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Neoadjuvant and adjuvant therapy of non-small-cell lung cancer

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The aim of the study was to evaluate the role of neoadjuvant and adjuvant therapy of non-small-cell lung cancer (NSCLC). Most of patients (pts) were diagnosed in stage III of the disease. Follow-up results of these pts were not satisfactory: within two years after surgery many pts died from a local relapse of tumour or of the progression of disease. Adjuvant treatment (radiotherapy, chemotherapy) could improve the survival of pts.

Materials and methods. At Thoracic Surgery Department of the Institute of Oncology, 2535 pts were treated surgically in the course of 54 years (1950–2003). Non-small-cell lung cancer was diagnosed in 2122 of these pts: 1534 pts had squamous cell carcinoma, 561 adenocarcinoma, 27 large cell carcinoma. This is a study of a combined treatment of 288 pts with NSCLC. Two groups of pts were investigated: group I of 140 pts who received adjuvant therapy, and group II of 148 control pts who were treated only surgically. In group I there were three subgroups. In subgroup 1, 54 pts after radical operation received four courses of chemotherapy (cisplatin + vinblastin) or radiotherapy. In subgroups 2 all pts were treated with radiotherapy. 26 pts of subgroup 2 received preoperative radiotherapy (7 Gy and 20 Gy). In subgroup 3, 48 pts received neoadjuvant therapy: two courses of chemotherapy (taxol and carboplatin) and after operation three courses of chemotherapy.

Results. The median survival of subgroup I pts was 23.1 (8.7÷27.5) months and of control pts 13 (10.1÷15.9). The median survival of 26 pts subgroup II was 19.9 (11.9÷26.5) months and of control pts 13.58 (10.4÷16.7). The median survival of 48 pts from subgroup III was 22.0 ± 2 months and of control pts 17.2 ± 2 months.

Conclusions. Adjuvant therapy of NSCLC improved the follow-up results of treatment 2. Pre- and postoperative radiotherapy can be recommended as adjuvant therapy for NSCLC. 3. Chemotherapy with taxol improves surgical treatment conditions.

Key words: non-small-cell lung cancer, surgical treatment, chemotherapy, radiotherapy

INTRODUCTION

Non-small- cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases. There were 1299 pts with lung cancer in Lithuania in 2004. According to the stage of the disease, 8.2% of pts had stage I, 14.9% II, 29.5% III and 32.6% stage IV of the disease; the stage of disease in 14.2% cases was not fixed (1).The follow-up results of patients in stage III of the disease were not satisfactory: in two years after surgery many patients died from local relapse of the tumour or of the progression of the disease. Adjuvant treatment (radiotherapy, chemotherapy) after resection of lung cancer could improve the survival of patients (2–4). The results of combined treatment of NSCLC patients are described in this paper.

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MATERIALS AND METHODS

At Thoracic Surgery Department of the Institute of Oncology, 2535 patients were treated surgically in the course of 54 years (1950–2003). Non-small-cell lung cancer was diagnosed in 2122 of these patients: 1534 pts had squamous cell carcinoma, 561 adenocarcinoma, 27 large cell carcinoma. This is a study of a combined treatment of 288 pts with NSCLC, in which all patients were treated surgically (pneumonectomy, bilobectomy, lobectomy). Two groups of patients were investigated: group I of 140 pts who received adjuvant therapy and group II of 148 control patients who were treated only surgically. In group I there were three subgroups. In subgroup 1, 54 pts after radical operation received four courses of chemotherapy

(cisplatin + vinblastin) or radiotherapy. In subgroup 2 all patients were treated with radiotherapy (42–50 Gy). 26 pts of subgroup 2 received preoperative radiotherapy (7 Gy and 20 Gy). In subgroup 3, 48 pts received neoadjuvant therapy: two courses of chemotherapy (taxol and carboplatin) and after operation three courses of chemotherapy.

Subgroup 1: completely resected non-small-cell lung cancer + adjuvant therapy

54 pts after complete resection within 60 days after operation received cisplatin 80 mg/m² in four cycles days (1, 22, 43, 64) and vinblastin 4 mg/m² infusion on days 1, 8, 15, 22, 29 and after two weeks on days 43, 57, 71, 85. After four courses of chemotherapy, according to randomization the patients received postoperative radiotherapy which consisted of 40–50 Gy delivered to mediastinal lymph nodes with conventional fractionation of the dose. In the cases N2 all patients received postoperative radiotherapy (40–50 Gy). Postoperative radiotherapy must be delivered 10 days after the last injection of chemotherapy. The characteristics of patients are shown in Table 1.

Table 1. **Characteristics of the patients**

Characteristic	Chemotherapy group	Control group
Pathological TNM stage	**n = 54**	**n = 45**
T2N0M0	1	0
T1N1M0	5	1
T2N1M0	17	19
T3N0M0	1	0
T3N1M0	12	11
T2N2M0	11	9
T3N2M0	7	5
Type of surgery		
Pneumonectomy	30	25
Bilobectomy	4	1
Lobectomy	20	19
Histologic type		
Squamuos cell carcinoma	34	30
Adenocarcinoma	16	15
Adenosquamous cell carcinoma	2	0
Large-cell carcnoma	2	0

Every patient after adjuvant therapy was examined every three months in the first year and twice in the second year. In the case of relapse of tumour or the progression of disease, the patient received treatment according to the pathological findings in the resected lung.

Subgroup 2: preoperative radiotherapy + surgical treatment of non-small-cell lung cancer

For preoperative radiotherapy two figure fields, anterior and posterior, were used. The field of radiation consisted of the primary tumour and a 2 cm margin around. Fifteen pts received a single fraction of 7 Gy, and 11 pts received radiation of a total dose of 20 Gy (4 Gy × 5 days).

The characteristics of the patients are shown in Table 2.

Table 2. **Characteristics of patients of the second subgroup**

Characteristic	Preoperative radiotherapy	Surgical treatment alone
Pathological TNM stage	**n = 26**	**n = 58**
T2N0M0	4	2
T2N1M0	4	24
T3N0M0	2	3
T3N1M0	2	10
T2N2M0	5	11
T3N3M0	2	0
T4N2M0	2	0
Type of surgery		
Pneumonectomy	10	26
Lobectomy	9	28
Segmentectomy	2	3
Thoracotomy	5	1
Histologic type		
Squamuos cell carcinoma	22	48
Adenocarcinoma	4	8
Large-cell carcinoma	0	2

In cases of subgroup 2 and after thoracotomy explorativa the patients received postoperative standard radiotherapy to a total dose of 50 Gy (1.5–2 Gy per fraction). All patients received preoperative radiotherapy according to the 2D plan. Operations were performed 1–2 days after radiotherapy. In five cases the tumour was not removed and the patients received postoperative radiotherapy to the tumour and mediastineal area.

Subgroup 3: neadjuvant chemotherapy + surgical treatment of non-small cell lung cancer

48 pts received induction chemotherapy with taxol (175 mg/m²) and carboplatina AUC—due to Calvert formula + surgical treatment; 45 pts were in the control group; they did not receive neadjuvant therapy before surgery. Characteristics of these patients are shown in Table 3.

Preoperative chemotherapy was provided in 3 h infusion started with taxol and followed by carboplatina. After three weeks the patients received a second course of chemotherapy. If the tumour decreased >50%, patients after complete resection of lung were treated with three courses of chemotherapy. If the regression of tumour was < 50%, the patients after surgical treatment received radiotherapy (50 Gy). After two courses of chemotherapy, in 39 cases (77%) there was regression of tumour by more than 50%. To 11 (22.9%) patients the operations were not performed: in 7 cases tumour was resistant to chemotherapy, two patients did not tolerate chemotherapy, and two patients refused surgical treatment. The complications after surgical treatment were adequate in both groups.

Table 3. **Characteristics of patients of subgroup 3**

Characteristic	Induction chemotherapy	Surgical treatment
Pathological TNM stage	**n = 48**	**n = 45**
T3N0M0	23	20
T3N1M0	12	10
T3N2M0	13	15
Type of surgery		
Pneumonectomy	22	20
Bilobectomy	10	11
Lobectomy	5	14
Histological type		
Squamuos cell carcinoma	39	40
Adenocarcinoma	12	3
Large-cell carcnoma	7	15

The follow-up results of treatment

In the first subgroup, 24 from 54 pts who received adjuvant chemotherapy died from relapse of the tumor or progression of the disease. The median survival in 54 pts of subgroup 1 who received adjuvant chemotherapy after radical operation was 23.1 (18.7÷27.2) months. The patients who were treated only surgically lived 13.0 (10.1÷15.9) months (Table 4). The patients who received radiotherapy before surgery lived longer – 19.2 (11.9÷26.5) months, and patients treated only surgically 13.58 (10.4 ± 16.7) months.

The median survival of patients who received neoadjuvant chemotherapy was 22 ± 2.0 months.The patients who did not have such treatment lived shorter – 17.0 ± 2.0 months. Local relapse of tumor in the first group was detected after 12 months and in the second group after 7 months. After 3 years, 45% of patients of subgroup 1 who were treated with chemotherapy lived without any progression of the disease, while in group 2 only 29% of patients survived. After induction chemotherapy, in 77% cases regression of tumour was received and the conditions for surgical treatment of patients were better after such treatment.

DISCUSSION

Analysis of the data in three subgroups where patients received additional treatment (chemotherapy, radiotherapy or both) has shown an improval of the late results of treatment, especially in IIIA stage of the disease. We treated with adjuvant chemotherapy and radiotherapy 7 pts who had pT3N2M0, and they lived 24.3 (10.7÷37.9) months. The median survival of 5 pts with pT3N2M0 who did not receive adjuvant therapy after surgery was 6.2 (0÷13.9) months. The follow-up results were moderate when radiotherapy was used for adjuvant treatment. Induction chemotherapy improved the results of surgical treatment in stage III of the disease. In our opinion, it is necessary to optimise the treatment of patients in N2 cases: induction chemoterapy before surgery with chemoterapy and radiotherapy after operation. The question of treatment of patients in stage III of the disease is especially actual in N2 cases (5–7). In a large International Trial of Adjuvant Therapy of non-small-cell lung cancer, 1867 pts underwent randomization. The median duration of follow-up was 56 months. Patients assigned to chemotherapy had a significantly higher survival rate than those assigned to observation (44.5% vs 40.4 at five years (469 deaths vs 504). Patients who received chemotherapy had a higher disease-free survival rate than those assigned to observation. According to the International Adjuvant Lung Cancer Trial, cisplatin-based adjuvant chemotherapy improves survival among patients with completely resected non-small-cell lung cancer (8).

Table 4. **Median survival of patients treated with adjuvant therapy**

Tumor according to pTNM	Number of patients	Median survival (in months) and 95% confidence interval	
T1N1M0	5	38.6	(32.4÷44.8)
T2N1M0	17	25.5	(17.2÷33.8)
T3N1M0	13	22.3	(9.80÷34.81)
T2N2M0	12	13.5	(8.39÷18.6)
T3N2M0	7	24.3	(10.7÷37.9)
Total	54	23.1	(18.7÷27.2)

CONCLUSIONS

1. Adjuvant therapy of NSCLC improved the follow-up results of treatment.

2. Pre- and postoperative radiotherapy can be recommended as adjuvant therapy for NSCLC.

3. Induction chemotherapy with taxol improves the conditions for surgical treatment of patients in the stage III of the disease.

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NESMULKIALĄSTELINIO PLAUČIŲ VĖŽIO NEOADJUVANTINĖ IR ADJUVANTINĖ TERAPIJA

S a n t r a u k a

Darbo tikslas – įvertinti nesmulkialąstelinio plaučių vėžio (NSPV) neoadjuvantinės ir adjuvantinės terapijos poveikį ligonių gyvenimo trukmei. Nemažam ligonių skaičiui diagnozuojamas III stadijos navikas. Tokių ligonių vėlyvieji tik chirurginio gydymo rezultatai nėra patenkinami: daug ligonių miršta per dvejus metus po operacijos atsiradus naviko recidyvui ar progresuojant ligai. NSPV sergančių ligonių pagalbinis gydymas (chemoterapija, radioterapija) gali prailginti jų gyvenimo trukmę.

Tiriamųjų kontingentas ir tyrimo metodai. Vilniaus universiteto Onkologijos instituto Torakalinės chirurgijos skyriuje per 54 metus (1950–2003 m.) buvo operuoti 2535 ligoniai, sergantys plaučių vėžiu. Nesmulkialąstelinis plaučių vėžys buvo diagnozuotas 2122 ligoniams: 1534 ligoniai sirgo plokščialąsteliniu plaučių vėžiu, 561 ligoniui nustatyta adenokarcinoma, 27 – didelių ląstelių karcinoma. 288 ligoniai, sergantys NSPV, buvo įtraukti į klinikinę studiją ir suskirstyti į dvi grupes: pirmos grupės ligoniai gavo papildomą gydymą, antros grupės ligoniams (148) buvo taikytas tiktai chirurginis gydymas. Pirmąją grupę sudarė trys pogrupiai: I pogrupio 54 ligoniams po radikalios operacijos buvo paskirti keturi chemoterapijos kursai (cisplatinas + vinblastinas) arba spindulinė terapija. Nustačius N2, visi ligoniai buvo švitinti. II pogrupio 26 ligoniams taikyta priešoperacinė spindulinė terapija (7 Gy ir 20 Gy). III pogrupio 48 ligoniai prieš operaciją gavo du chemoterapijos kursus (taksolį ir karboplatiną), po operacijos – tris chemoterapijos kursus.

Rezultatai. I pogrupio ligonių vidutinė gyvenimo trukmė buvo 23,1 (8,7 ± 27,5) mėnesio, tiktai operuotų – 13 (10,1 ± 18,7). II pogrupio ligonių – 19,9 (11,9 ± 26,5) mėnesio, tiktai operuotų – 13,58 (10,4 ± 18,7). III pogrupio ligonių – 22,0 ± 2 mėnesio, tiktai operuotų – 17,2 ± 2.

Išvados. NSPV adjuvantinė terapija pagerina vėlyvuosius gydymo rezultatus. Prieš ir po operacijos spindulinė terapija gali būti kaip papildomas gydymas. Priešoperacinė chemoterapija taksoliu pagerina ligonių operacinio gydymo rezultatus.

Raktažodžiai: nesmulkialąstelinis plaučių vėžys, chirurginis gydymas, chemoterapija, spindulinė terapija.