

Survival analysis of patients with locally advanced non-small cell lung cancer treated at the Nu-Med Radiotherapy Center in Elbląg

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Introduction. The study aimed to report the efficiency of radical radiotherapy and chemoradiotherapy in patients with non-small cell lung cancer (NSCLC) treated in the Nu-Med Radiotherapy Center in Elbląg.

Material and methods. Ninety-two patients diagnosed with NSCLC treated between 2013 and 2016 were included in the analysis. Overall survival (OS) was estimated by the Kaplan-Meier method.

Results. The 2-year OS for all patients was 36% (median 1.5 years). Two prognostic factors had a significant impact: treatment method and performance status (PS). Patients who underwent concurrent radiochemotherapy and were treated sequentially had a better 2-year OS in comparison with those treated with radiotherapy alone (respectively 46% and 37% vs. 25%, $p \leq 0.05$). Patients with PS 0–1 had better OS (median 1.6 years) compared with PS 2 (median 0.7 years, $p = 0.04$). Other prognostic factors analysed had no impact on OS in our study.

Conclusions. The treatment results of our patients are comparable to those in published trials and meta-analyses.

Key words: non-small cell lung cancer, chemoradiotherapy, radiotherapy, overall survival

Introduction

In 2013, of more than 12.7 million malignancies diagnosed worldwide, about 13% (1.6 million) were lung malignancies. In Poland, lung cancer is the most common type of cancer in men, and among women it ranks third. It's also the prime cause of death from malignancy for both sexes [1]. Cigarette smoking is the leading cause of lung cancer development. Smoking increases its risk 20–30 fold [2, 3]. The treatment method of patients diagnosed with lung cancer depends mainly on the clinical stage of the disease and patient comorbidities. One

of the reasons for the poor prognosis is late diagnosis, and therefore most patients are disqualified from radical surgery [4]. According to EUROcare 5 (EUROpean CANcer REgistry based study on the survival and care of cancer patients), the 5-year relative survival of lung cancer patients diagnosed between 2000 and 2007 was 14.3% for Poland, and the European average was 12.6% [5]. The most frequent histology of lung cancer is non-small cell lung cancer (NSCLC) [6]. The 5-year overall survival of patients diagnosed with NSCLC depending on clinical stage ranges 4–66% [7]. For patients with early-stage

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NSCLC surgery remains the primary treatment; for locally advanced non-small cell lung cancer chemoradiotherapy is the treatment of choice. However, the effectiveness of the latter leaves much to be desired. We have particularly high hopes for the addition of immunotherapy to chemoradiotherapy, which has significantly improved survival in inoperable patients [8].

However, there are some limitations to the data supporting treatment strategies in specific patient subsets and studies have included heterogeneous patient populations. The definition of clinical stage III has changed over time, and early reviews have often been inadequately powered to detect small differences in survival outcome, have not been randomised or have had limited time of follow-up. Development in therapy: the use of more active chemotherapy agents and refinements in radiation and surgical techniques also limit the interpretation of earlier clinical trials [9]. The aim of this study was to analyse and report the outcome of the treatment of non-small cell lung cancer patients with radical radiotherapy and chemoradiotherapy in our department.

Material and methods

A list of patients was generated from the institutional database, Mosaik and Clininet systems. The medical records of all patients were available for this study. The research was conducted on a group of 109 patients with primary, unresectable, non-metastatic cancers, with a histopathological diagnosis of non-small cell lung cancer, who underwent curative radio- and radiochemotherapy between 2013 and 2016 in the Nu-Med Radiotherapy Center in Elbląg. Seventeen patients were excluded from the analysis. The reason for exclusion was resection in 11 patients (10%), including nine patients treated with postoperative radiation and two patients treated with preoperative radiochemotherapy. Six patients (6%) who underwent therapy because of recurrence were also excluded from the analysis. All patients were staged with computed tomography of the chest and abdominal ultrasound, 57 (62%) had PET examinations, 87 (95%) had a spirometric evaluation.

The stage was determined by the UICC TNM classification of Malignant Tumours – 7th edition. A total dose of 66 Gy with fraction dose 2 Gy was administered in 55 patients, 66 Gy (fraction dose 2.2 Gy) in 8 patients, 60 Gy (fraction dose 2 Gy) in 27 cases and 50 Gy in 2 patients. Dose 60 Gy was prescribed for concomitant treatment, 66 Gy for the sequential scheme or for radiotherapy alone. The dose of 50 Gy was prescribed for tumours infiltrating vertebral bodies close to the spine. The CTV included lung tumour and pathological lymph nodes with 8 mm margins. In post-chemotherapy cases, the CTV consisted of residual lung tumour and lymph nodes with an 8 mm margin and initially involved mediastinal node groups. In both scenarios, the PTV was created by adding 7 mm margins radially and 10 mm in the craniocaudal direction.

Treatment plans were prepared using Prowess or Eclipse software. Radiotherapy was delivered with Artiste (Siemens)

Liniacs, using photons X 6 MV, with IMRT in 79 patients (86%) and 3D technique in 13 (14%). The method was chosen by attending a radiation oncologist, after DVH comparison.

Patients treated with chemoradiotherapy received different chemotherapy regimens: carboplatin-vinorelbine (KN) (6 patients), cisplatin-vinorelbine (PN) (47 patients), carboplatin-etoposide (KE) (1 patient), cisplatin-etoposide (PE) (6 patients), cisplatin (1 patient), cisplatin-pemetrexed (1 patient), KN+PN (1 patient), KN+PXL/CDDP (1 patient). The induction chemotherapy regimen was chosen and administered by medical oncologists from other hospitals.

The efficacy of radiotherapy and chemoradiotherapy was estimated by survival analysis from the date of the beginning of the treatment to the last follow-up visit/death. Variables that can impact patient survival (sex, age, BMI, place of residence, the distance between the place of residence and Nu-Med Center, baseline WHO PS, clinical stage, lymph node status, tumour localisation, type of histopathology, type of treatment) were analysed.

The proportion between subgroups: radiotherapy alone vs. sequential radiochemotherapy vs. concurrent radiochemotherapy in different factors were compared using the χ^2 test. Overall survival (OS) was estimated by the Kaplan-Meier method and differences in survival were compared by the log-rank test. Uni- and multivariable analysis was estimated through the Cox regression model. Univariate variables with $p < 0.25$ were included in the multivariable analysis. A p -value < 0.05 was considered to be significant. The analysis was performed using TIBCO Software Inc. (2017) and Statistica (a data analysis software system), version 13. <http://statistica.io>.

Results

Ninety-two patients were included in the analysis. The majority of patients were men (72; 78%) and lived in cities ≤ 100 thousand (44; 48%) and villages (31; 34%). The median age was 64 years. Half of the patients (47; 51%) were of PS (performance status) grade 0 according to the WHO/ECOG scale during the first visit. Most patients were treated in clinical stage IIIA (53; 58%) and IIIB (31; 34%), with T3–4 (70%), with N2–3 (80%), with squamous cell carcinoma (68; 74%) and adenocarcinoma (19; 21%), tumour localisation on right side (59; 64%). Over half (57; 62%) had a PET examination before treatment. 28 patients (30%) underwent radiotherapy only, 38 patients (41.5%) had sequential radiochemotherapy and 26 patients (28.5%) had concurrent radiochemotherapy. Most patients (58; 63%) were referred from Szpital Specjalistyczny in Prabuty (the regional pulmonological center) for treatment to the Nu-Med Center and the 34 remaining patients (37%) were diagnosed in hospitals in Elbląg (tab. I).

More patients who received radiotherapy alone were > 64 years compared with patients who underwent sequential or concurrent radiochemotherapy, respectively 89% vs. 32% vs. 23% ($p < 0.001$). There was a significant difference in perfor-

Table I. Characteristics of patients

Patient's characteristic	All		Radiotherapy alone		Sequential radio-chemotherapy		Concurrent radio-chemotherapy		Chi ² test
	N	%	N	%	N	%	N	%	p
	92	100	28	30	38	41.5	26	28.5	
Age (start of radiotherapy)	range: 46–82 years; median: 64 years								
≤64	49	53	3	11	26	68	20	77	<0.001
>64	43	47	25	89	12	32	6	23	
Sex									
women	20	22	5	18	9	24	6	23	0.84
men	72	78	23	82	29	76	20	77	
BMI	range: 15.8–46.1; median 26								
≤26	42	46	15	53.5	18	47	9	34.5	0.46
>26	42	46	12	43	16	42	14	54	
no data	8	9	1	3.5	4	11	3	11.5	
Place of residence									
village	31	34	9	32	13	34	9	34.5	0.08
cities ≤100 thous	44	48	14	50	22	58	8	31	
cities >100 thous	17	18	5	18	3	8	9	34.5	
Distance from place of residence to Nu-Med. Center	range: 0–616 km; median 67 km								
≤67	47	51	13	46	17	45	17	65	0.22
>67	45	49	15	54	21	55	9	35	
Performance status according WHO/ECOG during first visit									
0	47	51	10	36	17	45	20	77	0.02
1	37	40	14	50	17	45	6	23	
2	8	9	4	14	4	10	0	0	
Clinical stage									
IB	3	3	3	11	0	0	0	0	0.02
IIA	2	2	2	7	0	0	0	0	
IIB	3	3	2	7	1	3	0	0	
IIIA	53	58	16	57	19	50	18	69	
IIIB	31	34	5	18	18	47	8	31	
Lymph nodes status									
N+	79	86	20	71	35	92	24	92	0.03
N–	13	14	8	29	3	8	2	8	
Tumor localization									
right	59	64	17	61	26	68	16	61	0.97*
left	29	32	9	32	12	32	8	31	
mediastinum	3	3	2	7	0	0	1	4	
right and left	1	1	0	0	0	0	1	4	
Type of histopathology									
planoepitheliale	68	74	19	68	30	79	19	73	0.74^
adenocarcinoma	19	21	7	25	7	18	5	19	
undetermined	5	5	2	7	1	3	2	8	
PET									
yes	57	62	21	75	14	37	22	85	<0.001
no	35	38	7	25	24	63	4	15	

Patient's characteristic	All		Radiotherapy alone		Sequential radiochemotherapy		Concurrent radiochemotherapy		chi ² test
	N	%	N	%	N	%	N	%	p
Time of treatment from radiochemotherapy to end of radiotherapy	range: 15–208 days; median 47.5 days								
≤47.5	46	50	26	93	0	0	20	77	<0.001
>47.5	46	50	2	7	38	100	6	23	

*p-value – comparison of the percentages between subgroups: right and left tumor localization

^p-value – comparison of the percentages between subgroups: planoepitheliale and adenocarcinoma type of histopathology

mance status (PS) according to the WHO/ECOG classification during the first visit between patients treated with concurrent radiochemotherapy (no one with PS 2) vs. sequential radiochemotherapy (10% of patients with PS 2) or radiotherapy alone (14% of patients with PS 2) (p = 0.02). Patients who underwent a different type of treatment significantly differed in terms of characteristics: clinical stage, lymph node status, PET examination and the time of treatment from radiochemotherapy to the end of radiotherapy (tab. I).

The 2-year overall survival for all patients was 36%. The median OS (mOS) was 1.5 years (95% confidence interval (CI): 0.7–2.8 years; (fig. 1). 31 deaths (34%) were observed during the first year, including 13 patients treated with radiotherapy alone, 9 with sequential radiochemotherapy and 9 with concurrent radiochemotherapy. Patients who underwent

radiotherapy alone had a statistically significant worse 2-year OS (25%; mOS 1.1 years [95% CI: 0.5–1.9 years]) in comparison with patients treated with concurrent (46%; mOS 1.1 years [95% CI: 0.5–not reached]; p = 0.05) and sequential radiochemotherapy (37%; mOS 1.7 years [95% CI: 1.0–2.6 years]; p = 0.03). There was no significant difference observed between concurrent and sequential radiochemotherapy (p = 0.54) (fig. 2, tab. II). Patients with PS 0–1 during the first consultation had a significantly better mOS – 1.6 years (95% CI: 0.7–3.5 years) than patients with PS 2 – mOS 0.7 years (95% CI: 0.4–1.1 years; p = 0.04) (fig. 3, tab. II). Total treatment time, age, sex, BMI, place of residence, the distance from the place of residence to the Nu-Med Center, lymph node metastasis, tumour localisation, type of histopathology, clinical stage, PET examination had no impact on OS (tab. II).

Table II. Overall survival of patients

	2-year OS (%)	Median OS [years] (95% CI)	Log-Rank test p
All	36	1.5 (0.7–2.8)	
Age (at start of radiotherapy)			
≤64 years	39	1.6 (0.7–4.2)	0.17
>64 years	33	1.5 (0.6–2.2)	
Sex			
women	50	1.6 (0.7–2.9)	0.42
men	32	1.5 (0.6–2.2)	
BMI			
≤26	36	1.5 (0.5–2.3)	0.76
>26	36	1.6 (0.9–3.2)	
Place of residence			
village	39	1.5 (0.7–not reached)	0.72
cities ≤100 thous	32	1.5 (0.7–2.3)	
cities >100 thous	41	1.6 (0.2–3.7)	
The distance from place of residence to Nu-Med Center			
≤67 km	30	1.5 (0.5–2.2)	0.29
>67 km	42	1.6 (0.9–3.1)	

	2-year OS (%)	Median OS [years] (95% CI)	Log-Rank test p
Performance status according to WHO/ECOG scale during first visit			
0-1	39	1.6 (0.7-3.5)	0.04
2	-	0.7 (0.4-1.1)	
Clinical stage			
IB	33	1.9 (0.4-4.1)	0.63
IIA	50	0.2 (0.2-2.3)	
IIB	-	0.6 (0.5-1.7)	
IIIA-B	37	1.5 (0.7-3.1)	
Lymph node status			
N+	37	1.5 (0.7-2.6)	0.78
N-	31	1.7 (0.5-3.1)	
Tumor localization			
right	38	1.6 (0.7-2.6)	0.51*
left	38	1.6 (0.7-not reached)	
Type of histopathology			
planoepitheliale	32	1.5 (0.6-2.2)	0.29^
adenocarcinoma	47	1.6 (1.0-4.2)	
PET			
yes	40	1.5 (0.6-3.6)	0.52
no	28	1.5 (0.7-2.1)	
Time of treatment from radiochemotherapy to end of radiotherapy			
≤47.5 days	37	1.2 (0.5-2.6)	0.55
>47.5 days	35	1.6 (1.0-2.6)	
Type of treatment			
alone radiotherapy	25	1.1 (0.5-1.9)	0.07
sequential radiochemotherapy	37	1.7 (1.0-2.6)	
concurrent radiochemotherapy	46	1.1 (0.5-not reached)	

* patients with mediastinum tumor localization were excluded from the analysis

^ patients with undetermined type of histopathology were excluded from the analysis

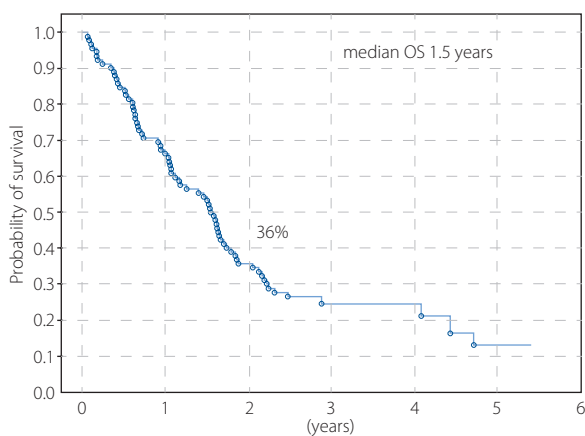


Figure 1. Overall survival for all patients

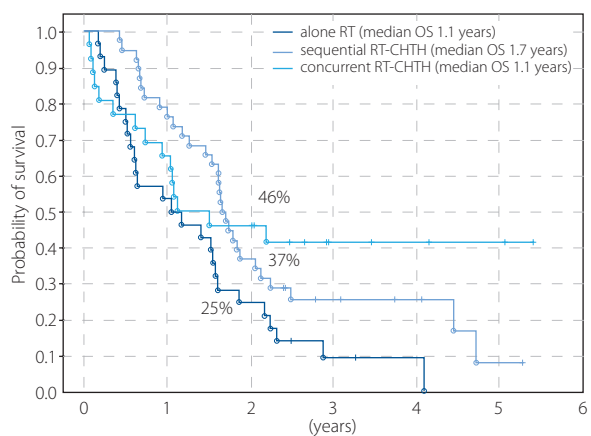


Figure 2. Overall survival by type of treatment

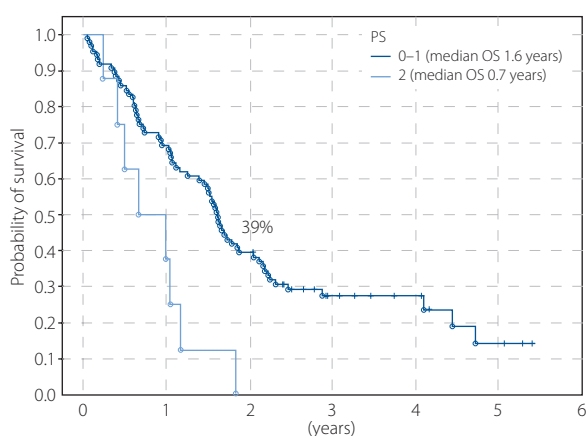


Figure 3. Overall survival by performance status during the first visit

In univariate analysis, only three factors met the inclusion criteria to a multivariate regression model ($p < 0.25$). In multivariate analysis, it was determined that performance status and type of treatment were independent factors influencing OS. The risk of death in patients with WHO/ECOG grade 2 increased by three times (PS 0–1 vs. 2, HR: 3.0; 95% CI: 1.4–6.6; $p = 0.006$). Increased risk of death was observed in patients treated with

radiotherapy alone (HR: 2.4; 95% CI: 1.0–5.6; $p = 0.04$) compared with concurrent radiochemotherapy (tab. III).

Discussion

The optimal management of NSCLC patients depends on multiple factors, including the clinical stage of the disease, the potential to achieve a complete resection, the patient's overall condition, comorbidities and preferences. The main option for CS I–IIIA (N0–1) NSCLC remains surgery, for clinical stages: IIIA (N2), IIIB, and unresectable I–IIIA (N0–1) the standard of care is radiochemotherapy [10].

The current analysis concerned patients qualified for treatment before and after the Polish National Program of Diagnosis and Treatment of Oncological Diseases was set. Before 2015, in our centre, the decision to use the appropriate treatment was made by a team of radiation oncologists, after disqualification from surgery by thoracic surgeons. In 2015, we started to present patients at a multidisciplinary board with a radiation oncologist, a medical oncologist, a radiologist and a thoracic surgeon, where an accurate treatment plan was chosen.

Curative radiotherapy alone was chosen for elders and patients with a poorer performance status, who had con-

Table III. Uni- and multivariate survival analysis by Cox regression model

Variables	Univariate analysis			Multivariate analysis		
	HR (95% CI)	p		HR (95% CI)	p	
Age (start of radiotherapy)						
≤64 years	1.0	reference		1.0	reference	
>64 years	1.4	(0.9–2.2)	0.17	0.79	(0.4–1.6)	0.50
Sex						
women	1.0	reference				
men	1.3	(0.7–2.3)	0.43			
BMI						
≤26	1.0	reference				
>26	0.9	(0.6–1.5)	0.76			
Place of residence						
village	1.0	reference				
cities ≤100 thous	1.2	(0.7–2.0)	0.59			
cities >100 thous	1.1	(0.6–2.2)	0.97			
Distance from place of residence to Nu-Med Center						
>67 km	1.0	reference				
≤67 km	1.3	(0.8–2.1)	0.30			
Performance status according to WHO/ECOG scale during first visit						
0–1	1.0	reference		1.0	reference	
2	2.9	(1.4–6.3)	0.006	3.0	(1.4–6.6)	0.006

		Univariate analysis		Multivariate analysis		
Clinical stage						
	IB	1.0	reference			
	IIA	1.3	(0.2–7.9)	0.77		
	IIB	2.1	(0.4–10.4)	0.38		
	IIIA–B	0.8	(0.3–2.7)	0.76		
Lymph nodes status						
	N–	1.0	reference			
	N+	1.1	(0.6–2.2)	0.78		
Tumor localization						
	left	1.0	reference			
	right	1.2	(0.7–2.0)	0.51*		
Type of histopathology						
	adenocarcinoma	1.0	reference			
	planoepitheliale	1.4	(0.7–2.4)	0.32^		
PET						
	yes	1.0	reference			
	no	1.2	(0.7–1.9)	0.51		
Time of treatment from radiochemotherapy to end of radiotherapy						
	>47.5 days	1.0	reference			
	≤47.5 days	1.2	(0.7–1.8)	0.55		
Type of treatment						
	concurrent radiochemotherapy				1.0	reference
	alone radiotherapy	2.1	(1.1–4.1)	0.02	2.4	(1.0–5.6) 0.04
	sequential radiochemotherapy	1.2	(0.7–2.3)	0.53	1.1	(0.6–2.1) 0.72

* patients with mediastinum tumor localization were excluded from the analysis

^ patients with undetermined type of histopathology were excluded from the analysis

traindications to chemotherapy or in whom the application of the combined treatment would significantly increase its toxicity. The 2-year overall survival of our patients treated with radiotherapy only was 25% and this was at the upper limit of the survival time reported in the literature: 5–28% [11–15].

Patients in good general condition without significant comorbidities were qualified for combined therapies. At multidisciplinary meetings, concurrent radiochemotherapy was the preferred option. Sequential treatment was selected when the baseline tumour volume excluded radical radiotherapy and chemotherapy would provide a chance to reduce tumour mass (more advanced clinical stage, positive lymph node status).

The addition of chemotherapy to radiation has been the subject of many trials and several meta-analyses. Firstly, its beneficial influence on survival was demonstrated in the case of sequential radiochemotherapy in comparison with radical

radiation alone. Adding induction chemotherapy to radiotherapy increased overall survival to 26–31% at two years [14, 16–18]. Secondly, the introduction of concurrent radiochemotherapy: although this intensification of treatment is associated with higher toxicity, most trials showed better survival with a concurrent association in comparison with sequential therapy [17, 19–24]. Combining chemotherapy and radiotherapy simultaneously increases 2-year overall survival to 35.6–55.6% [8, 17, 18, 23].

Our study showed the significant advantage of radiochemotherapy in survival outcomes when compared with radiotherapy alone. The 2-year survival of NSCLC patients treated with sequential and concomitant radiochemotherapy was 37% and 46% respectively. The results were comparable to those published in clinical trials and meta-analyses. However, this report did not manage to show a significant difference in

efficiency between sequential and concomitant therapy. This could be limited by the small size of the subgroups compared. Unfortunately, our center, especially in the first years of operation, had no impact on the choice of combination therapy (simultaneous vs. sequential). The majority of patients who were suitable for concurrent treatment were referred to our department with no initial PET-CT scan and after the administration of induction chemotherapy – without the decision of a multidisciplinary board.

In the multivariate analysis, the type of treatment and performance status were independent factors influencing OS. We estimated the statistically significant increasing risk of death in patients treated with radiotherapy alone in comparison with concurrent radiochemotherapy and in patients with WHO/ECOG grade 2 at the first consultation. Polish colleagues also confirmed that performance status had a significant association with overall survival [25]. In our analyses, four PS 2 patients were treated with sequential chemoradiotherapy, and their ECOG status was probably an effect of the extent of the disease and chemotherapy toxicity.

In Poland, apart from clinical trials, institutional reports on the effectiveness of oncologic treatment of lung cancer are still lacking. A similar type of institutional report with a survival analysis of NSCLC patients was noted in the case of patients treated in the Warmia and Mazuria Oncology Center in Olsztyn, Poland. The authors showed treatment results for 130 patients treated with chemoradiotherapy in CS IIIA–IIIB and the 2-year overall survival was 37% [25]. The results are consistent with those reported by our analysis.

Nonetheless, we are aware of the limitations of this study. It is a retrospective analysis, with a small sample and a short observation time. Comparison of the groups also has limited value because of the small subgroups and potential selection bias.

Conclusions

The survival data of NSCLC patients treated in the Nu-Med Radiotherapy Center in Elbląg is comparable to those published in other papers. Forty-six percent of patients treated with concurrent radiochemotherapy survived 2 years. The main risk factors which decreased OS were: the type of therapy and performance status. A significantly worse prognosis was noted in the case of radiation alone compared to radiochemotherapy, and poorer performance status during first consultation. Particular attention should be paid to the proper qualification of the lung cancer patient for the appropriate treatment – preferably during multidisciplinary meetings.

Conflict of interest: none declared

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