bone scan was performed only if clinically indicated. PET scans were not mandated. Brain imaging (either CT or magnetic resonance imaging) was mandatory at baseline. Toxicity assessments and CBC with platelets were obtained weekly throughout TP/IMRT. On completion of all assigned therapy, responses were to be confirmed within 4 weeks, and follow-up continued every 3 months for the first 2 years, every 6 months for years 2 to 5, and yearly thereafter, with repeat CT of chest through the adrenals on each visit.

2.4 Statistical Methods

The response was evaluated based on the RECIST (response evaluation criteria in solid tumors) criteria [13]. The primary end point of this study was to overall survival (OS) between the two assigned groups and observation group (icotinib concurrent IMRT vs TP concurrent chemoradiotherapy, icotinib monotherapy vs TP concurrent chemoradiotherapy). The secondary end points of this study included a comparison of progression-free survival (PFS) among the three groups and further characterization of the toxicities of the drugs. We assessed quality of life with the use of the fourth edition of the Functional Assessment of Cancer Therapy–Lung (FACT-L) questionnaire and the Lung Cancer Symptoms Scale (LCSS) [14]. Toxic effects were monitored and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0 [15]. To analyse PFS and OS, survival curves were drawn using the

Kaplan-Meier method. Survival differences were evaluated using the log-rank test. Clinical data were analysed using the Pearson's chi-square test. A two-tailed P <0.05 was considered significant. All analyses were performed using SPSS statistical software SPSS Version 19.0 for Windows, SPSS Inc, USA).

3. Result

3.1 Study population

From November 2011 until September 2013, 90 patients were entered onto the trial, and 78 patients for eligibility assessment. This is the analysis cohort in this report. Patient demographics and disease characteristics for enrolled patients (n = 78) are listed in Table 1.

Table 1 Patients Demographics and Disease Characteristics

Demographic Characteristic	Icotinib concurrent IMRT (n=24)	TP concurrent radiotherapy (n=27)	Icotinib monotherapy (n=27)
Sex			
Men	7（29%)	11(41%)	8(30%)
Women	17(71%)	16(59%)	19(70%)
Smoking			
Smokers	19(79%)	21(78%)	17(63%)
Non-smokers	5(21%)	6(22%)	10(37%)
PS			
0–1	20(83%)	23(85%)	13(48%)
2	4(17%)	4(15%)	14(52%)
Disease stage			
IIIA	2(8%)	3(11%)	4(15%)
IIIB	22(92%)	24(89%)	23(85%)
EGFR Mutant			
18	0	0	0
19	12(50%)	16(59.3%)	20(74.1%)
20	1(4.2%)	0	0
21	9(37.5%)	9(33.3%)	5(18.5%)
19、21	2(8.3%)	2(7.4%)	2(7.4%)
Age（years)			
40-50	0	5(18.5%)	0
51-60	9(37.5%)	15(55.6%)	3(11.1%)
61-70	12(50%)	7(25.9%)	12(44.4%)
71-80	3(12.5%)	0	10(37.1%)
>80	0	0	2(7.4%)
Staged by PET	3(12.5%)	2(7.4%)	3(11.1%)
FEV1 > 2/ L	10(42%)	16(60%)	9(33.2%)

Abbreviations: PS, performance status; PET, positron emission tomography.

Approximately two third of patients entered were female, and approximately 12% had stage IIIA disease. All patients had an FEV1 of more than 1 L at baseline, and almost half of the patients had an FEV1 of more than 2 L. Approximately 1% of patients were staged by PET. There is considerable variation among the three groups. There were a higher percentage of patients on the icotinib monotherapy group than the TP concurrent chemoradiotherapy group (88.9% v 25.9%, respectively; P=0.003) greater than60. Compared the age structures between the icotinib concurrent IMRT group and TP concurrent chemoradiotherapy group, There was significant difference in patient characteristics between the two groups greater than 60(62.5% v 25.9%, respectively; P = 0.005).

3.2 Toxicity

Table 2 lists adverse events, drug-related adverse events and grade 3 and 4 adverse events. In patients receiving TP concurrent chemoradiotherapy, (85.19%) experienced nausea, (3.70%) had grade 3 to 4. (74.07%) experienced leucopenia, (14.81%) had grade 3 to 4. (88.89%) experienced loss of appetite, (11.11%) had grade 3 to 4. In comparison, only 12.5% of patients in icotinib concurrent with IMRT group experienced grade 3 to 4 rash during a comparable period of time. Furthermore, 94% of patients required hospitalization during TP/IMRT. During the 8 weeks after enrolled, 92% of patients required hospitalization during TP concurrent chemoradiotherapy treatment compared with 79% of patients in icotinib monotherapy group and 86% of patients in icotinib concurrent IMRT group. More patients in TP concurrent chemoradiotherapy group (29%) required a blood transfusion compared with patients in icotinib monotherapy group (15%) and icotinib concurrent IMRT group (19%). This difference, however, did not reach statistical significance (P =0.190).

Table 2 Adverse events and drug-related adverse events

	All adverse events			Grade 3–4 adverse events			Drug-related adverse events		
	Icotinib concurrent IMRT (n=24)	Icotinib monotherapy (n=27)	TP concurrent radiotherapy (n=27)	Icotinib concurrent IMRT (n=24)	Icotinib monotherapy (n=27)	TP concurrent radiotherapy (n=27)	Icotinib concurrent IMRT (n=24)	Icotinib monotherapy (n=27)	TP concurrent radiotherapy (n=27)
Rash	9(37.5%)	13(48.14%)	1(3.70%)	3(12.5%)	2(7.41%)	0	4(16.67%)	7(25.93%)	0
Diarrhoea	3(12.5%)	6(22.22%)	2(7.41%)	0	0	0	2(8.33%)	2(7.41%)	0
Pain	7(29.17%)	8(29.63%)	9(33.3%)	2(8.33%)	1(3.70%)	2(7.41%)	1(4.17%)	3(11.11%)	2(7.41%)
Hypohepatia	2(8.33%)	1(3.70%)	7(25.93%)	0	0	2(7.41%)	0	0	2(7.41%)
Pneumonitis	6(25.0%)	0	10(37.04%)	0	1(4.17%)	2(7.41%)	0	0	0
RT esophagitis	6(25.0%)	0	10(37.04%)	0	1(4.17%)	3(11.11%)	0	0	0
Loss of appetite	14(58.33%)	9(33.33%)	19(88.89%)	0	0	3(11.11%)	9(37.5%)	3(11.11%)	23(85.19%)
Vomiting	3(12.5%)	0	21(77.78%)	0	0	1(3.70%)	1(4.17%)	0	20(74.07%)
Oral ulcer	0	0	5(18.52%)	0	0	1(3.70%)	0	0	2(7.41%)
Leucopenia	5(20.83%)	5(18.52%)	20(74.07%)	1(4.17%)	0	4(14.81%)	3(12.5%)	1(3.70%)	15(55.56%)
Nausea	4(16.67%)	2(7.41%)	23(85.19%)	0	0	1(3.70%)	1(4.17%)	0	18(66.67%)
Alopecia	0	0	22(81.48%)	0	0	1(3.70%)	0	0	21(77.78%)
Total patients*	19(79.17%)	20(74.07%)	23(85.18%)	5(20.83%)	1(4.17%)	8(29.63%)	16(66.3%)	14(51.85%)	22(81.48%)

All adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0)*Total number of patients who had at least one adverse event in each group; some patients had more than one adverse event.

3.3 Treatment Administe

Of 90 patients entered, 78 (86.7%) were enrolled (24 patients to the icotinib concurrent IMRT group, 27 patients to the icotinib monotherapy group and 27 patients to the TP concurrent chemoradiotherapy group). 12 patients were not enrolled as a result of the following reasons: toxicities during PE/IMRT (4.4%), progressive disease duration of the 4-8 weeks treatment period(2.2%), patient decision (1.1%), death duration of the 4-8 weeks treatment period.(2.2%), physician decision (1.1%), and miscellaneous reasons such as not completing TP/IMRT for other reasons, requiring a procedure, insurance issues, and so on (2.2%).

3.3 Efficacy

The unplanned interim analysis of this study showed that icotinib concurrent with IMRT group has a good clinical efficacy. There were 18 (75%) patients in the icotinib concurrent with IMRT group had an event (13 [54.17%] progressions and 5 [20.83%] deaths） as did 23 (85.19%) patients of those in icotinib monotherapy group (16 [59.26%] progressions and 7 [25.93%] deaths）and 17 (62.96%) patients in TP concurrent chemoradiotherapy group (11 [40.74%] progressions and 6 [20.22%] deaths.

Current data (as of March 1, 2013) of the 78 patients considered adhere to this established trend. The median follow-up time was 312 days. Progression free survival was defined as the duration between the date of beginning and the date of the earliest occurrence of disease progression or death. Overall survival was defined as the time between the date of beginning and the date of death due to any cause. Time to progression was defined as the duration between the date of beginning and the date of the earliest

occurrence of disease progression.

Progression free survival was consistent across clinical subgroups such as disease stage, sex, ECOG performance status, smoking status and EGFR-status. In the full analysis set, median progression-free survival was 289 days [95% CI: 245.152-332.848] in icotinib concurrent with IMRT and 269 days [95% CI: 247.405-290.595] in TP concurrent chemoradiotherapy (log-rank P=0.549). There was no difference in progression-free survival between the two groups (Fig. 1).

Fig.1

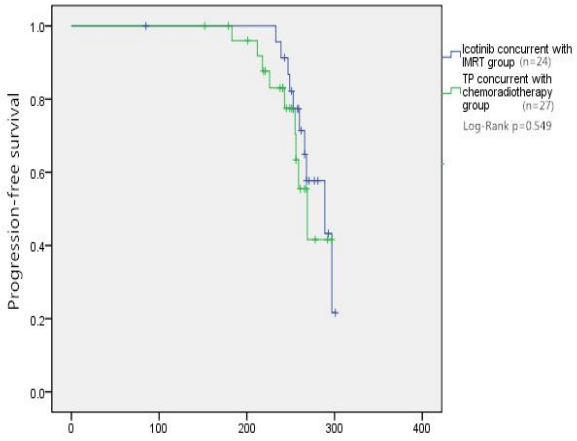

Fig. 1 Median progression-free survival was 269 days [95% CI：247.405-290.595] in the TP concurrent chemoradiotherapy group and 289 days [95% CI: 245.152–332.848] in the Icotinib concurrent IMRT group (log-rank P =0.549).

This difference was significant in Icotinib monotherapy group VS TP concurrent chemoradiotherapy group (log-rank P=0.001). The progression-free survival in the full analysis set,Median progression-free survival was 159 days (95% CI: 155.572-162.428) in icotinib monotherapy group and 269 days (95% CI: 247.405-290.595) in TP concurrent chemoradiotherapy (Fig. 2).

Fig.2

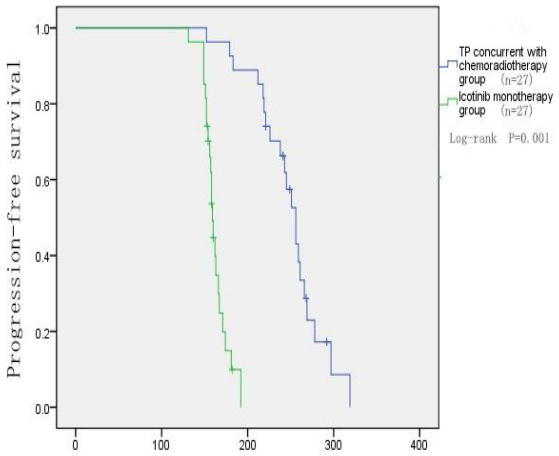

Fig. 2 Median progression-free survival was 269 days [95% CI: 247.405-290.595] in the TP concurrent chemoradiotherapy group and 159 days [95% CI: 155.572-162.428] in Icotinib concurrent with IMRT (log-rank P =0.01).

We obtained overall survival data in 30 September 2013. By that time 56 patients had died, 15 (62.50%) in the icotinib concurrent with IMRT group, 23 (85.19%) in the icotinib monotherapy group and 18 (66.67%) in the TP concurrent with chemoradiotherapy group.

We noted overall survival was significantly longer with TP concurrent chemoradiotherapy group than icotinib concurrent with IMRT group. Median overall survival was 411 days in the TP concurrent chemoradiotherapy group and 377 days in the icotinib concurrent IMRT group (Fig. 3).

There was also significant difference in the overall survival between TP concurrent chemoradiotherapy group and icotinib monotherapy group. Median overall survival time of 411 days in the TP concurrent chemoradiotherapy group and 337 days in the icotinib monotherapy group (Fig. 4).

Fig.3

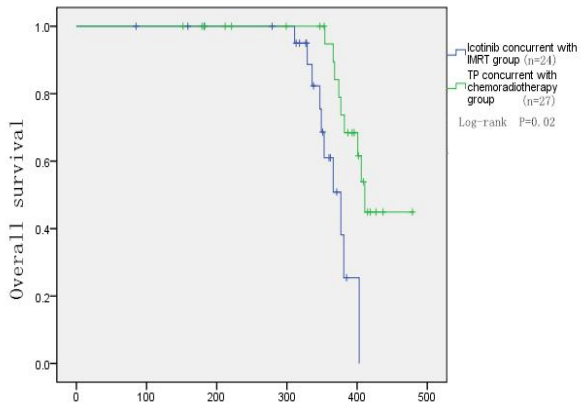

Fig. 3 Median overall survival was 411 days [95% CI：395.472–426.528] in the TP concurrent chemoradiotherapy group and 377 days [95% CI: 345.629–408.37] in the Icotinib concurrent IMRT group (log-rank P =0.02).

Fig.4

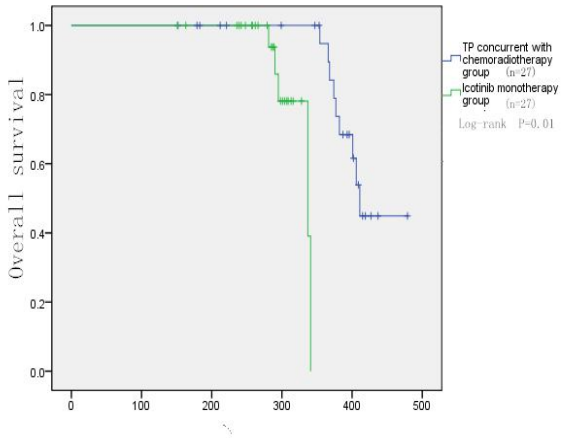

Fig. 4 Median overall survival was 411 days [95% CI: 395.472–426.528] in the TP concurrent chemoradiotherapy group and 337 days [95% CI: 277.591–396.409] in the Icotinib monotherapy group (log-rank P =0.01).

Objective responses were noted in much the same proportion of patients in icotinib concurrent IMRT group and TP concurrent chemoradiotherapy group (Table 3); disease control was also similar in both groups.

Table 3 Best response by RECIST n（%）

	Icotinib concurrent IMRT group (n=24)	TP concurrent radiotherapy group (n=27)	Icotinib monotherapy group (n=27)
Complete response	1（4.17%）	0	0
Partial response	15(62.5%)	17 (62.96%)	8(29.6%)
Stable disease	7(29.16%)	8 (29.63%)	14(51.9%)
Progressive disease	1(4.17%)	2 (7.41%)	5(18.5%)
Objective response	16（66.67%）	17 (62.96%)	8（29.6%）
Disease control	23(95.8%）	25 (92.6%)	22(81.5%)

4. Discussion

Despite this prospective study failed to achieve the primary objective of improved overall survival (OS) with the icotinib concurrent IMRT for this population of patients with stage III NSCLC, Icotinib concurrent IMRT regimen in this study resulted in improved progression-free survival (PFS) and local control rate superior to TP concurrent chemoradiotherapy and icotinib monotherapy group. Our study also demonstrated that TP concurrent chemoradiotherapy substantially increases the risk for leucopenia, grade 3 to 4 pneumonitis (defined as requiring supplemental oxygen or mechanicalventilation), hospitalization, and premature death in some patients. An increased risk for pneumonitis and worse outcomes in patients with a volume of lung receiving at least 20 Gy exceeding 35% have previously been reported[16].Therefore, caution should be used when considering this regimen in patients with a high volume of lung receiving at least 20 Gy, particularly those with significantly compromised lung function (FEV1 < 2 L). There was a slight imbalance (P = not significant) of patients who had an FEV1 ≥ 2 L, favoring the control arm. This may have partially contributed to the higher rates of pneumonitis in the docetaxel arm. The rates of toxicities observed with TP concurrent chemoradiotherapy on this study are

consistent with those seen in other studies. Given the results of our trial, we recommend the use of icotinib concurrent IMRT can be used as a treatment for non small cell lung cancer, especially suitable for in elderly patients with EGFR mutation.

Why did our study fail? Our study has several limitations. First, we used one-sided type I error of 0.05 designed as a non-inferiority trial. However, insufficient sample size had little effect on type I error because median progression-free survival was 289 days, which was longer than that TP concurrent chemoradiotherapy for 269 days. Second, the patient and disease characteristics in this study was incomplete similarity, we non-selected the eligible patients with non-small-cell lung cancer. The retrospective study contained different therapy regimens， different performance status and other baseline characteristics. Apart from different therapy regimens, patients' ages and performance status may main factors which affected the survival rate. Therefore, it could impact on the overall survival of the patients. Third, other potential selection biases should be considered. For example, the TP concurrent chemoradiotherapy group had more patients who received just one regimen of chemotherapy than did the icotinib concurrent with IMRT group and icotinib monotherapy group. However, this limitation does not seem to have distorted our retrospective findings.

Significant improvements in outcomes for patients with stage III NSCLC will be realized when advances in systemic therapy are discovered. This remains a challenge because NSCLC is a biologically and clinically heterogeneous disease. Local control of disease is necessary but not sufficient to significantly improve outcomes. The vast majority of patients with stage III NSCLC have systemic disease at diagnosis, evidenced by the poor long-term survival rates with local modalities, namely XRT or surgery, alone. However, many clinical trials show that use of chemotherapy drug alone, the survival phase can only maintained 8 to 10 months, the 1-year survival rate is 35%, the 2-year survival rate was close to 15% to 20% [17], so traditional chemotherapy has reached the “bottleneck effect”. Discovery of mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) gene in lung adenocarcinoma greatly stimulated biomarker research on predictive factors for EGFR tyrosine kinase inhibitors (TKI), such as icotinib. Patients with activating mutations of the EGFR generally respond to EGFR-TKIS very well, therefore, strategies to improve outcomes by applying more effective systemic treatment have generally tested the use of more EGFR-TKIS.

In addition to our prospective study, at least three randomized trials evaluating the role of EGFR-TKIS with concurrent radiotherapy for NSCLC has been reported [18-20]. Collectively, these studies has reported concurrent EGFR-TKIs with individualized RT shows a favorable safety profile and promising outcome, therefore serving as a therapeutic option for patients with locally advanced or metastatic NSCLC. However, these data fail to support further trials of EGFR-TKIs and thoracic radiation therapy (TRT) for unselected NSCLC patients. This therapeutic strategy may hold promise, particularly suitable for locally or advanced NSCLC in patients with sensitizing EGFR mutations. In addition, these trials support that concomitant treatment was well tolerated, with promising activity and a significant improvement of Quality Of Life (QL) in a Chinese population from NSCLC the use of one chemotherapy regimen over another.

It seems that we have reached a plateau in survival using current chemotherapy agents against stage III NSCLC. In view of these findings, strategies to incorporate newly available molecularly targeted agents into chemoradiotherapy approaches are of high interest. Orally administered epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIS), such as icotinib, are theoretically attractive in this setting. EGFR is frequently over expressed in NSCLC and correlates with a poor prognosis [21-23]. Moreover, these agents have proven to be clinically effective. With increased

awareness for genetic counseling and testing, early detection and treatment, the odds can be improved. Complex therapy is a progress direction of tumor therapy. Icotinib concurrent chest radiation is a valid therapeutic option for patients with non-small-cell lung cancer as a first-line or second-line treatment, although patients might find taking icotinib three times a day an inconvenience. This treatment is particularly suitable for older and worse performance status patients. Furthermore, clinical observation found that patients with 19 gene locus mutations are more likely to benefit from icotinib than those without. To date, there is sufficient evidence indicating that EGFR-TKIS concurrent chest radiation further improves survival rates. However, many questions remain unanswered in the treatment of stage III disease, including defining individualizing XRT dose and schedule based on pulmonary function, tumor volumes, and newer XRT technologies.

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