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Clinical outcome and side effects of concomitant chemoradiotherapy in the treatment of locally advanced inoperable non-small cell lung cancer: our experiences

Klinički ishod i neželjena dejstva primene istovremene hemioradioterapije u lečenju lokalno uznapredovalog inoperabilnog nemikrocelularnog karcinoma pluća: naša iskustva

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Abstract

Background/Aim. About 1.8 million new lung cancer cases are diagnosed worldwide every year, and about 1.6 million cases have a fatal outcome. Despite improvements in treatment in the previous decades, the survival of patients with lung cancer is still poor. The five-year survival rate is about 50% for patients with localized disease, 20% for patients with regionally advanced disease, 2% for patients with metastatic disease, and about 14% for all stages. The median survival of patients with untreated non-small cell lung carcinoma (NSCLC) in the advanced stage is four to five months, and the annual survival rate is only 10%. The aim of the study was to determine the results of treatment with concomitant chemoradiotherapy (CHRT) in terms of efficacy and toxicity in selected patients with advanced inoperable NSCLC. **Methods**. The study included data analysis of 31 patients of both sexes who were diagnosed and histopathologically verified with NSCLC in inoperable stage III and were referred by the Council for Malignant Lung Diseases to the Radiotherapy Department of the Military Medical Academy in Belgrade, Serbia for concomitant CHRT treatment. Upon expiry of the three months from the performed radiation treatment (RT), the tumor resonance was assessed based on multislice computed tomography (MSCT) examination of the chest and upper abdomen according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. According to the same criteria, progression-free survival (PFS), as well as overall survival (OS), was assessed every three months during the first two years, then every 6 months or until the onset of disease symptoms. **Results.** The median PFS was 13 months, and the median OS was 20 months. During and immediately after RT, 9 (29%) patients had a grade 2 or higher adverse events. **Conclusion.** The use of concomitant CHRT in patients in the third stage of locally advanced inoperable NSCLC provides a good opportunity for a favorable therapeutic outcome with an acceptable degree of acute and late toxicity and represents the standard therapeutic approach for selected patients in this stage of the disease.

Key words:
carcinoma, non-small-cell lung; disease progression; drug-related side effects and adverse reactions; chemoradiotherapy; survival.

Apstrakt

Uvod/Cilj. Godišnje se u svetu dijagnostikuje oko 1,8 miliona novoobolelih, a umre oko 1,6 miliona obolelih od karcinoma pluća. Uprkos poboljšanjima u lečenju tokom prethodnih decenija, preživljavanje bolesnika sa karcinomom pluća je i dalje loše. Petogodišnja stopa preživljavanja je oko 50% za bolesnike sa lokalizovanom bolešću, 20% za bolesnike sa regionalno uznapredovalom bolešću, 2% za bolesnike sa metastatskom bolešću, a za sve stadijume oko 14%. Srednje preživljavanje bolesnika sa nelečenim nesitnoćelijskim karcinomom pluća (NSCLC) u odmaklom stadijumu bolesti je četiri do pet meseci, a na godišnjem nivou stopa preživljavanje iznosi svega 10%. Cilj rada bio je da se utvrdi efikasnost i toksičnost istovremene hemioradioterapije (CHRT) kod odabranih bolesnika sa uznapredovalim inoperabilnim NSCLC. **Metode.** Studija je obuhvatila analizu podataka 31 bolesnika oba pola, koje je

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uputio Konzilijum za maligne bolesti pluća na Odeljenje radioterapije Vojnomedicinske akademije u Beogradu, kod kojih je dijagnostikovan i patohistološki verifikovan NSCLC u III inoperabilnom stadijumu radi sprovođenja konkomitantne CHRT. Po isteku tri meseca od sprovedene terapije zračenjem (RT) vršena je procena odgovora tumora na RT primenom multislajsne kompjuterizovane tomografije (MSCT) grudnog koša i gornjeg abdomena po kriterijumu *Response Evaluation Criteria in Solid Tumors* (RECIST) verzija 1.1. Po istom kriterijumu vršena je i procena preživljavanja do progresije bolesti (PFS) i ukupno preživljavanje bolesnika (OS) svaka tri meseca tokom prve dve godine, zatim na 6 meseci ili do pojave simptoma bolesti. **Rezultati.** Medijana PFS iznosila je 13 meseci, a medijana OS 20 meseci. Tokom i neposredno nakon RT, neželjeni događaj gradusa 2 ili većeg imalo je 9 (29%) bolesnika. **Zaključak.** Primena istovremene CHRT kod bolesnika koji su u trećem stadijumu lokalno uznapredovalog inoperabilnog NSCLC daje dobru mogućnost za povoljan terapijski ishod, uz prihvatljiv stepen akutne i kasne toksičnosti i predstavlja standardni terapijski pristup za odabrane bolesnike u tom stadijumu bolesti.

Ključne reči:
pluća, nesitnoćelijski karcinom; bolest, progresija; lekovi, neželjeni efekti i neželjene reakcije; radiohemioterapija; preživljavanje.

Introduction

Lung cancer is a significant health problem globally due to its frequency and the fact that it belongs to the group of the most deadly forms of cancer. According to the results of GLOBOCAN from 2018, about 1.8 million new patients are diagnosed worldwide every year, and about 1.6 million die from lung cancer [1, 2]. Despite improvements in treatment in previous decades, the survival of patients with lung cancer is still poor. The five-year survival rate is about 50% for patients with localized disease, 20% for patients with regionally advanced disease, 2% for patients with metastatic disease, and about 14% cumulatively for all stages [3]. The median survival of patients with untreated non-small cell lung carcinoma (NSCLC) in the advanced stage of the disease is four to five months, and the annual survival rate is only 10% [4].

The primary goal in treating all cancers is healing, which unfortunately is not possible in a large number of cases. The secondary goal is to stop the further progression of this chronic disease and improve patients' quality of life.

The main problem in the treatment of lung cancer is that a large number of patients are detected only when the symptoms and/or signs appear, i.e., when the disease has already progressed, when the chances of being cured are much lower, and the therapeutic approach is more complex. The main types of lung cancer therapy are surgery, radiotherapy (RT), chemotherapy (CHT), and target therapy.

The therapeutic approach depends on the type of tumor, the stage of the disease, the general condition of the patient, and the patient's motivation to accept a certain type of treatment. In patients with disease limited to the lung parenchyma, the optimal approach is resection of the affected lobe and mediastinal lymph nodes [5, 6]. At the same time, in patients with advanced disease, the best way to ensure optimal treatment is a multidisciplinary approach by surgeons, medical oncologists, and radiation oncologists who make joint decisions regarding treatment based on current guides for the treatment of cancer patients [7–10]. Locally advanced NSCLC refers to a heterogeneous group of patients in stage III of the disease. It includes patients with tumor spread to extrapulmonary structures (T3-4) or mediastinal lymph nodes (N2-3) without distant metastases (M0). In locally advanced diseases, surgery is less commonly used, especially as the primary approach [11, 12]. The multimodal approach is the basic therapeutic principle (CHT and/or RT, possibly surgery), and the decision on the modality of treatment largely depends primarily on the precisely determined stage of the disease. The status of mediastinal lymph nodes (N2) is especially important when deciding on the therapeutic approach from the aspect of the malignant cells invasion, localization, the number of affected nodes, and the time of their pathohistological diagnosis (before, peri- or postoperative). Patients with N2 are between patients with resectable and unresectable diseases and thus represent a group with the most complex treatment. Patient selection affects not only the response to therapy but also how well the patient will tolerate therapy, i.e., whether possible acute complications will affect the course of therapy and cause temporary or permanent interruption or lead to serious impairment of the patient's health and even death. The treatment of locally advanced NSCLC is very challenging and must be individualized.

Methods

This research was conducted at the Radiotherapy Department of the Institute of Radiology of the Military Medical Academy in Belgrade, Serbia and has had a retrospective-prospective character. The study included data analysis of 31 patients of both sexes who were diagnosed and pathohistologically verified with NSCLC in inoperable stage III and were referred by the Council for Malignant Lung Diseases to the Radiotherapy Department of the Military Medical Academy for concomitant chemoradiotherapy (CHRT) treatment.

Determination of the stage of the disease was performed based on VIII revision of the tumor, node and metastasis (TNM) classification for malignant tumors of the lungs and pleura [13]. It also included insight into medical history and clinical examination of a patient, chest multislice computed tomography (MSCT) not older than one month, abdominal ultrasound, bronchoscopy with an endoscopic evaluation of tumors, and nodal status.

Inclusion criteria were as follows: histopathologically diagnosed NSCLC [14], inoperable stage III disease, a decision indicated by the council on combined CHRT, performance status (PS) 0 or 1, complete blood count laboratory values, liver

enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatinine, hemoglobin, leukocytes, erythrocytes within the reference values, and the patient's consent to therapeutic procedures. Exclusion criteria were as follows: performance status 2 or higher, previously diagnosed and/or treated malignant diseases of the chest, and previously applied RT of the chest.

In all selected patients, treatment was based on concomitant CHRT, with CHT administered according to the cisplatin/etoposide protocol in two cycles (cisplatin 50 mg/m^2 for 1, 8, 29, and 36 days, etoposide 50 mg/m^2 for 1–5 and 29–33 days), and on RT performed according to 3DCRT protocol in a standard fractionation regimen of 2 Gy per day in total TD 60Gy for 6 weeks [15, 16]. Standardized recommendations of the International Commission on Radiation Units and Measurements – ICRU 50 and ICRU 62, were used to delineate air volumes – gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV), as well as organ at risk (OAR) [17].

Upon expiry of the three-month period from the performed RT, the response to the therapy was assessed based on MSCT examination of the chest and upper abdomen according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [18]. According to the same criteria, the assessment for progression-free survival (PFS) was executed, which was routinely performed every three months during the first two years, then every 6 months, or until the onset of symptoms of the disease.

Assessment of the degree of toxicity of concomitant CHRT was performed according to the criteria of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 [19]: grade I implies mild symptoms, grade II – moderate symptoms, grade III – significant complications, grade IV – life-threatening complications, grade V – the death of a patient.

The IBM Statistical Package for the Social Sciences (SPSS) Statistics package version 24 was used for statistical data processing. Numerical features were presented through means (median, arithmetic mean) and measures of variability (standard deviation, range of values). Attribute features are shown using frequencies and percentages. The Likelihood Ratio Test was used to test the relationship between the two categorical variables. Mortality rates were calculated, as well as overall survival (OS) and PFS. Cox regression was used to test the influence of individual variables on OS and PFS.

The value of significance level $p \leq 0.05$ was considered statistically significant.

Results

The study included 31 patients of both sexes with histopathologically verified NSCLC in stage III inoperable, with an average age of 65.67 ± 8.28. There were 14 (45.2%) respondents in stage IIIA, while 17 (54.8%) were in stage IIIB. There were no patients in stage IIIC to meet the criteria to enter the study. Fourteen patients had histopathologically verified adenocarcinoma and squamous cell carcinoma, while no histopathological tumor subtype (NSCLC NOS) was specified for three patients. The largest number of patients included in the study, 13 (41.9%), had histological grade (HG) 2, 10 (32.3%) subjects had HG 3, and 8 (25.8%) subjects had HG 1.

Tumor response was assessed based on MSCT of the chest and upper abdomen according to RECIST 1.1. criteria. Evaluation and comparison were carried out between the ini-

Table 1

Progression-free survival in relation to research subgroups

Parameter	Average	SE	95% confidence interval		Median	SE	95% confidence interval		Log Rank (Mantel-Cox)	df	*p*
			lower limit	upper limit			lower limit	upper limit			
Stage											
IIIA	14.143	1.508	11.188	17.098	15.000	0.598	13.829	16.171			
IIIB	11.532	1.107	9.362	13.702	12.000	0.606	10.812	13.188	2.840	1	0.092
Total	12.796	0.940	10.953	14.639	13.000	0.651	11.723	14.277			
HT											
AdenoCa	13.455	1.417	10.677	16.233	13.000	0.833	11.367	14.633			
SCC	11.143	1.374	8.449	13.836	12.000	0.926	10.185	13.815	2.633	2	0.268
NSCLC	17.333	1.856	13.696	20.971	16.000	0.816	14.400	17.600			
Total	12.796	0.940	10.953	14.639	13.000	0.651	11.723	14.277			
HG											
1	11.375	2.645	6.190	16.560	11.000	4.950	0.000	16.702			
2	12.538	1.293	10.005	15.072	13.000	0.540	11.942	14.058	0.401	2	0.818
3	14.175	1.113	11.993	16.357	15.000	1.243	12.564	17.436			
Total	12.796	0.940	10.953	14.639	13.000	0.651	11.723	14.277			
ECOG status											
0	12.659	1.120	10.464	14.854	13.000	0.581	11.862	14.138			
1	13.600	0.927	11.782	15.418	14.000	2.191	9.706	18.294	0.059	1	0.809
Total	12.796	0.940	10.953	14.639	13.000	0.651	11.723	14.277			
Localization											
left	13.467	1.521	10.486	16.448	13.000	1.932	9.213	16.787			
right	12.007	1.072	9.905	14.109	13.000	0.588	11.848	14.152	0.744	1	0.388
Total	12.796	0.940	10.953	14.639	13.000	0.651	11.723	14.277			

SE – standard error; AdenoCa – adenocarcinoma; SCC – squamous cell carcinoma; NSCLC – non-small cell lung carcinoma; HT – histopathological types of cancer; HG – histological gradus; ECOG – Eastern Cooperative Oncology Group.

tial scan (before starting the combined treatment) and the control scan, which was performed three months after the end of the treatment. Six (19.4%) respondents had a complete response (CR), seven (22.6%) had stable disease (SD), and seventeen (54.8%) respondents had a partial response (PR). The disease was progressive (PD) in one subject (3.2%).

If CR, PR, and SD were taken for a "favorable" response to therapy, we concluded that 30 (96.8%) respondents would have had a "favorable" response.

PFS was routinely evaluated with chest and upper abdominal MSCT every three months for the first two years, then every 6 months, or until symptoms of the disease appeared.

The obtained results (Table 1) did not show a statistically significant difference between the median time to disease progression in patients with IIIA and IIIB stage, 15 months vs. 12 months. There was no statistically significant difference between the median PFS in patients with adenocarcinoma, patients with squamous cell carcinoma, and patients with NSCL NOS (13 vs. 12 vs. 16 months, respectively). The PFS median for subjects with HG1 was 11 months, with HG2 was 13 months, and with HG3 was 15 months. For patients in the Eastern Cooperative Oncology Group (ECOG) PS 0, the median PFS was 13 months, and for ECOG PS1, the median was 14 months. PFS median in subjects with tumor localization on the left or right side was the same and amounted to 13 months (Table 2).

The mortality rate in the examined sample was 83.9%. The total number of survivors at the end of the follow-up period was 5 (16.1%), and the average survival time for patients was 20 months. The median of survivors was 28 months (Figure 1).

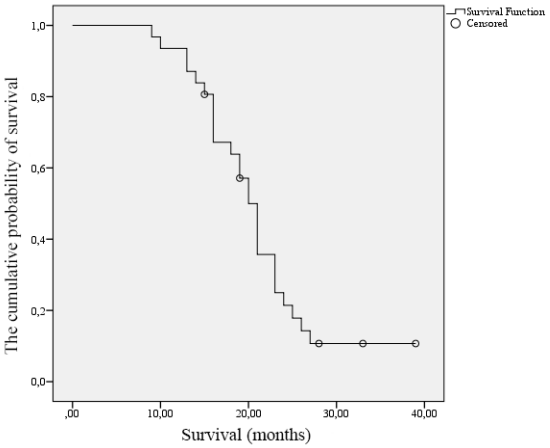


Fig. 1 – Overall survival in patients with non-small cell lung carcinoma.

In order to examine whether OS was similar or different for different study groups, we used the Log Rank test (Table 3).

Table 2

Median time to disease progression for patients with non-small cell lung carcinoma (NSCLC)

Average	SE	95% confidence interval		Median	SE	95% confidence interval	
		lower limit	upper limit			lower limit	upper limit
12.796	0.940	10.953	14.639	13.000	0.651	11.723	14.277

SE – standard error.

Table 3

Median overall survival of patients with non-small cell lung carcinoma (NSCLC) in relation to research subgroups

Parameter	Average	SE	95% confidence interval		Median	SE	95% confidence interval		Log Rank (Mantel-Cox)	Average	SE
			lower limit	upper limit			lower limit	upper limit			
Stage											
IIIA	23.461	2.181	19.185	27.737	23.000	1.304	20.443	25.557			
IIIB	18.892	1.395	16.158	21.627	18.000	1.372	15.311	20.689	2.407	1	0.121
Total	21.129	1.401	18.383	23.875	20.000	0.858	18.318	21.682			
PH											
AdenoCa	24.085	2.746	18.703	29.468	21.000	4.014	13.132	28.868			
SCC	18.000	1.301	15.450	20.550	19.000	1.871	15.333	22.667	5.002	2	0.082
NSCLC NOS	24.000	2.517	19.067	28.933	26,000	5.715	14.798	37.202			
Total	21.129	1.401	18.383	23.875	20.000	0.858	18.318	21.682			
HG											
1	18.875	2.997	13.001	24.749	18.000	3.536	9.070	22.930			
2	20.846	1.865	17.191	24.501	21.000	2.516	16.068	25.932	1.298	2	0.523
3	21.756	1.324	19.160	24.351	21.000	1.304	18.444	23.556			
Total	21.129	1.401	18.383	23.875	20.000	0.858	18.318	21.682			
ECOG status											
0	20.657	1.484	17.747	23.566	20.000	0.929	18.179	21.821			
1	21.200	1.927	17.424	24.976	21,000	2.191	16.706	25.294	0.240	1	0.624
Total	21.129	1.401	18.383	23.875	20.000	0.858	18.318	21.682			
Localization											
left	21.687	2.394	16.994	26.380	23.000	4.112	14.940	31.060			
right	20.167	1.183	17.849	22.485	20.000	0.614	18.797	21.203	0.554	1	0.457
Total	21.129	1.401	18.383	23.875	20.000	0.858	18.318	21.682			

SE – standard error; PH – pathohistological types of cancer; AdenoCa – adenocarcinoma; SCC – squamous cell carcinoma; HG – histological gradus; ECOG – Eastern Cooperative Oncology Group; NOS –not otherwise specified.

The obtained results did not show a statistically significant difference between the median OS of patients with stage IIIA and IIIB (23 vs. 18 months, respectively). There was no statistically significant difference between median OS in patients with adenocarcinoma and patients with squamous cell carcinoma (21 vs. 19 months, respectively). There was a statistically significant difference compared to NSCLC NOS, 26 months, but due to the small sample, these results should be interpreted with caution. The median survival of subjects with HG1 was 18 months, and for HG2 and HG3, it was 21 months. The median OS of patients with NSCLC is shown in Table 4.

Out of the total number of patients (n = 31) during RT treatment, adverse events (AEs) – grade 2 and more were found in 9 (29%) patients, while patients with AEs – grade 1 were not recorded, because their condition did not require any medical treatment (Table 5). Each of the 9 patients had exactly one AE. In 5 patients, there was a break in the RT treatment, but not longer than two weeks. AEs did not cause discontinuation of therapy in any patient.

Table 4

Median overall survival of patients with non-small cell lung carcinoma (NSCLC)

Average	SE	95% confidence interval		Median	SE	95% confidence interval	
		lower limit	upper limit			lower limit	upper limit
21.129	1.401	18.383	23.875	20.000	0.858	18.318	21.682

SE – standard error.

Table 5

Adverse events during radiotherapy

Adverse events	Frequency	Percentage (%)
Radioesophagitis grade 2	5	16.1
Radioesophagitis grade 3	2	6.5
Pneumonitis grade 3	1	3.2
Radiodermatitis grade 2	1	3.2
No higher stage complications	22	71.0
Total	31	100.0

Discussion

The main controversies in the treatment of NSCLC are related to its third stage, where, due to the heterogeneity of this group, all three therapeutic disciplines – surgery, CHT, and RT – can be applied. Numerous studies have tried to answer which method of treatment is the most effective and for which subgroup within the third stage of the disease. Phase III RTOG 94-10 study [20] and the Japanese study [21] deal with the difference in the effectiveness of bimodal treatment between concomitant and sequential CHRT, where the results in terms of OS and PFS were unequivocally in favor of concomitant CHRT.

Phase III RTOG 93-09 study [22] yielded results on efficacy and toxicity between treatments using trimodal (induction CHRT and surgery) and definitive concomitant CHRT in stage III patients, with an emphasis on the thoracic surgeon. Depending on his/her assessments of potential resectability, the appropriate treatment model will be applied, but it should be noted that lobectomy imposed itself as a more effective therapeutic approach, while pulmectomy has no benefit in PFS and OS compared to definitive CHRT [22]. Most guidelines for the treatment of locally advanced NSCLC are based on the results of these studies. New studies, primarily Pacific Trial [23], have shown the benefit of using immunotherapy after concomitant CHRT in PFS and OS, and its inclusion in routine practice is expected.

The results of OS of patients with NSCLC in our study demonstrate that the median survival is 20 months. Out of the total number of survivors, 75% of patients had a survival of 16 months, 50% of patients had 20 months, and 25% of patients had a survival of 23 months. The results of PFS of patients with NSCLC demonstrate a median of 13 months.

If we compare our results with the results obtained in countries with a similar health care system, we can see that the results are approximately the same. In a study conducted by Liu et al. [24] at the Radiation Oncology Department in Beijing, 251 patients with concomitant CHRT were treated; an average PFS of 10 months and an average OS of 21 months were obtained. The study conducted by Yilmaz et al. [25] at the Department of Pulmonology at the University Clinic in Bolu, Turkey, examined the efficacy and safety of concomitant CHRT in inoperable stage III NSCLC. Eighty-two patients were treated with concomitant CHRT (two cycles of cisplatin etoposide and RT 1.8-2 Gy *per* fraction in TTD 60-66Gy); an average PFS of 9 months and an average OS of 20 months were obtained. Toxicity of therapy in grades 2-3 was diagnosed in 19.2% of patients as radiation pneumonitis and in 8.5% as radiation esophagitis. The study conducted by Crvenkova [26] at the University Clinic for Radiotherapy and Oncology in Skopje, North Macedonia examined the average survival and sequential side effects of concomitant CHRT in inoperable stage III NSCLC. The results demonstrate average survival in concomitant CHRT of 19 months and in sequential 13 months, PFS 16 months in concomitant and 9 months in sequential CHRT. Grade 3 radiation esophagitis occurred only with concomitant therapy and was the result of RT discontinuation, but no longer than 7 days. The conclu-

sion was that concomitant CHRT (RT according to the 3DCRT protocol) is the optimal therapeutic choice for patients with locally advanced inoperable NSCLC, with an acceptable level of acute complications. Moreover, the RTOG studies 94-10, 91-06 [27] and the SWOG 90-19 [28] study gave similar results.

In studies PROCLAIM [29] and SWOG 95-04 [30], the results are somewhat better, primarily due to the diagnostic use of positron emission tomography/computed tomography (PET/CT), which achieves a more precise selection of patients in stage III inoperable compared to stage IV occult, more precisely applied RT and the use of consolidation chemotherapy. With the introduction of PET/CT in our routine practice in diagnosing and planning radiation therapy, the results are expected to be better.

Compared to RTOG trials and studies of the surrounding countries, we obtained approximate results in the form of AEs. Acute radiation-induced esophagitis is the most common AE of concomitant CHRT in the treatment of lung cancer [31]. Although a competitive use of CHRT and higher doses in RT treatment have been associated with the development of esophagitis, advances in RT techniques (3D planned radiation) have reduced the frequency and severity of complications. Five patients had radiation esophagitis grade 2 [5/31 (16.1%)]; in one patient, RT treatment was paused for 7 days. Radioesophagitis grade 3 was present in two patients [2/31 (6.5%)], leading to a two-week RT treatment break. Radiation pneumonitis occurred in one patient and led to a two-week break in RT treatment.

Based on the results, we noticed that at the beginning of ECOG treatment, 64.5% of subjects had PS 0, and 35.5% had PS 1. The initial difference in PS did not lead to a statistically significant difference in "tumor response" between these two groups, nor in PFS and OS. At the end of therapy, 17 (54.8%) patients had PS 0 or 1, and 14 (45.2%) patients had PS 2 or higher. These results speak in favor of the high toxicity of CHRT and confirm the reason that for this type of treatment, patients must initially be in good general condition. Five patients are alive, and two still have no disease progression. The median follow-up of all patients was 20 months, the median of survivors was 28 months, and the median without progression was 33.5 months.

Conclusion

This paper demonstrates the feasibility of combined RT and CHT in our population in patients with inoperable stage III NSCLC, with a median OS of 20 months and a median PFS of 13 months, with an acceptable number of AEs during treatment. Proper patient selection for combined CHRT implies a conciliatory-indicated decision referring to a patient diagnosed with locally advanced inoperable NSCLC in the presence of an experienced thoracic oncologist (who will rule out resectability), provided the patient is in good general condition (PS 0 or 1), with less than 5% of body weight loss, that the basic laboratory values are within the reference values, that the cardiopulmonary reserve is preserved, and that the patient is motivated for this type of treatment. Combined CHRT provides the greatest opportunity for patients in stage III locally advanced inoperable NSCLC, for a favorable therapeutic outcome, with an acceptable degree of acute and late toxicity, and represents the standard therapeutic approach for selected patients in this stage of the disease.

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