

Prognostic Factors Influencing the Survival of Patients with Metastatic Non-Small Cell Lung Cancer in the Moroccan Population: Retrospective Study of 405 Cases

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Abstract

Introduction: Non-small cell lung cancer is the most common lung cancer. Despite the therapeutic advances, its prognosis is very reserved. **Aim:** Determine the different prognostic factors of patients with metastatic non-small cell lung cancer and their correlation with patient survival. **Methods:** A retrospective study was conducted at the medical oncology department of Hassan II University Hospital in Fez, collecting 405 patients during a period of 10 years, from January 2008 to January 2018. The statistical analysis of the results was done by the software SPSS version 23, the survival was calculated by the Kaplan-Meier method. The Cox method was used to study prognostic factors. **Results:** The average age of our patients was 59 years, with a sex ratio M/F of 6.1. In multivariate analysis, we found a significant correlation between the deterioration of survival and an age greater than 75 years ($p = 0.023$), a general degraded state ($p < 0.001$), presence of a biological inflammatory syndrome ($p < 0.001$), anemia ($p < 0.001$) and hypoalbuminemia ($p < 0.001$). In addition, no significant association was found in patients with toxic habits or multiple metastatic sites. **Conclusion:** The prognostic factors of metastatic NSCLC in our patients were PS, age, anemia, hypoalbuminemia and inflammatory syndrome. We propose to validate all the factors identified by retrospective studies by prospective studies in order to guarantee the best chances of survival for patients.

Keywords

Non-Small Cell Lung Cancer, Prognostic, Survival

1. Introduction

Bronchopulmonary cancer is the most common cancer in the world and is the leading cause of cancer death in men [1]. The number of incident cases is constantly increasing (2.1 million new cases in 2018 versus 1.6 million in 2008). The mortality rate was estimated at 1.8 million deaths in 2018 versus 1.4 million in 2008 [1]. Nationally, according to data from the cancer registry for the Grand Casablanca region, lung cancer is the most common cancer in humans with a rate of 23% of cases recorded during the period between 2008 and 2012 [2]. Regarding the incidence of this cancer, there has been a significant increase in new cases over the years, especially advanced forms, which makes the prognosis poor. Considering the stage of the tumor at the time of diagnosis is the main prognostic factor [3].

Prognostic factors are defined as things that can predict a patient's prognosis before treatment is started. Several publications have been made in this direction, taking these factors into account is of great importance, more particularly in the choice of treatment. In this article, we will study these different factors and their influence on survival.

2. Methods

A descriptive retrospective study was carried out in the medical oncology department of the Hassan II University Hospital in Fez, collecting 405 patients with metastatic NSCLC over a period of 10 years, from January 2008 to January 2018. The inclusion criteria were: patients with histologically proven non-small cell lung cancer, classified as stage 4. The exclusion criteria were: patients with non-histologically proven NSCLC and incomplete medical records. Descriptive statistics were used to describe the characteristics of these tumors using the mean \pm standard deviation for continuous variables and frequencies for categorical variables. Survival was calculated by the Kaplan-Meier method. Cox's method was used to study prognostic factors. The significance level for all tests was set at 0.05. Statistical analysis of the results was done by SPSS version 23 software.

3. Results

Between January 2008 and January 2018, we included 405 patients with metastatic NSCLC in the medical oncology department of CHU Hassan II in Fez. The average age of our patients was 59 years, the percentage of patients with an age greater than or equal to 70 years was 17.8%. The majority of patients were male with a percentage of 86% (sex ratio M/F: 6.1). Smoking was the main risk factor (78%), the notion of alcoholism and cannabis use was found in 12.8% and 8.1% of cases respectively. The notion of occupational exposure was reported in 4.2% of cases. The most common symptoms were cough (41%), haemoptysis (33%), dyspnea (29%) and chest pain (20%). 65.2% of patients were in good general condition (PS 0 to 1) at the time of diagnosis. The most common histologic type

was adenocarcinoma (59.5%), followed by squamous cell carcinoma (22.5%) then other carcinomas (18%). According to the TNM classification, 62% of patients were classified as T4 and lymph node invasion N2 and N3 was found in 29% and 35% of cases respectively. 39% of patients had more than one metastatic site after extension workup. The most frequent elective sites of metastases were: lung (50.4%), bone (32.6%) pleura (22%), brain (21.2%) and liver (17.5%). All patients performed a biological workup including a count blood, an assay of the level of albumin, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), calcium level and C-reactive protein (CRP); this assessment had demonstrated anemia in 58.8% of patients, hyperleukocytosis in 45.9% of cases, thrombocytosis in 13.8% of cases, hypoalbuminemia in 49.6% of cases, an increase in the level of LDH and ALP in 34.3% and 29% of cases respectively and hypercalcemia in 4% of cases.

The first-line treatment was essentially based on chemotherapy, it was indicated in 87.1% of which 83% of patients received a doublet based on platinum salts \pm BEVACIZUMAB (13%) and 17% received NAVELBINE as monotherapy.

Anti-EGFR TKIs were administered to 2.5% of patients with the EGFR mutation (**Table 1**). After an average number of 3 cures, the objective response rate was 18.6%.

After a median follow-up of 18 months, the median progression-free survival (PFS) was 4.6 months and that of overall survival (OS) was 6.5 months (**Figure 1**).

In multivariate analysis, we found a significant correlation between the deterioration of survival and an age greater than 75 years ($p = 0.023$), a deteriorated general condition ($p < 0.001$), presence of a biological inflammatory syndrome ($p < 0.001$), anemia ($p < 0.001$) and hypoalbuminemia ($p < 0.001$). Furthermore, no significant association was found in patients with toxic habits or presenting several metastatic sites (**Table 2** and **Table 3**).

Table 1. Patient characteristics.

Characteristics	Number (%)	
Gender	Male	349 (86.2)
	Female	56 (13.8)
Age	<70 years	333 (82.2)
	>70 years	72 (17.8)
Toxic habits	Smoking	316 (78)
	Alcoholism	52 (12.8)
	Cannabism	33 (8.1)
Clinical signs	Professional exposure	17 (4.2)
	Cough	166 (40.9)
	Hemoptysis	134 (33.1)

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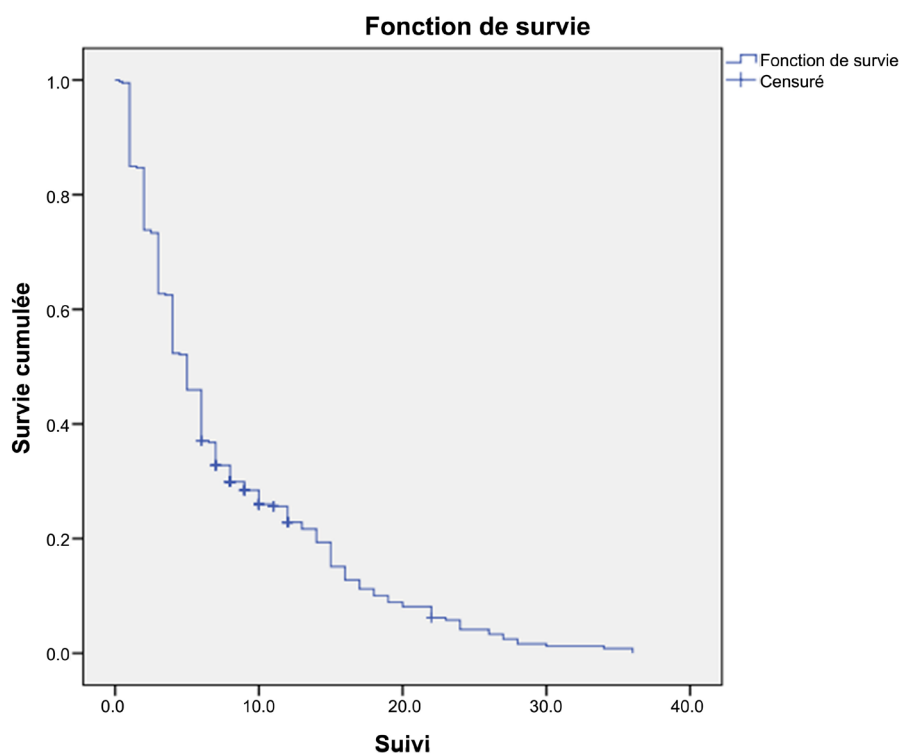
	Dyspnea	117 (28.8)
	Chest pain	81 (20)
Performance status (PS)	0 - 1	264 (65.2)
	2	89 (22)
	3 - 4	52 (12.9)
	Adenocarcinoma	241 (59.5)
Histological type	Squamous cell carcinoma	91 (22.5)
	Undifferentiated carcinoma	54 (13.3)
	Neuroendocrine carcinoma	11 (2.7)
	Sarcomatoid carcinoma	5 (1.3)
	Carcinoid tumor	3 (0.7)
Tumor size	T1	4 (1)
	T2	28 (7)
	T3	122 (30)
	T4	251 (62)
Lymph node involvement	N1	146 (36)
	N2	117 (29)
	N3	142 (35)
Metastatic sites	Lung	204 (50.4)
	Bone	132 (32.6)
	Pleura	89 (22)
	Brain	86 (21.2)
	Liver	71 (17.5)
Number of metastatic sites	1	247 (61)
	>1	158 (39)
Biological disturbances	Anemia	238 (58.8)
	Hyperleukocytosis	186 (45.9)
	Thrombocytosis	56 (13.8)
	Hypoalbuminemia	201 (49.6)
	High LDH level	139 (34.3)
	High LAP rate	117 (29)
	High level of CRP (>10 ng/l)	322 (79.5)
First line treatment	Hypercalcemia	16 (4)
	Conventional chemotherapy	353 (87.1)
	TKI anti-EGFR	10 (2.5)
	Supportive care	42 (10.4)
	Platinum based doublet	247 (70)
Conventional chemotherapy	Platinum based doublet + BEVACIZUMAB	46 (13)
	NAVELBINE (monotherapy)	60 (17)

Table 2. Univariate analysis of factors influencing overall survival.

Characteristics	P-value	Odds-ratio (OR)	95% confidence interval
Age \geq 75 years	0.021	0.64	[0.43 - 0.93]
Smoking	0.731	0.95	[0.73 - 1.24]
Professional exposure	0.828	1.05	[0.64 - 1.73]
PS > 1	<0.001	1.73	[1.37 - 2.19]
Anemia	<0.001	1.55	[1.24 - 1.94]
Hyperleukocytosis	0.626	0.94	[0.75 - 1.18]
Thrombocytosis	0.276	1.19	[0.86 - 1.64]
Metastatic site > 1	0.318	1.11	[0.89 - 1.39]
Hypoalbuminemia	<0.001	3.20	[2.65 - 3.85]
Raised CRP	<0.001	2.98	[2.21 - 3.45]

Table 3. Multivariate analysis of factors influencing overall survival.

Characteristics	P-value	Odds-ratio (OR)	95% confidence interval
Age \geq 75 years	0.023	0.64	[0.44 - 0.94]
PS > 1	<0.001	1.71	[1.37 - 2.15]
Anemia	<0.001	1.57	[1.25 - 1.96]
Hypoalbuminemia	<0.001	3.21	[2.67 - 3.86]
Raised CRP	<0.001	2.99	[2.23 - 3.46]

**Figure 1.** Curve of overall survival estimated according to Kaplan-Meier.

4. Discussion

Lung cancer is the leading cause of cancer death worldwide, with 1.8 million deaths in 2018, which represents nearly 1 in 5 cancer deaths [1]. In men, it is the leading cause of death in countries in Europe, Asia and Africa [1]. The incidence of this cancer remains generally low in Africa, although it varies from medium to high between the countries of the North and the South, in particular in South Africa (28.2 in 100,000) and in Morocco (31.9 in 100,000) [1]. Among the prognostic factors widely studied in the literature are: the performance status; it is considered to be a powerful prognostic factor, this factor has been studied in several phase III studies, confirming the reproducibility of this factor with hazard ratios varying between 0.60 and 0.70 [4] [5] [6]. The 2nd clinical factor is sex; according to some authors, it has been shown in several studies that overall survival in women is much better than in men [7], this was confirmed by a meta-analysis [8] including 39 studies with more than 86,000 patients, this meta-analysis combined the odds ratios of the uni and multivariate analyzes and they were 0.79 and 0.78, respectively; both $p < 0.0001$ in favor of the female sex. Age is another factor that has been studied in several clinical trials, but there are few studies that have confirmed the prognostic significance of age > 70 years on survival [9] [10]. In our study, we found a significant improvement in survival in patients in good general condition aged less than 70 years. On the other hand, no correlation has been demonstrated between gender and reduced survival. Smoking is also considered a poor prognostic factor, it has a negative impact on survival, proven in several studies [11] [12] [13], it has been shown in these trials that patients who smoked over 20 PA are more likely to have aggressive and less differentiated histological types. And for those who smoked above 60 PA, the risk of developing distant metastases is 41% (95% CI: 1.03 - 1.94) [12]. In our series, smoking was not associated with decreased survival on univariate analysis.

Another factor has also been studied; this is the histological type. Its role in predicting the prognosis remains controversial, according to Blanchon and his colleagues [14], a study was carried out including 5667 patients, showing that patients with squamous cell carcinoma had better survival ($p < 0.001$) compared to those with large cell neuroendocrine carcinoma ($p < 0.001$). Conversely, other authors have confirmed in studies that squamous cell carcinoma has a poor prognosis than adenocarcinoma [15] [16]. In our series, histological type was not correlated with survival ($p = 0.15$). With regard to the number of sites and the location of metastases; few studies have been conducted in this direction, Wakelee and colleagues [17], have suggested that the presence of a single metastatic site in the lungs is a good prognosis. In our series, the presence of more than one metastatic site was not a factor in the decline in survival. The association between the presence of a biological abnormality and reduced survival has also been studied. Beginning with anemia; researchers have suggested that the presence of anemia before initiation of treatment is an independent prognostic factor for survival in patients with lung cancer and may be associated with higher

mortality [8] [18] [19], this has been demonstrated in our study. The presence of hyperleukocytosis and thrombocytosis is significantly correlated with decreased survival [20] [21] [22], this is inconsistent with the results of our study; patients with these hematologic abnormalities at the time of diagnosis did not have a significant difference in survival compared to those with correct biology. Among the potential serum biomarkers, we cite lactate dehydrogenase (LDH) which is an enzyme released by rapidly growing tumors, it has a correlation with tumor burden. Recent studies have shown that a high level of LDH before the initiation of treatment is generally associated with poor results in terms of survival, its presence makes the prognosis poor especially when it is increased by 1 to 2.5 times the upper normal limit (ULN) [23] [24]. Serum albumin levels reflect the nutritional status of cancer patients; it is an important determinant of survival in many types of cancer. This parameter has been reported as a negative prognostic factor for survival in advanced NSCLC in several studies [25]. Serum CRP has been identified as a significant prognostic factor in patients with colorectal, esophageal and hepatic carcinoma [26]. However, the nature of this association in patients with metastatic NSCLC remains controversial at present, data from Ali-fano's study [27] did not reveal a significant difference in terms of survival between the groups of patients with high and normal CRP, however the results of a meta-analysis [28] including 8 studies with more than 1600 patients demonstrated that a high CRP level could predict the prognosis in patients with NSCLC. Our results demonstrated that elevated LDH, hypalbuminemia and inflammatory syndrome are unfavorable prognostic factors determining deterioration in survival in patients with NSCLC. Systemic anti-tumor treatment has shown its benefit in terms of survival versus supportive care. Several meta-analyses that have been carried out in this direction [29] [30], showing the clear benefit of anti-tumor treatment on the survival of patients with metastatic NSCLC.

5. Conclusion

Through this retrospective study, the presence of these following factors (PS > 1, age > 75 years, anemia, hypoalbuminemia and elevated CRP) was associated with a poor prognosis, these factors must be taken into consideration to define optimal management and guide the clinician in the choice of the best therapeutic protocol, we propose as perspectives to validate all the factors identified in retrospective studies by prospective work in order to guarantee the patient the best chances of survival.

Conflicts of Interest

The authors declare that they have no competing interests.

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