Прилози, Одд. биол. мед. науки, МАНУ, XXX, 2, с. 197–207 (2009)
Contributions, Sec. Biol. Med. Sci., MASA, XXX, 2, p. 197–207 (2009)
ISSN 0351–3254
УДК: 616.24-006.6-085.38

SEQUENTIAL CHEMORADIOTHERAPY COMPARED WITH CONCURRENT CHEMORADIOTHERAPY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER: OUR EXPERIENCE

Crvenkova S., Krstevska V.

University Radiotherapy and Oncology Clinic, Medical Faculty
Skopje, R. Macedonia

A b s t r a c t: The aim of the study was to compare the survival impact of concurrent versus sequential treatment with radiotherapy and chemotherapy in inoperable stage III non-small cell lung cancer (NSCLC). 85 patients were randomly assigned to one of the two treatment groups. In the sequential group, 45 patients had previously received sequential chemotherapy with 4 cycles of carboplatine and etoposide followed by conformal radiotherapy (RT). In the second concurent group 40 patients received concomitant chemotherapy of cisplatine and etoposide and conformal RT followed by two cycles of consolidation chemotherapy of carboplatine and etoposide. We described all phases of the conformal three dimensional (3-D) RT.

From November 2005 to October 2008, 93 patients were enrolled. Eight patients were not eligible, seven had stage IV and one had pleural effusion. All these were initially considered to have stage IIIB disease. The median survival was 13 months for the patients in the sequential group and 22 months in the concurrent treatment group. The difference was statistically significant (log-rank test $p = 0.001$). The disease-free survival was 9 months in the sequential group and 17 months in the concurrent treatment group. The difference was statistically significant (log-rank test $p = 0.001$) The 1- and 2-year survival rates were 73.6% and 39.7% in the concurrent group and 54.9% and 13.7% in the sequential group, respectively (log-rank test, $p = 0.0011$).

Treatment-related toxicities were assessed according the RTOG/EORTC criteria. Acute esophagitis and incidence of neutropenia were higher with the concurrent than with the sequential treatment. Grade 3 esophagitis was characteristic only of concurrent treatment and it was a reason for radiotherapy interruption, but no longer than 7 days. Secondary anaemia was more frequent in the sequential treatment group.

The statistical significant differences in survival sugest that concurrent chemotherapy and conformal three-dimensional radiotherapy is the optimal strategy for patients with locally advanced NSCLC.

Key words: sequential and concurrent chemoradiotherapy, three-dimensional conformal radiotherapy, inoperable NSCLC.

Introduction

Lung cancer remains a worldwide epidemic. Approximately 1.2 million people die from lung cancer each year. Non-small cell lung cancer represents > 80% of all lung cancers. Of the patients with NSCLC, 60–70% present with stage III or IV disease. In the late 1980s, radiotherapy was the standard treatment for these patients [1]. Randomized trials and a 1995 overview subsequently showed that combination chemoradiotherapy was superior to radiotherapy alone [2]. Many chemotherapeutic agents active in NSCLC possess radiosensitizing properties, thereby improving the probability of local control. In addition, chemotherapy administered concurrently with thoracic radiation may act systemically and potentially eradicate distant micrometastases. Several studies showed the feasibility of the cisplatin-etoposide combination plus radiotherapy for patients with stage III disease [3]. The primary end point of this study was the effect of sequential and concurrent chemoradiotherapy on overall survival.

Material and methods

This study was started in the Radiotherapy and Oncology Institute in Skopje, November 2005. The 85 eligible patients were aged between 18 and 70 years, had an Eastern Cooperative Oncology Group (ECOG) Score ≤ 1, and had ≤ 10 % weight loss in the period of 3 months before inclusion. They had previously untreated histological or cytological proven NSCLC, unrespectable stage IIIA-N2 disease, or stage IIIB disease without pleural effusion. Stage IIIB disease was assigned either by N3 (contralateral mediastinal or supraclavicular nodes) or by T4 from invasion of mediastinal structures. The following laboratory values were required: leucocytes ≥ 1.5 × 10³/l, platelets ≥ 100 × 10/l, AST and ALT ≤ 2 × the upper limit of the referent range. Ineligibility criteria were as follows: uncontrolled infection, or fever over 38ºC, unstable cardiovascular disease and previous malignancy.

Before enrolment, the patients gave their full medical histories and underwent a clinical examination with assessment of performance status (PS). In the sequential group, responses were assessed 8 weeks after the end of radiotherapy. In the concurrent group, responses were assessed 8 weeks after the end of the consolidation chemotherapy. Imaging studies, x-ray and/or computed tomo-

graphy (CT) could be repeated at all times when clinically indicated. Complete and partial responses were based on RECIST criteria. Toxicity was graded according RTOG/EORTC criteria. Follow-up visits were conducted every 2 months during the first year and after that every 3 months. Patients were randomly assigned to receive sequential or concurrent therapy. In the sequential group 45 patients received four cycles of chemotherapy. They were administered the first, consisting of carboplatine (AUC × 6) on day 1 and etoposide on days 1–3, repeated every 3 weeks. The radiotherapy began 4 weeks after the fourth cycle of chemotherapy administration. Chemotherapy and radiotherapy began simultaneously in the concurrent arm consisting of 40 patients. The radiotherapy schedule was identical to that in the sequential group. The first cycle with cisplatin 30 mg/m² and etoposide 100 mg/m² was administered on days 1 to 3 and the second 3-days cycle was administered in the last 3 days of radiotherapy. After 4 weeks of the concurrent chemoradiotherapy schedule, two cycles of consolidation chemotherapy began, consisting of carboplatine (AUC × 6) and etoposide 100 mg/m² on days 1 to 3.

Conformal radiotherapy in both groups consisted of 60 Gy in 30 fractions of 2 Gy per fraction for 5 days a week given over a period of 6 weeks. A treatment planning CT was required to define the gross tumor volume (GTV). Each patient was positioned on an immobilization device-wing board in the treatment position on a flat table. CT slices with 5 mm thickness were obtained starting from the cricoid cartilage and extending inferiorly to the level of the L1 vertebral body. The GTV, clinical target volume (CTV), planning target volume (PTV) and normal organs were outlined on all CT slices (Figure 1). The normal tissues

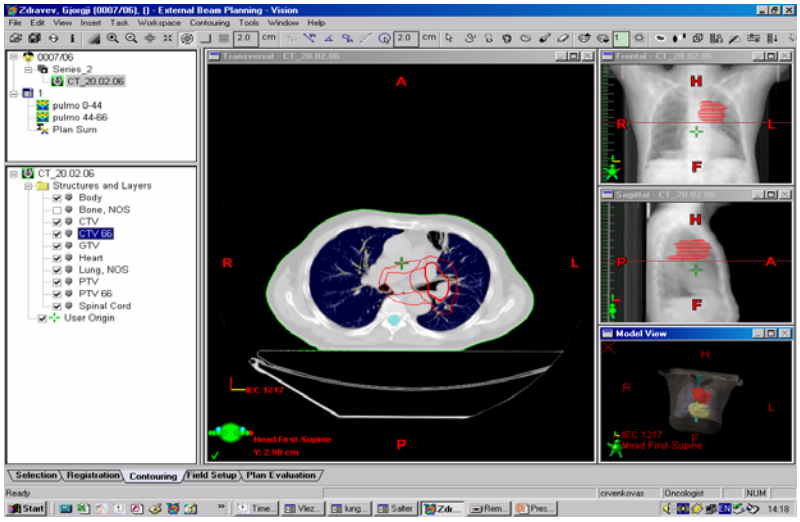

Figure 1 – Conturing of the tumour volumes
Слика 1 – Контурирање на туморските волумени

contoured included both lungs (as the total lung volume), heart, spinal cord and oesophagus. The CTV included the entire GTV plus 0.7 cm and the PTV included CTV plus another 0.7 cm adding margin. PTV44 was treated with parallel-opposed anterior-posterior fields and PTV60 was treated with any combination of fields depending on spinal cord constraint (Figure 2). If radiotherapy had to be delayed for more than 7 days, the patient was withdrawn from the study. Patients with evidence of progression at any time were removed from the study but continued to be evaluated for survival and toxicity. Survival and the interval to recurrence or progression were measured from the date of the first treatment session.

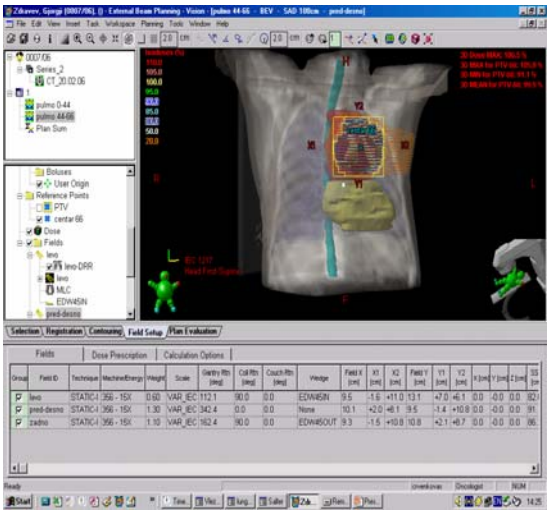

Figure 2 – Dose-calculation after spinal cord exclusion
Слика 2 – Пресметување на дозата по ексклузија на спиналниот мозок

Results

From November 2005 to October 2008, 93 patients were enrolled. Eight patients were not eligible, seven had stage IV and one had pleural effusion. All these were initially considered to have stage IIIB disease. The characteristics of the 85 patients are listed in Table 1.

Forty-five patients in the sequential group and 40 in the concurrent group received 60 Gy of radiotherapy. The objective response rate was evaluated at the end of each treatment sequence. Nine complete responses and 36 partial responses were obtained with sequential treatment. Twenty-four complete responses and 16 partial responses were obtained in the concurrent group. The difference between the two groups was statistically significant $p = 0.002$.

Table 1 – Табела 1

Patient characteristics
Карактеристики на пациентите

Patients characteristic	**Sequential treatment**	**Concurrent treatment**	**P**
No of eligible pts	45	40	
Age			
Median	59	57	0.55
Range	38–70	46–70	
Sex			
Male	40	35	0.19
Female	5	5	
Performance status			
0	28	27	0.62
1	17	13	
Weight loss ≥10 %	5	3	
Histology			
Squamous cell	34	22	
Adenocarcinoma	6	10	0.51
Large cell	2	3	
Unspecified	3	5	
N status			
N1	15	12	
N2	26	24	0.8
N3	4	4	
Tumour ≤ 5 cm	14	15	
Tumour > 5 cm	31	25	0.6

Survival was analysed on July 2009 after a median follow-up of 3 years. The median survival was 13 months in the sequential arm and 22 months in the concurrent treatment. The difference was statistically significant (log-rank test p = 0.0011; Fig 3). The disease-free survival was 9 months in the sequential group and 17 months in the concurrent treatment. The difference was statistically significant (log-rank test p = 0.0002; Fig 4). The 1- and 2-year survival rates were 73.6% and 39.7% in the concurrent group and 54.9% and 13.7% in the sequential group, respectively (log-rank test, p = 0.0011). Treatment-related toxicities according to RTOG/EORTC are listed in Table 2. Acute oesophagitis and incidence of neutropenia were higher with the concurrent than with the sequential treatment. Grade 3 oesophagitis was characteristic only of concurrent treatment and it was the reason for radiotherapy interruption but no longer than 7 days. Secondary anaemia was more frequent in the sequential treatment group.

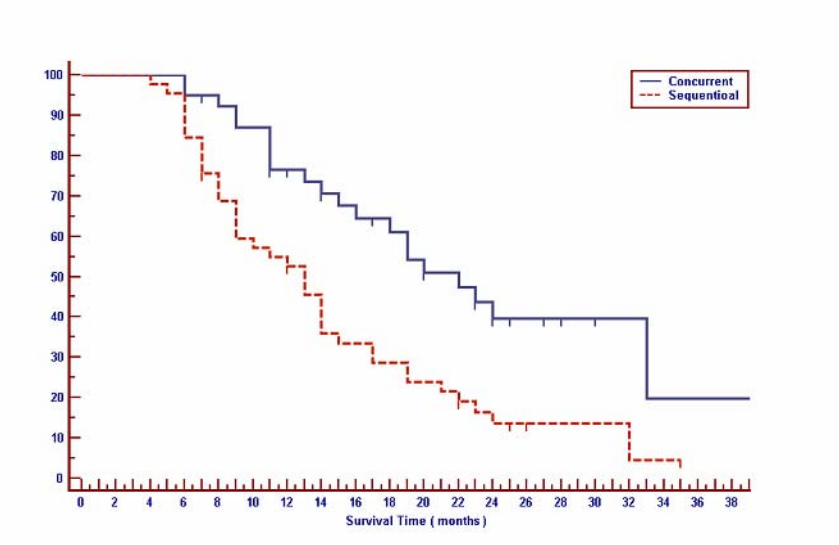

Figure 3 – Overall survival according to treatment
Слика 3 – Вкупно преживување според применетиот третман

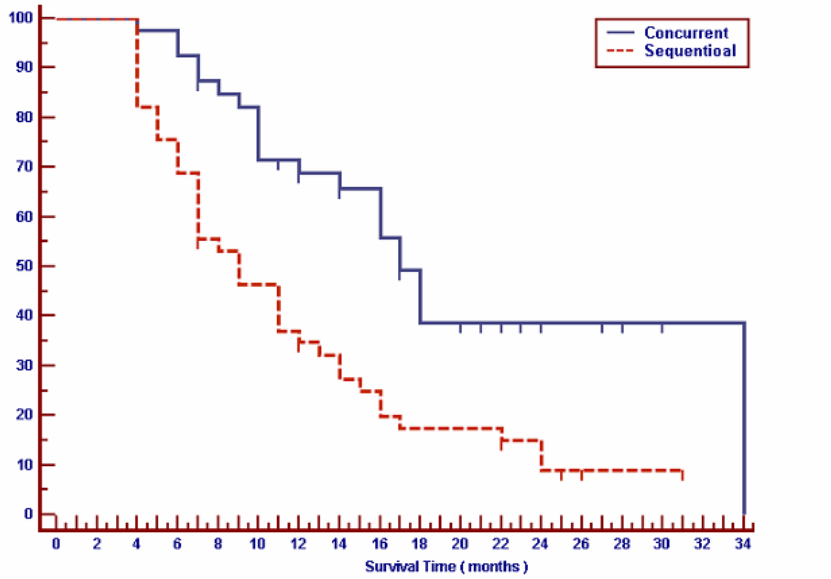

Figure 4 – Disease-free survival according to treatment
Слика 4 – Преживување без болест според применетиот третман

Table 2 – Табела 2

Treatment-related toxicities in the two groups
Токсичност-зависна од применетиот третман, кај двете групи

Toxicities RTOG/EORTC		Sequential arm				Concurrent arm			
		grade 0	grade 1	grade 2	grade 3	grade 0	grade 1	grade 2	grade 3
Late	Lung	28	8	9	0	8	21	11	0
	Oesophagus	45	0	0	0	37	3	0	0
Acute	Lung	29	13	3	0	25	14	1	0
	Oesophagus	17	20	8	0	2	20	15	3
	Hemoglobin	24	14	7	0	39	0	1	0
	Leukocyte	41	2	2	0	13	11	14	2

Discussion

A randomized phase III trial comparing sequential and concurrent administration of chemotherapy and radiation therapy for NSCLC was published in 1999 [4]. In the study of Furuse *et al.* [4] chemotherapy combined cisplatin, vindesine and mitomycin C. The total dose of radiotherapy was 56 Gy, and in the concurrent group, in a split-course schedule was administered, with a rest period of 10 days. Median survival was significantly higher with concurrent therapy than with sequential therapy (16.5 and 13.3 months, respectively; $p = 0.0398$). The 2-, 3-, and 5-year survival rates were 34.6%, 22.3% and 15.8% in the concurrent arm, and 27.4%, 14.7% and 8.9% in the sequential group, respectively. Radiation Therapy oncology Group (RTOG) study 94–10 [5] compares sequential treatment with concurrent therapy in which the same dose of radiotherapy, 63 Gy, was administered during the two cycles of cisplatine-vinblastine therapy, and with concurrent treatment using a bi-fractionated and accelerated irradiation 69.6 Gy combined with two cycles of cisplatin-etoposide. The median survival rate in the concurrent treatment with cisplatin-vinblastine and standard radiotherapy was significantly better than that in the sequential group (17 v 14.6 months; $p = 0.046$). The median survival rate with bi-fractionated irradiation was 15.2 months. The third study which supports a concomitant approach is by Zatloukal PV [6]. Chemotherapy in both groups consisted of 4 cycles of cisplatin and

vinorelbine every 4 weeks. Radiotherapy of 60 Gy was started in the concurrent group with a second cycle and in sequential group 2 weeks after completion of the chemotherapy. The median survival time in the concurrent group was 16.8 months and in the sequential group it was 12.9 months ($p = 0.0216$, log-rank test). Median time to progression was 11.9 in the concurrent group and 8.5 in the sequential group, respectively [6].

Our study compared sequential and concurrent chemoradiation therapy in locally advanced NSCLC. We found the benefit of concurrent therapy greater than in previous listed trials, in terms of overall and disease-free survival (22 vs 13; 17 vs. 9 mounths), and the difference was significant with a log-rank test. When our study was designed, the cisplatin-etoposide combination was mostly used concurrently with radiotherapy [7]. Consolidation chemotherapy with two cycles of carboplatin-etoposide was administered in the concurrent group to balance the dose of platinum-based chemotherapy in the two groups. This consolidation chemotherapy administered after concurrent chemoradiotherapy seems promising in terms of survival, as shown in the Southwest Oncology Group (SWOG) S9504 and Locally Advanced Multimodality Protocol (LAMP) studies [8, 9]. In the SWOG S9504 study, consolidation docetaxel following concurrent chemoradiotherapy, showing median survival of 26 months and median progression-free survival of 16 months. Our concurrent-consolidation group showed similar results (OS 22 months and DFS 17 months). In our study, the local relapse rate was lower in the concurrent group than in the sequential arm. In the RTOG 94–10 [5] study, local failure rates at 2 years were significantly lower in the concurrent group. Thus it seems that the superior survival observed with concurrent treatment is associated with better local control.

We did not observed major toxicity in our study. The incidence of grade 3 oesophagitis was lower than in the RTOG 94–10 study and the possibility of incidence reduction in our study was performed by conformal 3D RT. The same findings are shown by Socinski *et al.* [10, 11].

Conclusion

Given the high toxicity in the concurrent-consolidation schedule, it should be reserved for patients younger than 70 years of age, with good performance status and minimal weight loss. In our study of the dose-limiting toxicity, oesophagitis was reduced by performing conformal radiotherapy. Conformal thoracic radiotherapy allows dose-escalating and can probably improve survival and local control. The North Central Cancer Treatment Group (NCCTG) reported a phase I trial escalating the dose of RT with 3-D planning between 70 and 78 Gy [12, 13] They defined the maximum-tolerated dose as 74 Gy and reported an impressive median survival time of 37 months. The dose-limiting toxici-

ties were mainly pulmonary. These results suggest that the dose and technical aspects of RT delivery are important in the combined modality approach for stage III NSCLC.

REFERENCES

1. Le Chevalier T., Arriagada R., Quoix E. *et al*. (1991): Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable NSCLC: First analysis of a randomized trial in 353 patients. *J Natl Cancer Inst;* 83: 417–423.

2. NSCLC Collaborative Group Chemotherapy in NSCLC. (1995): A meta-analysis using updated data on individual patients from 52 randomized clinical trials. *BMJ;* 311: 899–909.

3. Cfriess G., Balkadi M., Harvey WH. *et al*. (1987): Concurrent cisplatin and etoposide with radiotherapy in locally advanced NSCLC. *Cancer Treat Rep;* 71: 681–684.

4. Furuse K., Fukuoka M., Kawahara M. *et al.* (1999): Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine and cisplatin in unresectable stage III NSCLC. *J Clinic Oncol;* 17: 2692–2699.

5. Curran WJ., Scott CB., Langer CJ. *et al.* (2003): long-term benefit is observed in phase II comparison of sequential vs concurrent chemoradiotherapy for patients with unresectable stage III NSCLC: RTOG 94–10. *Proc Am Soc Clin Oncol;* 22: 621a (abstr 2499).

6. Zatloukal PV., Petruzelka I., Zemanova M. *et al*. (2004): Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized faze II study. *Lung Cancer;* 46: 87–98.

7. Albain KS., crowwley JJ., Turrisi AT. *et al*. (2002): Concurrent cisplatin, etoposide and chest radiotherapy in pathologic stage IIIB NSCLC: A Soutwest Oncology Group phase II study, SWOG 9019. *J Clin Oncol;* 20: 3454–3460.

8. Gandara DR., Chansky K., Alban KS. *et al.* (2003): Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB NSCLC: Phase II Southwest Oncology Group phase II study, SWOG s9504. *J Clin Oncol;* 21: 2004–2010.

9. Choy H., Curran WJ., Scot CB. *et al.* (2002): Preliminary report of locally Advanced Multimodality Protocol (LAMP): ACR 427: A randomized phase II study of three chemo-radiation regimens with paclitaxel, carboplatin and thoracic radiation (TRT) for patients with locally advanced NSCLC (LA-NSCLC). *Proc Am Soc Clin Oncol;* 21: 291a (abstr 1160).

10. Xiong Wei, Liu H., Tucker S. *et al.* (2006): Risk factors for acute esophagitis in NSCLC patients treated with concurrent chemotherapy and three-dimensional conformal radiotherapy. *Int J Radiat Oncol Biol Phys;* 66: 100–107.

11. Socinski MA., Rosenman JG., Halle J. *et al*. (2001): Dose escalating conformal thoracic radiation therapy with induction and concurrent carboplatin/paclitaxel in unresectable stage IIIA/B NSCLC. *Cancer;* 92: 1213–1223.

12. Schild SE., Mc Ginnis WLG., Graham D. *et al.* (2006): Results of a phase I trial of concurrent chemotherapy and escalating doses of radiation for unresectable non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys;* 65: 1106–1111.

13. Bradley JD., Graham M., Suzanne S. *et al.* (2005): Phase I results of RTOG L-0117: A phase I/II dose intensification study using 3-D RT and concurrent chemotherapy for patients with inoperable NSCLC. *J Clin Oncol;* 23: 636s (abstr 7063).

Резиме

СЕКВЕНЦИОНА ХЕМОРАДИОТЕРАПИЈА КОМПАРИРАНА СО КОНКУРЕНТНА ХЕМОРАДИОТЕРАПИЈА КАЈ ЛОКАЛНО-НАПРЕДНАТ НЕМИКРОЦЕЛУЛАРЕН БЕЛОДРОБЕН КАРЦИНОМ: НАШИ ИСКУСТВА

Црвенкова С., Крстевска В.

Универзитетска клиника за радиотерапија и онкологија, Медицински факултет, Скопје, Р. Македонија

Апстракт: Целта на студијата е да се компарира, влијанието врз преживувањето, од употребениот конкурентен или секвенционен начин на третман кај иноперабилниот стадиум III немикроцелуларен белодробен карцином (NSCLC). Осумдесет и пет пациенти се рандомизирани во две групи. Во секвенционата група се вклучени 45 пациенти и тие прво беа третирани со 4 циклуси на хемотерапија со carbopalatin и etoposide, по што следуваше конформална радиотерапија (RT). Во втората конкурентна група 40 болни беа истовремено третирани со хемотерапија, cisplatin и etoposide и конформална RT, по што следуваше апликација на 2 циклуса на консолидирачка хемотерапија со carboplatin и etoposide. Воедно опишани се сите фази на конформалната тродимензионална (3D) RT.

Од ноември 2005 до октомври 2008 испитувани се 93 пациенти. Осум пациенти се веднаш исклучени од студијата. Кај седум од нив утврден е стадиум IV на болеста, а кај еден пациент утврдено е постоење на плеурален излив. За овие пациенти претходно се мислело дека се погодни за вклучување, односно дека припаѓаат на стадиум IIIB. Добиено е средно време на преживување од 13 месеци за секвенционата група и 22 месеци кај конкурентната група. Разликата е статистички значајна (log-rank test p = 0.001). Преживувањето без болест за секвенционата група беше 9 месеци и 17 месеци за конкурентната група. Разликата исто така е статистички значајна (log-rank test p = 0.001). Едногодишната и двогодишната процентуална стапка на преживување беше 73.6% и 39.7% кај конкурентната група и 54.9% и 13.7% кај секвенционата група, последователно (log-rank test, p = 0.0011). Несаканите ефекти од третманот беа оценувани според RTOG/EORTG кри-

териумите. Инциденцата на акутниот езофагитис и инциденцата на неутропенија беше поголема кај конкурентната група во однос на болните во секвенционата група. Езофагитисот од 3-ти степен беше карактеристика само на конкурентната група и беше причина за прекин на RT, но не поголем од 7 дена. Секундарната анемија беше почеста кај групата на болни третирани со секвенционен пристап.

Статистички значајната разлика во преживувањето укажува дека конкурентана хеморадиотерапија и конформалната 3D RT се оптимална стратегија на третман кај болни со локално напреднат NSCLC.

Клучни зборови: секвенциона и конкурентна хеморадиотерапија, тридимензионална конформална радиотерапија, иноперабилен NSCLC.

Corresponding Author:

Crvenkova Simonida,
University Clinic of Radiotherapy and Oncology,
Medical Faculty,
Skopje, R. Macedonia,
Tel: 070338687, 3111430.

E-mail: simonidac@hotmail.com