RESULTS OF CONCURRENT CHEMORADIOTHERAPY OF 30 PATIENTS WITH INOPERABLE STAGE III NON-SMALL CELL LUNG CANCER, USED PET/CT PLANNING RADIATION PLAN AT 108 MILITARY CENTRAL HOSPITAL

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Summary

Objectives: To evaluate the results of concurrent chemoradiotherapy in patients with inoperable stage III non-small cell lung cancer using FDG-PET/CT to plan radiotherapy. ***Subjects and methods:*** A prospective, interventional, non-controlled, longitudinal study on 30 patients with inoperable stage III non-small cell lung cancer. PET/CT was used for staging, planning radiation therapy in concurrent chemoradiotherapy, and evaluating treatment results. Chemotherapy regimen was Paclitaxel/Carboplatin. Intensive modulated radiotherapy (IMRT) was applied with a target radiation dose of 60 Gy. ***Results:*** Based on PERCIST 1.0, the proportions of complete, partial response, stable disease and progressive disease followed by 33.33%, 43.33%, 10%, respectively, and 10%, with median progression-free survival time being 21.03 months and mean overall survival being 26.27 months. The probability of survival after 1, 2, and 3 years was 0.89; 0.83 and 0.83. Side effects on the hematopoietic system and outside the hematopoietic system mainly belonged to grade 1 - 2. ***Conclusion*:** Using PET/CT in stage diagnosis and planning radiotherapy in concurrent chemoradiotherapy improved progression-free survival time and overall survival of patients.

** Keywords: Stage III inoperable non-small-cell lung cancer (stage III NSCLC); Concurrent chemoradiotherapy (CHRT); PET/CT; Chemotherapy; Radiotherapy.*

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INTRODUCTION

Lung cancer is one of the most common ones and the leading cause of cancer death worldwide. Lung cancer is histologically divided into 2 main types, including small cell lung cancer and non-small cell lung cancer (NSCLC), with the proportions being about 15% and 85%. Despite significant advances in early diagnosis and treatment, the 5-year survival rate of patients is still the lowest of all cancers. Concurrent chemoradiotherapy (CHRT) remains the therapeutic standard for locally advanced inoperable NSCLC [1]. PET/CT has a much higher sensitivity and specificity than CT, and distinguishes tumor lesions from collapsed lung areas, thus not only helping to accurately diagnose the stage for NSCLC but also is also being used for simulation, planning radiation therapy and helping to avoid missing lesions. PET/CT technique has been applied in Vietnam since 2009 but is mainly used to diagnose the NSCLC stage. Its role in planning radiotherapy simulation in concurrent chemoradiotherapy and assessment of treatment results for inoperable stage III NSCLC patients has still been hardly studied. Therefore, this research was conducted: *To evaluate the results of concurrent chemoradiotherapy in patients with inoperable stage III non-small cell lung cancer using FDG-PET/CT for radiotherapy planning.*

SUBJECTS AND METHODS

1. Subjects

A convenience sample of 30 patients with inoperable stage III NSCLC was selected and subjected to concurrent chemoradiotherapy, PET/CT based diagnosis, radiotherapy planning and treatment outcome assessment at 108 Military Central Hospital, from September 2015 to January 2022.

* *Selection criteria:*

- Definite diagnosis of NSCLC by histopathology

- Classifying inoperable stage III according to the TNM staging criteria version 8 by the International Society for Thoracic Cancer (IASLC 2016). Patients with data collected prior to 2017 will be transitioned to this classification. The patients were staged by PET/CT scan and brain magnetic resonance imaging (MRI) within 28 days before treatment. Patients were diagnosed with inoperable stage III NSCLC including stage IIIB and IIIC. Particularly, stage IIIA is selected only in the case of stage T4 with invasive large tumor, invasive N2 or N1 lymph nodes grown over 2 cm, or inoperable lymph node stages [1, 2].

- $FEV_1 \geq 50\%$ predicted. Overall score with WHO/ECOG index 0 - 1. Age: < 75 years old.

- The indexes of blood tests, heart function, liver, and kidney function were within normal limits.

** Exclusion criteria:*

- The patient was previously treated by other methods such as surgery, chemotherapy, or radiation therapy.

- There were any contraindications to chemotherapy with Paclitaxel/ Carboplatin chemotherapy regimens.

- Plan radiotherapy for lung volumes receiving doses ≥ 20 Gy (V20) in more than 35% of total lung volume, cardiac volumes receiving radiation doses > 50 Gy (V50) in more than 25% of total heart volumes.

- Patients had other cancers.

- Histopathology was a mixture of squamous cell carcinoma and small cell carcinoma.

- Patient had an acute infectious disease.

- The patient did not agree to participate in the study.

2. Methods

** Study design:* A prospective, interventional, no control, longitudinal follow-up.

** Sample size:* Convenient sample size.

** Research content:*

- Evaluation of completion of chemotherapy and radiotherapy procedures.

- Assessment of response after 3 months of treatment according to PERCIST 1.0 criteria.

- The relationship between the SUVmax value and the level of treatment response.

- Progression-Free Survival (PFS) and overall survival (OS).

- The relationship between PFS and some clinical and subclinical characteristics.

- The relationship between OS and some clinical and subclinical characteristics.

- Overall survival rate at 1 year, 2 years, 3 years.

- Assessment of treatment-related side effects.

** Procedure of research:*

- Patients who meet the requirements for inclusion and exclusion criteria will be thoroughly explained about the treatment process and sign a written consent to participate.

- Planning radiation therapy to draw GTV_T and GTV_N on simulated CT images, draw reGTV_T and reGTV_N on simulated PET/CT images according to the process of PERTAIN study, with

consistent coordination between radiation therapists and nuclear medicine doctors.

- Concurrent chemoradiotherapy

Consists of 6 cycles of Paclitaxel/ Carboplatin administered concurrently with 60Gy - 30 fractional doses of radiotherapy. Chemical Paclitaxel 45 mg/m^2, Carboplatin AUC2 on days 1, 8, 15, 22, 28 and 36. Radiotherapy on the Varian radiotherapy system was conducted on the first day after chemotherapy with a fraction of 2 Gy/day x 5 days/week for 6 weeks. The total duration of treatment should not exceed 7 weeks. Consolidation chemotherapy for 2 more cycles if the patient's condition is eligible, the disease has not progressed [4].

- Follow-up of patients after treatment: patients are periodically followed up every 3 months for 2 years and then every 6 months: Clinical examination, liver and kidney function and blood count, chest CT scan - Abdominal, cranial MRI, bone scan. Particularly 3 months after treatment, more PET/CT was taken.

** Evaluation methods:*

Criteria for assessing response: Overall response rate (ORR), progression-free survival (PFS), overall survival (OS), overall survival at 1, 2, 3 years after treatment and side effects.

** Data processing*

Data were collected and analyzed by the statistical software SPSS 22.0. Compare the means using the t-student test. The survival time was expressed by the Kaplan Meier curve. Using Logrank test, there is statistical significance when $p \leq 0.05$.

3. Research ethics

The patients were selected for chemotherapy and radiation therapy at the same time according to the guidelines of the American cancer network NCCN and the Ministry of Health of Vietnam. Patients voluntarily participated in the study.

RESULTS

Table 1: Average radiation dose of the study group.

Radiation dose (Gy)	**n**	**%**
50 - < 60	2	6.67
60	28	93.33
n	30	100
Average (Min - max)	59,53 ± 2,81 (50 - 66)	

Most patients (93.33%) received 60 Gy of radiotherapy. The mean radiation dose was 59.53 ± 2.81 Gy.

Table 2: Number of chemotherapy cycles of the study group.

Cycles	n	%
Completed 6 chemical cycles + 2 adjuvant cycles (1)	17	56.76
Completed 6 chemical cycles (2)	11	36.67
Completed 6 or more chemical cycles (1 + 2)	28	93.33%
Complete 4-5 chemical cycles	2	6.67%

Most patients (93.33%) completed 6 or more cycles of chemotherapy, 56.67% of subjects received 2 additional cycles of adjuvant therapy and there were 2 cases (6.67%) with only 4 - 5 cycles.

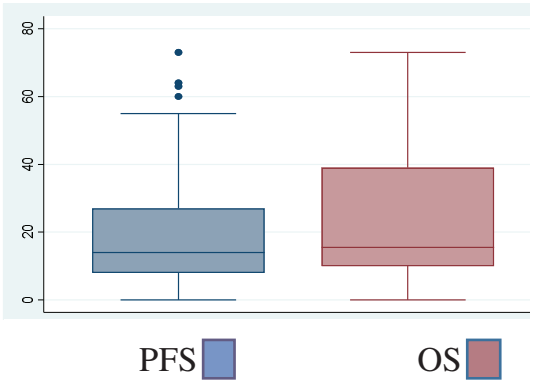
Table 3: Treatment response according to PERCIST 1.0 versus RECIST 1.1 (n = 29).

Response	PERCIST 1.0		RECIST 1.1	
	n	%	n	%
Complete response	10	34.48	4	13.79
Partial response	13	44.84	17	58.63
Stable disease	3	10.34	5	17.24
Progressive disease	3	10.34	3	10.34
n	29	100	29	100

* There was one patient who died right after the end of concurrent chemoradiotherapy, so it was not evaluated.

Evaluation according to PERCIST 1.0, the complete response rate was 34.48 %, the partial response rate was 44.84%, and stable disease rate was 10.34 %.

There is a difference between the response rate assessed by PERCIST 1.0 and RECIST 1.1. Especially the complete response rate based on PERCIST 1.0 criteria is considerably higher (34.48%) compared to that based on RECIST 1.1 criteria (13.79%).



Time (months)	Average	Min-max
Progression-free survival (PFS)	21.03 ± 21.12	0 - 73
Overall survival (OS)	26.27 ± 22.30	0 - 73

Figure 1: Progression-free survival and overall survival.

- The mean progression-free survival was 21.03 (months), and the mean overall survival was 26.27 (months).

- The patient had the longest progression-free survival time of 73 months until stopping the study.

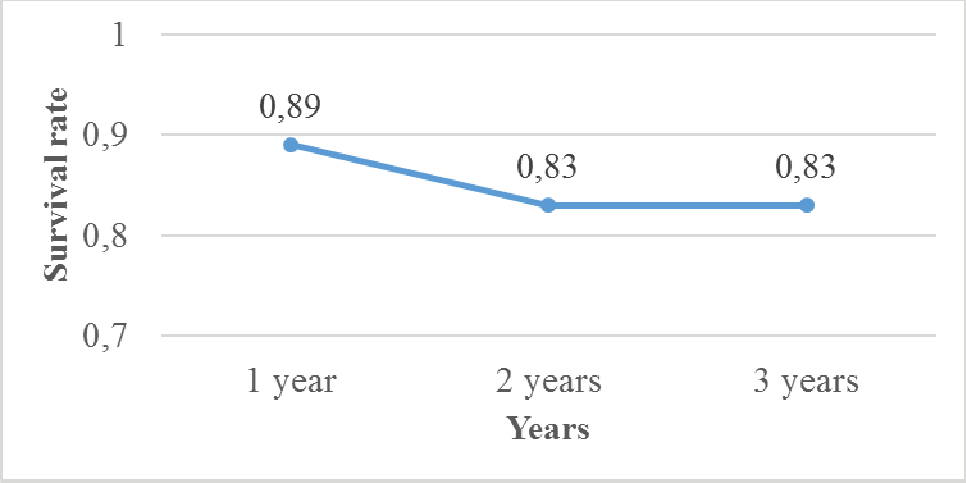


Chart 1: Probability of patient survival at time points.

The probability of patient survival at 1 year, 2 years, 3 years, respectively, follows by 0.89, 0.83, and 0.83.

Table 4: Most severe side effects per patient.

Side effects	n	%
Grade 0	0	0
Grade 1	10	33.33
Grade 2	12	40
Grade 3	7	23.33
Grade 4	0	0
Grade 5	1	3.33
n	30	100.0

The rate of the most severe side effects in each patient had the highest rate of grade 2 with 40%, followed by grade 1 with 33.33%, and grade 3 with 33.33%. Only 1 patient, equivalent to 3.33%, had the most severe side effect at grade 5 of fatal pneumonia.

DISCUSSION

1. Radiotherapy dose

In our study design, the indicated radiation dose was 60 Gy with IMRT. As a result, all patients received radiation therapy with radiation doses ranging from 50 to 60 Gy, of which 28/30, corresponding to 93.33%, received a radiation dose of 60 Gy, and only 2/30 cases, respectively, 6.67% received a radiation dose < 60 Gy, average radiation dose was 59.53 ± 2.81 Gy (*Table 1*). Radiation dose completion depends on the tolerance limit of each individual with healthy organs such as lungs, esophagus, spinal cord, and heart. These figures are in line with those of domestic and international studies. Le Thi Yen (2019) reported that 80% of patients received radiation dose ≥ 60 Gy, while the number of patients receiving radiation dose < 60 accounted for 20% in concurrent chemoradiotherapy for stage IIIB NSCLC patients at K Hospital [3]. Nguyen Duc Hanh (2018) recorded that up to 95.5% of patients achieved radiation dose ≥ 60 Gy [4]. The study by Konert T. (2019) included 69 patients with stage III NSCLC receiving concurrent chemotherapy and radiation with PET/CT. The radiation dose of 60 - 66 Gy was divided into prescribed doses in 30 - 33 fractions. , the average prescribed dose is 60.7 ± 1.7 Gy. However, studies have shown that radiation doses below 60 Gy have

poorer local control rates. However, the high radiation dose of 74 Gy was not more beneficial compared with the 60 Gy dose published at the 2011 ASTRO Conference [5].

2. Concurrent chemotherapy

In our study, most patients completed 6 cycles of chemotherapy with 93.33%, patients treated at least 4 cycles. 2/30 cases, respectively 6.67%, obtained < 6 cycles of treatment due to complications of grade 3-leukopenia. The dose had to be reduced by 10%, resuming the chemotherapy after the treatment aimed to normalize the leukocyte reduction. There were 56.67% of subjects treated with 2 additional cycles of adjuvant therapy (*Table 2*). This result shows some differences compared with the work of domestic and international authors. Le Thi Yen (2019) recorded that 65.7% completed 7 cycles, 21.4% completed 6 chemotherapy cycles, and 12.9% were treated in < 6 chemotherapy cycles [3]. Nguyen Duc Hanh (2018) reported that the majority of patients completed 6 cycles of chemotherapy with 95.5%, and the rate of 2 more cycles of consolidation chemotherapy after chemotherapy and radiation reached 85.1%, much higher than in our study [4]. Author Davila R. S. (2014) showed that patients received an average of 5 cycles, of which 46.8% received six or seven cycles [6]. In general, the weekly chemotherapy regimen of Paclitaxel/Carboplatin is a well tolerated regimen when used concomitantly with radical radiotherapy for inoperable stage III NSCLC.

3. Results of concurrent chemoradiotherapy

** Response to treatment:*

Evaluation of treatment response according to PERCIST 1.0 criteria with the advantage of both assessing tumor structure and assessing tumor metabolism helps to provide valuable response information at an earlier time, it distinguishes the remaining tumor, necrotic tissue, or scar tissue due to residual tumor tissue is especially valuable for patients with stage III NSCLC receiving chemotherapy and radiation concurrently [5].

The results showed that the disease control rate was 89.66%, of which 34.48% complete response, and 44.84% partial response, 10.34% stable disease (*Table 3*).

Compared with the assessment of treatment results according to RECIST 1.1 criteria, there was a significant difference. According to RECIST criteria, the disease control rate remained unchanged at the level of 89.66%, but the complete response rate was only 13.79%, partial response 58.63%, and 17.24% stable disease. In

which the concordance between these two methods of assessing this group was only in 17/29 patients (58.62%), and the difference was in 12/29 patients (41.38%) (*Table 3*). The level of accuracy in the assessment of treatment outcomes plays a very important role in the prognosis and selection of the next treatment strategy for each patient, increasing the chances of receiving appropriate treatment in the next steps, helping to improve progression-free survival and overall survival for patients.

This result is consistent with the study by Manus M. P. (2003) when studying 73 NSCLC patients after radical radiotherapy and chemotherapy, the poor consistency between PET/CT and CT response, similar only in 40 patients. % of patients, the author also noted that PET/CT response was significantly associated with survival time ($p < 0.0001$) [7]. Compared with domestic and international studies, the disease control rate of this study is equal to or higher. However, the complete response rate is much higher than in previous studies. In Vietnam, Le Tuan Anh (2015) studied chemoradiotherapy simultaneously on 60 patients with the same chemotherapy regimen and radiation dose as in our study. The only difference is their use of the 3D radiation technique, that reached a disease control rate of 84%, of which the complete response was 5.4%, the partial response was 51.7%, and the disease remained unchanged in 26.8% [8]. Le Thi Yen (2019) studied 70 patients and recorded a disease control rate of 82.9%, of which the complete response was only 2.9%, the partial response was 75.7%, the disease remained the same. 4.3% and disease progression 17.1% [3]. Study WJTOG0105 by Nobuyuki Y. (2010) recorded a disease control rate of 83.3%, of which the rate of complete response was only 3.4%, 59.9% partial response, and 21% stable disease, and disease progression was 10.9% [9].

Our study has a higher complete response rate than previous studies. The reasons can be given as follows: Firstly, all patients selected for the study have PET/ CT, therefore in the early diagnosis can be more accurate compared to studies using conventional imaging techniques; second, we use PET/CT to plan radiotherapy. Thus the lesions detected on PET/CT were simulated accurately, thirdly, we used PET/CT to assess the response to treatment, fourthly, all the patients were irradiated with IMRT modulated radiation technique, while previous studies mainly used 3D radiation technique.

* *Progression-free survival and overall survival:*

In our study, the mean progression-free survival was 21.03 months and the mean overall survival was 26.27 months. Especially, there were patients with the highest progression-free survival time of 73 months up to the time of data collection for the study (*Figure 1*). Compared with domestic and foreign studies, our results showed a higher duration of progression-free survival and a similar or higher overall survival.

Bui Cong Toan (2013) reported the average progression-free survival time was 15 months, the mean overall survival was 25 months, in which the overall survival time of stage IIIA patients was 18 months, longer than the group of stage IIIB patients with 14 months (p = 0.0004) [10]. Nguyen Duc Hanh (2018) found that the mean progression-free survival was 16.9 months, the mean overall survival time was 20.9 months, of which 69.3% were overall survival at 1 year, 35.5% overall survival at 2 years, both lower than in our study [4]. According to Bradley J. D. (2015), in the RTOG 0617 trial in the 60 Gy standard concurrent radiotherapy arm, the Paclitaxel/Carboplatin chemotherapy regimen with 2 adjuvant cycles gave the best results with survival time. The median progression-free disease was 11.8 months, and the mean overall survival time was 28.7 months. This study also demonstrated that IMRT improved outcomes compared with 3D imaging radiotherapy, besides that increasing radiation dose and Cetuximab did not improve treatment outcomes [11]. Huber R. M. (2006), in the CTRT99/97 study, applied the concurrent Paclitaxel/Carboplatin chemotherapy with 2 adjuvant cycles, the overall survival time was 18.7 months, and the progression-free survival was 11.5 months [12].

* *Survival rate:*

In this study, we recorded the overall survival probability of patients at 1 year, 2 years, 3 years, respectively, followed by 0.89, 0.83, and 0.83 (*Chart 1*). Compared with domestic and international authors, this rate is much higher. Le Thi Yen (2019) reported the overall survival at 1 year, 2 years, and 3 years was 78%, 67%, and 37%, respectively [3]. Le Tuan Anh (2015) recorded the 1-year and 2-year overall survival rates at 55% and 37.5%, respectively [8]. Nguyen Duc Hanh (2018) recorded a 1-year overall survival rate of 69.3%, and a 2-year survival rate of 35.5% [4]. MacManus M. P. (2013) used diagnostic PET/CT and concurrent chemoradiotherapy for

50 patients with stage III NSCLC and recorded survival rates of 1 year and 4 years, respectively. 77.5% and 35.6% [7].

4. Side effects

In this study, we evaluated the toxicity classification according to CTCAE Version 4.0. The common recorded complications were leukopenia of 56.67%, followed by esophagitis of 90%, fatigue of 60%, and 1 patient who died of pneumonia. 73.33% of patients had the most severe complications of grade 1 - 2, 23.33% showed the most severe complications of grade 3 - 4, with 3.33% facing of pneumonia of grade 5 conducive to death (*Table 4*). Research by Tran Mai Phuong (2009) pointed out that 100% of concurrent chemoradiotherapy had side effects, of which the most severe side effects, grades 3 - 4 accounted for 66.1%, higher than our study. [13].

CONCLUSION

Studying 30 patients with inoperable stage III non-small cell lung cancer receiving concurrent chemoradiotherapy, using PET/CT in diagnosis, radiotherapy planning, and treatment outcome evaluation, we had some following conclusions:

- Evaluation of treatment response according to PERCIST 1.0 criteria, the proportions of treatment response were high, the disease control rate was 89.66%, of which 34.48% complete response, 44.84% partial response, 10.34% stable disease.

- Overall survival and progression-free survival improved: The median progression-free survival time was 21.03 months, the mean overall survival time was 26.27 months, and the probability of survival after 1, 2 and 3 years are 0.89, 0.83, and 0.83.

- Lower proportions of severe side effects, with 73.33% of the patients only having complications of grade 1 - 2, and 23.33% of grade 3 - 4. Only 3.33 % had fatal complications of pneumonia.

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