

## LIFE EXPECTANCY IN PATIENTS WITH STAGE III A NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH NEOADJUVANT CHEMORADIOTHERAPY (NCRT), NEOADJUVANT CHEMOTHERAPY (NCT), NEOADJUVANT CHEMOTHERAPY + ADJUVANT RADIATION THERAPY (NCT + ADJUVANT RT)

### PRZEWIDYWANA DŁUGOŚĆ ŻYCIA U PACJENTÓW Z NIEDROBNOKOMÓRKOWYM RAKIEM PŁUCA W STADIUM III A (NSCLC) PODDANYCH NEOADJUVANTOWEJ CHEMORADIOTERAPII (NCRT), NEOADJUVANTOWEJ CHEMIOTERAPII (NCT), NEOADJUVANTOWEJ CHEMIOTERAPII + ADJUVANTOWEJ RADIOTERAPII (NCT + ADJUVANTOWA RT)

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Wkład autorów:

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- B. Data collection/entry  
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- C. Data analysis/statistics  
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- D. Data interpretation  
interpretacja danych
- E. Preparation of manuscript  
przygotowanie artykułu
- F. Literature analysis/search  
wyszukiwanie i analiza literatury
- G. Funds collection  
zebranie funduszy

#### Summary

**Background.** This work is a comparative study of survival in patients with stage III A non-small cell lung cancer (NSCLC) treated with neoadjuvant chemoradiotherapy (NCRT), neoadjuvant chemotherapy (NCT) and neoadjuvant chemotherapy and adjuvant radiation therapy (NCT + adjuvant RT).

**Material and methods.** Three groups of 65 people were selected. The first group received NCT, the second group – NCT, and the third group – NCT + adjuvant radiation therapy. The NCRT group received radiation therapy of 30 Gy. Survival was assessed using the Kaplan and Mayer scale and according to the log rank criteria.

**Results.** The statistical criterion for NCRT in relation to NCT was -3.51279,  $r=0.00044$ . The statistical criterion for NCRT in relation to NCT + adjuvant RT was -2.88568,  $r=0.00391$ . Less reliable dependence was observed between NCT and NCT + adjuvant RT (the statistical criterion =1.809508,  $p=0.070307$ ).

**Conclusions.** Performing NCT, NCRT or NCT + RT and the status of complete morphological response (CMR) during the revision of histological material, it is possible to predict survival for a period of up to 36 months. NCRT is the optimal method of treatment.

**Keywords:** neoadjuvant therapy, pneumonectomy, lobectomy, non-small cell lung cancer, overall survival

#### Streszczenie

**Wprowadzenie.** Niniejsza praca stanowi badanie porównawcze przeżycia u pacjentów z niedrobnokomórkowym rakiem płuca w stadium III A (NSCLC) w leczeniu neoadjuwantową chemioradioterapią (NCRT), neoadjuwantową chemioterapią (NCT) oraz neoadjuwantową chemioterapią i adjuwantową radioterapią (NCT + adjuwantowa RT).

**Materiał i metody.** Wyłoniono 3 grupy po 65 osób. Pierwsza grupa otrzymała NCT, druga grupa – NCRT, a trzecia grupa – NCT + radioterapię adjuwantową. Grupa NCRT otrzymała radioterapię w dawce 30 Gy. Przeżycie oceniano za pomocą skali Kaplana i Mayera oraz według kryteriów log rank.

**Wyniki.** Kryterium statystyczne NCRT w stosunku do NCT wyniosło -3,51279,  $r=0,00044$ . Kryterium statystyczne NCRT w stosunku do NCT + adjuwantowej RT wyniosło -2,88568,  $r=0,00391$ . Mniej wiarygodna zależność została zaobserwowana między NCT a NCT + adjuwantowa RT (kryterium statystyczne = 1,809508,  $p=0,070307$ ).

**Wnioski.** Wykonując NCT, NCRT lub NCT + RT oraz status całkowitej odpowiedzi morfologicznej (CMR) podczas rewizji materiału histologicznego, można przewidzieć przeżycie na okres do 36 miesięcy. NCRT jest optymalną metodą leczenia.

**Słowa kluczowe:** terapia neoadjuwantowa, pneumonektomia, lobektomia, niedrobnokomórkowy rak płuca, choroby, przeżycie całkowite

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## Introduction

The method of treating stage III A non-small cell lung cancer (NSCLC) remains a difficult question, because, despite the complex treatment used, the survival rate of patients does not exceed 58% per year from the moment of diagnosis [1].

Treatment of NSCLC III A is difficult for many reasons. The main ones are:

- detection of NSCLC in locally common forms;
- the need for a large-scale operation, which complicates local control and requires highly qualified surgeons;
- the need for long-term and toxic neoadjuvant therapy, often contraindicated in patients with cardiovascular diseases;
- there is no standardized method of neoadjuvant or adjuvant therapy [2].

The method of choosing the treatment tactics for stage III A NSCLC is still a debatable issue, since the world clinical protocols (such as National Comprehensive Cancer Network (NCCN)) offer neoadjuvant chemotherapy (NCT), neoadjuvant chemoradiotherapy (NCRT) or neoadjuvant chemotherapy and adjuvant radiation therapy (NCT + adjuvant RT) as acceptable methods of treatment. Some studies call chemoradiotherapy without surgery the gold standard of treatment; however, this does not fully correlate with the NCCN standards [3]. None of the clinical studies and retrospective observations have shown convincing benefits, so research in this area continues. The overall survival, relapse-free survival, as well as the number of side effects of each treatment method are compared and the degree of reliability for each indicator is established [4-17]. There are data from various randomized studies on increasing the effectiveness of treatment when using NCRT at a dosage of 60-74 Gy, but with an increased risk of cardiovascular insufficiency. At lower doses of radiation therapy (up to 45 Gy), data on hematological toxicity are recorded, and there are no data on serious and critical adverse reactions. However, we cannot fully take into account the data of such studies as a starting point for the effectiveness of NCRT as a method of treating stage III A NSCLC, since although the total dose of radiation therapy in the combined studies in one group coincides, chemotherapy regimens vary significantly, and in some studies are not specified in detail at all [3].

The aim of this work is a comparative study of survival in patients with stage III A NSCLC treated with NCRT, NCT and NCT + adjuvant RT.

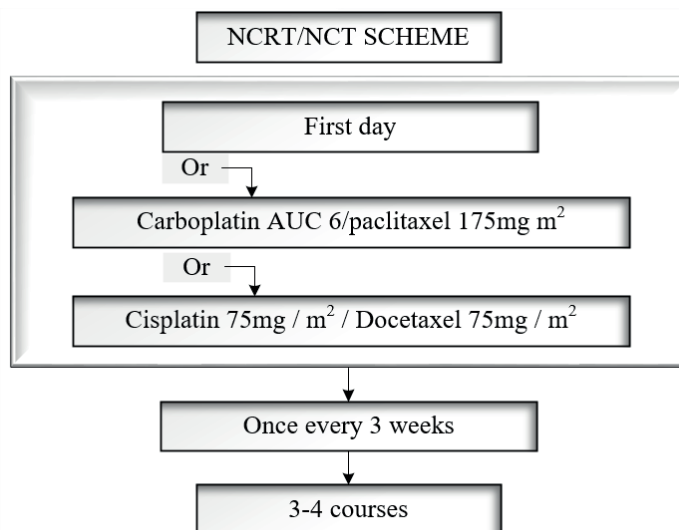
## Material and methods

Three groups of 65 people were selected for the study in accordance with the recommended NCCN treatment methods. The essence of their disease, possible options for the development of the clinical situation and the essence of the treatment methods offered to them, as well as the possible impact of a particular treatment on the course of their disease were explained to all the patients. Informed consent was signed by all the patients. The ethical approval of the study was obtained from the Bioethics Committee (Approval number 3 27.01.2020). The clinical cases of patients treated in the department of chest and mediastinal tumors of the National Cancer Institute from 1999 to 2021 were analyzed. The age and gender composition is shown in Table 1 [18-23].

**Table 1.** Age and gender composition

The first group										
- chemotherapy before surgery, radiation therapy after surgery										
Men									Total	%
30-35	35-40	40-45	45-50	50-55	55-60	60-65	65-70	70-75		
-	1	4	6	7	11	14	8	5	56	86
Women									Total	%
-	-	1	1	-	1	3	2	1		
The second group										
- chemotherapy - radiation therapy (radiation therapy - chemotherapy) before surgery										
Men									Total	%
1	-	1	5	8	20	10	6	1		
1	-	1	5	8	20	10	6	1	52	80
Women									Total	%
-	2	-	1	4	4	1	1	-		
The third group										
- chemotherapy - radiation therapy (radiation therapy - chemotherapy) - after surgery										
Men									Total	%
-	1	2	6	12	11	11	7	1		
-	1	2	6	12	11	11	7	1	51	78
Women									Total	%
-	-	-	1	2	6	2	2	1		

The first group received NCT; the second group received NCRT, and the third group received NCT + adjuvant RT. Chemotherapy for all groups was the same – according to the scheme - docetaxel (paclitaxel) and cisplatin (carboplatin). The chemotherapy regimen is shown in Figure 1.



**Figure 1.** NCT regimens in patients with stage III A NCRT

The structure of operations was also the same for all the groups – lobectomy, bilobectomy or pneumonectomy. The NCT group received radiation therapy at a dose of 30 Gy per chest and mediastinum simultaneously with chemotherapy. The complete morphological response was established microscopically, and in some cases it was confirmed immunohistochemically. Radiation therapy was performed on a VARIAN Clinac 2100cd linear accelerator. Survival was assessed using the Kaplan and Major scales. Calculations were made in the statistics program. The degree of reliability of the survival assessment was assessed using the Lagrange criterion [19-23].

## Results

At 6 months, survival rates without complete morphological response (CMR) in the NCRT and NCT groups are approximately the same, and in the NCT + adjuvant RT group it is significantly higher. In patients with CMR, survival rates are equal.

With a 12-month survival rate, the highest level of decline in survival rates was observed in the NCT group. Patient indicators in the NCRT and group NCT + adjuvant RT without CMR are approximately equal. Survival rates in the NCRT group with CMR fell slightly. When cumulative survival is set at 18 months in the NCT and NCT + adjuvant RT groups, survival rates in the group without CMR drop sharply and become the same, and in the NCRT group without CMR they fall to a lesser extent. In the groups with CMR, the lowest rates are in the NCT group; in the NCRT group, survival rates are lower than when followed up at 12 months, but remain consistently high.

With a survival period of 24 months, the cumulative survival rates without CMR in the NCT + adjuvant RT group are low; in the NCT group, there are no such patients at all; in the NCRT group, NCRT falls relative to previous results, but remains the highest. In the NCT and NCT + adjuvant RT groups, the survival rates of patients with CMR are higher than without CMR, but significantly lower than in the NCRT group.

With a survival period of 36 months in the NCT and NCRT groups, no patients are observed in patients without CMR. In the NCT + adjuvant RT group, the results remain the same as for a period of 24 months. In the groups of patients with CMR, the results of NCT + adjuvant RT and NCRT are approximately the same.

Since NCRT showed the best survival result in the long term, the long-rank criterion was used to compare survival with NCRT with other methods. The survival results were reliable. The statistical criterion for NCRT in relation to NCT was  $-3.51279$ ,  $r=0.00044$ . The statistical criterion for NCRT in relation to NCT + adjuvant RT was  $-2.88568$ ,  $r=0.00391$ . The relationship between NCT and NCT + adjuvant RT is less reliable (the statistical criterion =  $1.809508$ ,  $p=0.070307$ ).

Taking into account the results of the log-rank criteria, the cumulative survival results can be considered as an imitation of the survival results for each type of treatment. Accordingly, when performing NCT, NCRT or NCT + RT and receiving or not receiving CMR during the revision of histological material, it is possible to predict survival for up to 36 months, taking into account the cumulative survival rates corresponding to this treatment method and CMR status.

The cumulative survival results are presented in Table 2 while Figures 2-5 show the cumulative unprecedented survival rates of the patients.

**Table 2.** Cumulative survival outcomes

Month	Method of treatment	Cumulative survival
<b>NCT</b>		
6	CMR	0.64
	Without CMR	0.6
12	CMR	0.35
	Without CMR	0.21
18	CMR	0.29
	Without CMR	0.18
24	CMR	0.19
	Without CMR	0
36	CMR	0.095
	Without CMR	0

NCT + adjuvant RT		
6	CMR	0.97
	Without CMR	0.81
12	CMR	0.53
	Without CMR	0.38
18	CMR	0.4
	Without CMR	0.18
24	CMR	0.28
	Without CMR	0.8
36	CMR	0.7
	Without CMR	0.8
NCRT		
6	CMR	0.97
	Without CMR	0.61
12	CMR	0.88
	Without CMR	0.39
18	CMR	0.82
	Without CMR	0.29
24	CMR	0.79
	Without CMR	0.19
36	CMR	0.6
	Without CMR	0

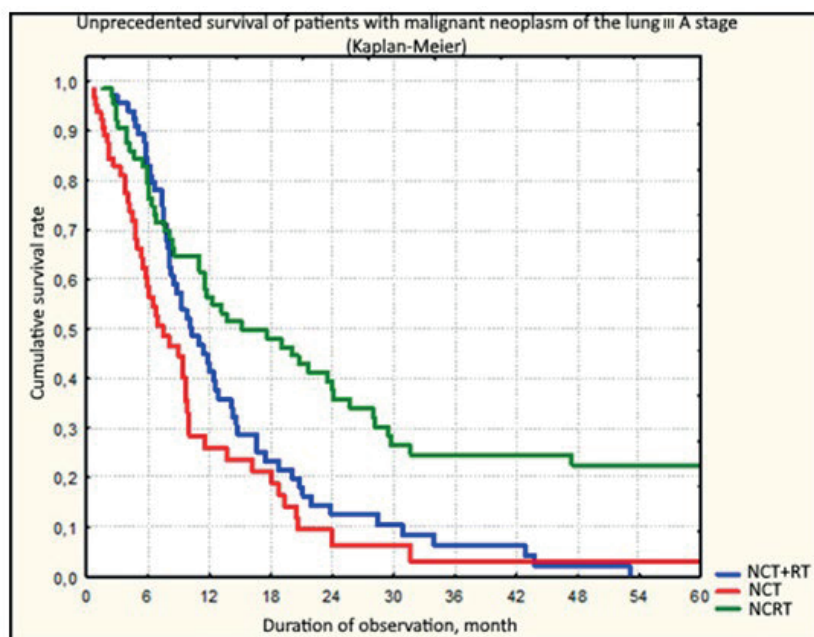


Figure 2. Cumulative unprecedented survival rates of patients with NCT, NCRT, NCT+ adjuvant RT

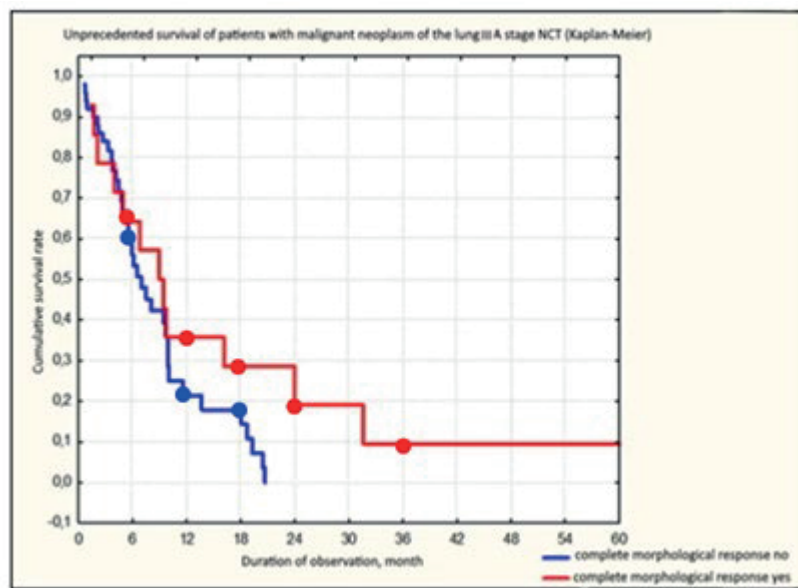


Figure 3. Cumulative unprecedented survival of patients with NCT (Kaplan-Meire)

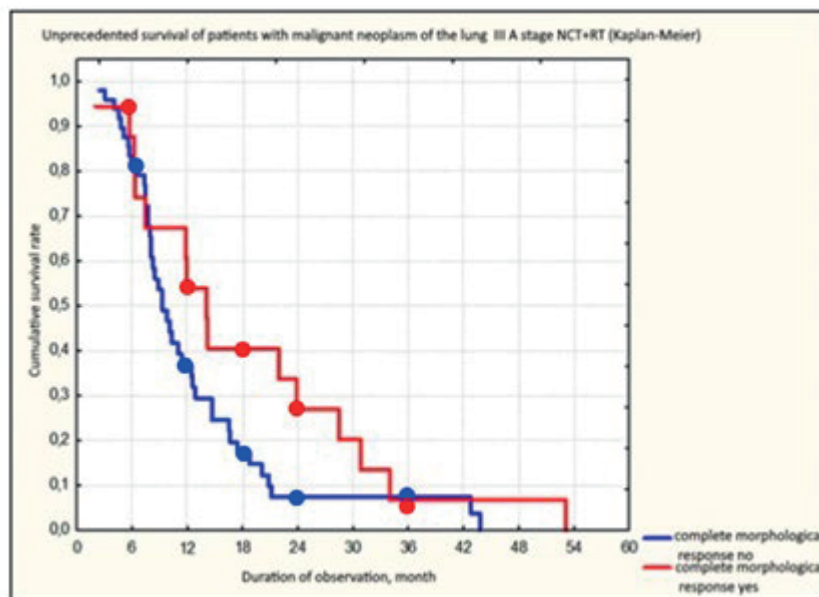
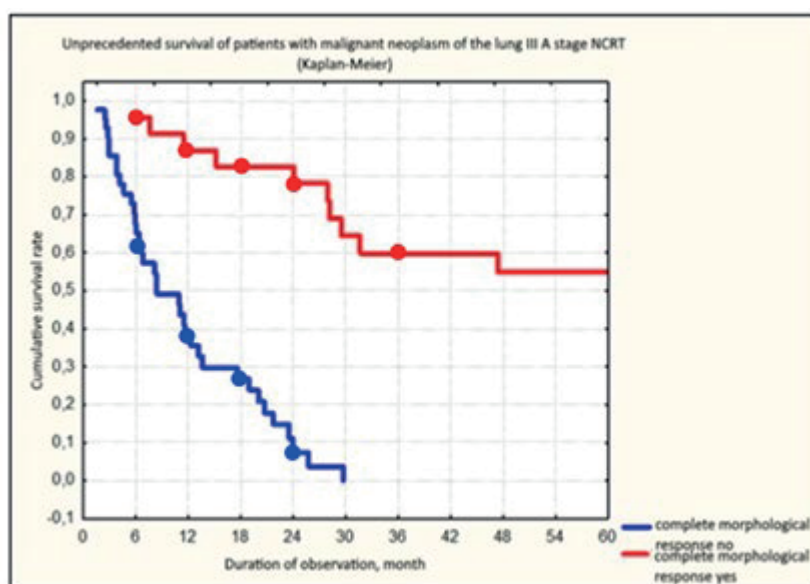


Figure 4. Cumulative unprecedented survival of patients with NCT + adjuvant RT (Kaplan-Meire)



**Figure 5.** Cumulative unprecedented survival of patients with NCRT (Kaplan-Meire)

## Discussion

Currently, there is no single clinical opinion on the correct tactics for the treatment of stage III A NSCLC. So, in 2022, European Society for Medical Oncology (ESMO) published a large article studying the issue of neoadjuvant and adjuvant treatment strategies, and this study could not show the advantages of either NCT or NCRT or adjuvant radiation therapy. As an explanation for their work, the authors from the ESMO organization indicated that “a higher quality of research and histological material is required”, so the question of the best strategy for the treatment of stage III A NSCLC is still open in world science [24]. The most likely reason for such differences is the lack of standardization of studies – all the works that we found in the NCBI scientometric database differed in key data of the study design (the number of Grays in the radiation therapy scheme, the chemotherapy scheme up to the use of schemes with and without platinum drugs, the volume of lymph dissection). Thus, in order to finally resolve the issue of the feasibility of the NCRT at the stage of NSCLC III A, the world scientific community needs more studies of higher quality on this topic [25].

In our work, uniformity of stage III A NSCLC, chemotherapy regimens, radiation therapy regimen, type of surgery and type of lymph dissection was observed [3-7,10].

We obtained the following results: in the short term (up to 6 months), the best results are shown by the NCT + adjuvant RT group; in the time interval from 6 to 36 months, the best survival results are determined in the NCRT group.

At 36 months, survival rates in the presence of CMR are the same for the NCT + adjuvant RT and NCRT groups, and survival rates without CMR are better in the NCT + adjuvant RT group. We do not know the reasons for this phenomenon. Significantly better results in each group are determined in the presence of CMR. The cumulative survival results were tested for validity using the log-rank criteria; therefore, they can be considered reliable and used as a predictor of survival depending on the type of treatment and the presence or absence of CMR.

A limited number of patients can be considered the disadvantage of this work, which does not allow us to speak unequivocally about the evidence of the NCRT technique as unambiguously recommended for patients with stage III A NSCLC; although this work clearly indicates the expediency of continuing research in this direction.

Also, taking into account the highest survival rate in the case of NCT+RT in the early period (up to 6 months), it is necessary to study the feasibility of preventive radiation in the postoperative period.

Our study shows the most similar results to those presented in the work Guo et al. [24]; yet this work does not offer a reliable understanding of which chemotherapy was used, and in what amount exactly, for which group of patients and how much Gray each patient received during radiation therapy.

## Conclusions

The study yielded the following results:

1. The best cumulative survival rates are observed with the NCRT treatment method starting at 12 months.
2. The timing of the best cumulative survival with different treatment methods varied in different time periods, which may be the reason for contradictory data in the world literature.
3. After radical treatment, the best cumulative survival rates were observed in the NCT + adjuvant RT group, which raises the question of studying the feasibility of adjuvant RT for any treatment tactic.
4. The highest cumulative survival was almost always observed with CMR. The phenomenon of CMR was most common in NCRT, the cumulative survival values in this group with CMR were higher than in patients treated with other methods.

Accordingly, the data obtained during the study indicate NCRT as the optimal method of treatment.

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