RAPID COMMUNICATION

"High Tumor Burden" in Metastatic Non-Small Cell Lung Cancer: Defining the Concept

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Purpose: Identifying patient characteristics that define a worse disease prognosis or "high tumor burden" (HTB) status is essential for clinical decision-making and treatment selection in metastatic non-small cell lung cancer (mNSCLC). We aimed to define this concept based on the experience of oncologists in clinical practice.

Patients and Methods: A representative sample of Spanish experts was selected and asked to complete an online survey regarding the definition of HTB according to their personal experience.

Results: HTB was identified by the oncologists (N = 81) as one of the principle factors influencing first-line treatment decision-making. According to the experts, HTB is mainly defined by the number of metastatic lesions (n = 45, 56%), location (n = 34, 42%), tumor size (sum of diameters of target lesions; n = 26, 32%) and liver involvement (n = 24, 30). High lactate dehydrogenase (LDH) levels were also associated with HTB. Almost half of respondents (n = 33, 41%) believed that one metastatic lesion was sufficient to consider a patient as presenting HTB, 72% (n = 58) considered that two were necessary and 99% (n = 80) three. Liver (n = 76, 100%) followed by brain (n = 65, 86%) were the main metastatic sites associated with HTB. Tumor size ranging from 6 cm to 10 cm as well as high LDH levels (three times the upper limit) defined the concept for 82% (n = 62) and 100% (n = 76) of oncologists, respectively.

Conclusion: In the real-world setting, according to experts, HTB is defined by the number of metastatic lesions, location of metastases, tumor size and by high LDH levels. Given the relevance of this concept, efforts should be made to unify its definition and to further explore its potential as a prognostic factor for mNSCLC patients.

Keywords: non-small cell lung cancer, "high tumor burden", number of metastases, tumor size, metastatic locations, lactate dehydrogenase

Introduction

Lung cancer is the leading cause of cancer death among men and the second among women worldwide.[1] Non-small cell lung cancer (NSCLC) is the most prevalent subtype, accounting for 80% to 85% of all lung cancer diagnoses.[2] Given that it is frequently diagnosed in the advanced stage[3] and is associated with poor survival rates,[4] accurate prognosis is essential for clinical decision making and treatment selection. Prognostic factors can be used to construct homogenous patient groups, helping guide therapy in some cases, for example by identifying subgroups of individuals according to their therapy requirements. Additionally, they can be used as stratification factors.[5]

The tumor-nodes-metastasis (TNM) classification system for cancer staging published by the Union for International Cancer Control (UICC)[6] has been one of

the most reproducible methods for establishing prognosis to date. However, this system classifies patients into different stages, each representing a range of disease extent that may not best reflect individual patient prognosis,[7] especially in patients with more advanced stages of the disease (stage IVb). New statistical models that combine multiple variables have recently been developed to improve the prognosis of cancer patients.[8,9] In the real-world setting, the identification of patient characteristics that define a worse disease prognosis or "high tumor burden" (HTB) status is essential in these advanced stages. Classifying patients based on this concept may help guide treatment decision making, offering more specific alternatives for patients with metastatic NSCLC (mNSCLC). Given the special medical requirements of this group, our aim was to define the concept of HTB based on the experience of oncologists in clinical practice.

Methods

A representative sample of Spanish experts was surveyed. Inclusion in the survey required the oncologist to be the primary decision maker for the treatment of ≥10 mNSCLC patients per month and to have experience in immunotherapy regimens.

The experts were asked to complete an online survey containing some general questions and specific questions regarding the definition of HTB according to their personal experience in clinical practice (Supplementary Material). Data were collected between 29 November 2019 and 14 January 2020 and processed by an independent market research company (Ipsos Healthcare, London, UK). Categorical data are presented as frequencies and continuous variables as mean ± standard deviation (SD).

Due to the non-interventional nature of the study and in accordance with Spanish legislation, ethics committee approval and informed consent were not required (Ministerial Order 1090/2015, 4 December 2015; available at: https://www.boe.es/eli/es/rd/2015/12/04/1090).

Results

A total of 81 experts participated in the survey, resulting in a sampling error of 10.3% with a 95.5% confidence level and $p = 0.045$. The general characteristics of the respondents are shown in Table 1.

Regarding first-line treatment decision making, oncologists indicated that Eastern Cooperative Oncology Group Performance Status (ECOG PS) at diagnosis (n = 68, 84%), PD-L1 expression levels (n = 50, 62%) and

Table 1 General Characteristics of Respondents

Characteristics	Total Respondents (N = 81)
Origin, n (%)	
North of Spain	17 (21)
Northeast/Levante	25 (31)
Center of Spain	23 (28)
South of Spain	16 (20)
Years of experience	
≤15 years	58% (47)
>15 years	42% (34)
Number of cancer patients per month, mean ± SD	218 ± 107
Lung cancer patients	101 ± 74
NSCLC patients	72 ± 53
mNSCLC patients	50 ± 38

Abbreviations: NSCLC, non-small cell lung cancer; mNSCLC, metastatic non-small cell lung cancer; SD, standard deviation.

comorbidities (n = 40, 49%) were the main factors influencing their choice of treatment (Figure 1A). Tumor burden (n = 27, 33%) was also included as one of the five main factors considered by the experts when prescribing treatments in the first-line setting. Notably, when assessing the degree of importance of those factors, HTB, considered as a key variable in the decision-making process for the majority of oncologists (n = 49, 61%), was classified as "important" (mean score of 5.6/7) (Figure 1B).

According to the experts, the factors that mainly defined the concept of HTB were the number of metastatic lesions (n = 45, 56%); location of metastases (n = 34, 42%); tumor size (sum of diameters of a maximum of five target lesions, considering no more than two lesions/organ; n = 26, 32%); and liver involvement (n = 24, 30%) (Figure 2A). These factors, along with high lactate dehydrogenase (LDH) levels, were moderately-strongly associated with the concept of HTB by most participants (Figure 2B).

Regarding the minimum number of metastatic lesions needed to consider HTB, almost half of respondents (n = 33, 41%) considered that patients with one metastatic lesion present HTB; this percentage increased to 72% (n = 58) for patients with two metastatic lesions and to 99% (n = 80) for patients with three metastatic lesions.

Liver (n = 76, 100%) followed by brain (n = 65, 86%) are the main metastatic sites associated with the concept of HTB. Lung, bone and other locations were indicated by 46% (n = 35), 40% (n = 30) and 17% (n = 13) of the
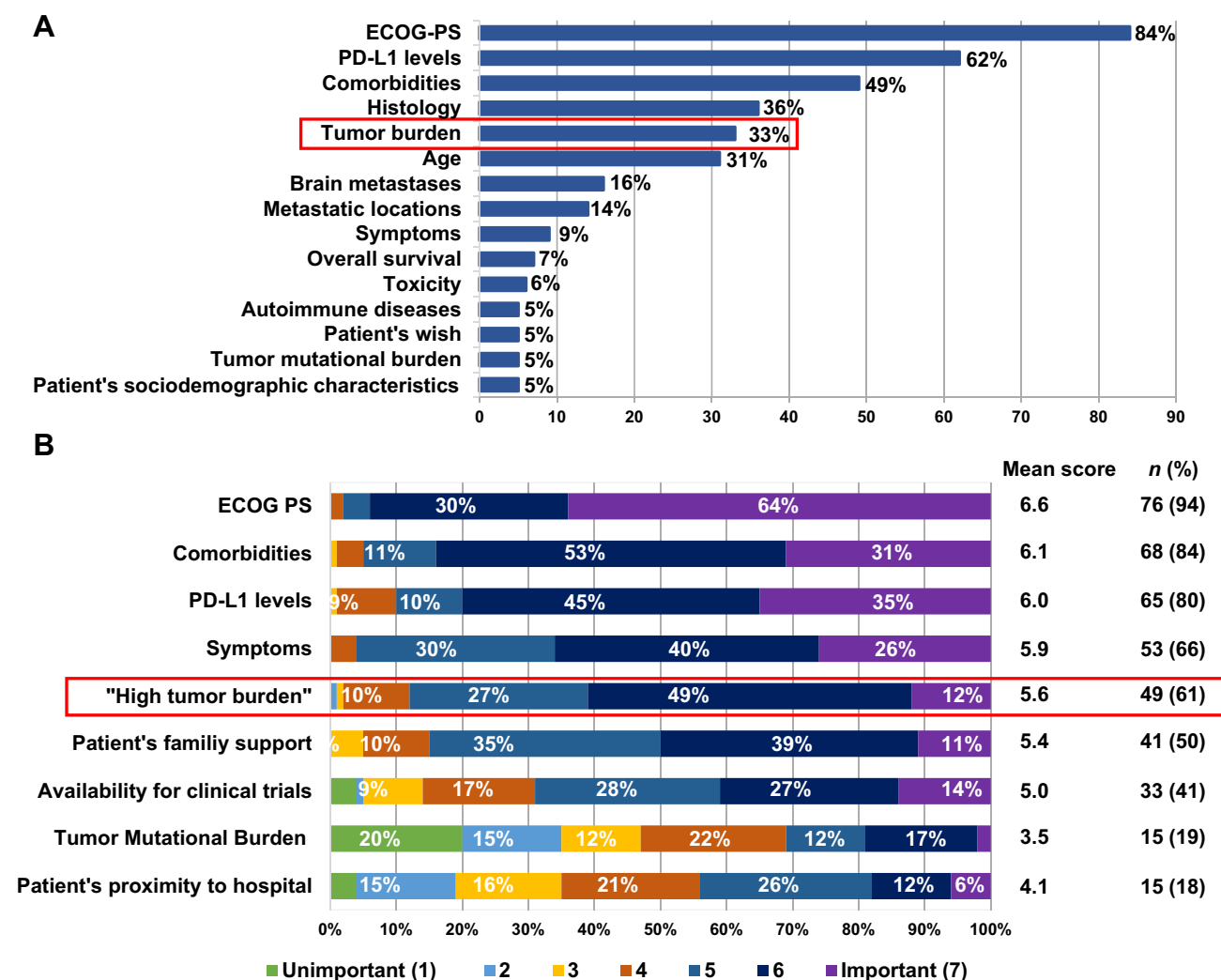
A

B

Figure 1 Factors influencing experts' first-line treatment decision (**A**) and degree of importance of those factors evaluated through a scoring system (scale from 1 to 7 where 1 is "Unimportant" and 7 "Important") (**B**).
Abbreviations: ECOG PS, Eastern cooperative oncology group performance status; PD-L1, programmed death-ligand 1.

experts, respectively (participants who did not consider metastatic sites as a relevant factor were excluded; N = 76).

In terms of tumor size, 82% (n = 62) of oncologists identified HTB when the sum of diameters of target lesions ranges between 6 cm and 10 cm (participants who did not consider tumor size as a relevant factor were excluded; N = 76).

In the case of LDH, 46% (n = 35) of respondents consider HTB when LDH levels are twice the upper limit of normal (ULN), and 100% (n = 76) consider HTB when levels are three times the ULN (participants who did not consider LDH levels as a relevant factor were excluded; N = 76). Finally, 68% considered the patient had HTB when they had weight loss of at least 15% (n = 48)

(participants who did not consider LDH levels or weight loss as relevant factors were excluded; N = 76 and N = 70, respectively).

Discussion

The concept of "high tumor burden" remains unclear. Its definition and implementation as a prognostic factor in the landscape of lung cancer could help to design individualized treatment plans that would not only improve efficacy outcomes and patient quality of life, but also reduce the incidence of adverse effects.[10]

Our survey found, first, that in the real-world setting, HTB is identified by oncologists as an important variable to consider when choosing first-line treatment. This concept is mainly defined based on the number of metastatic
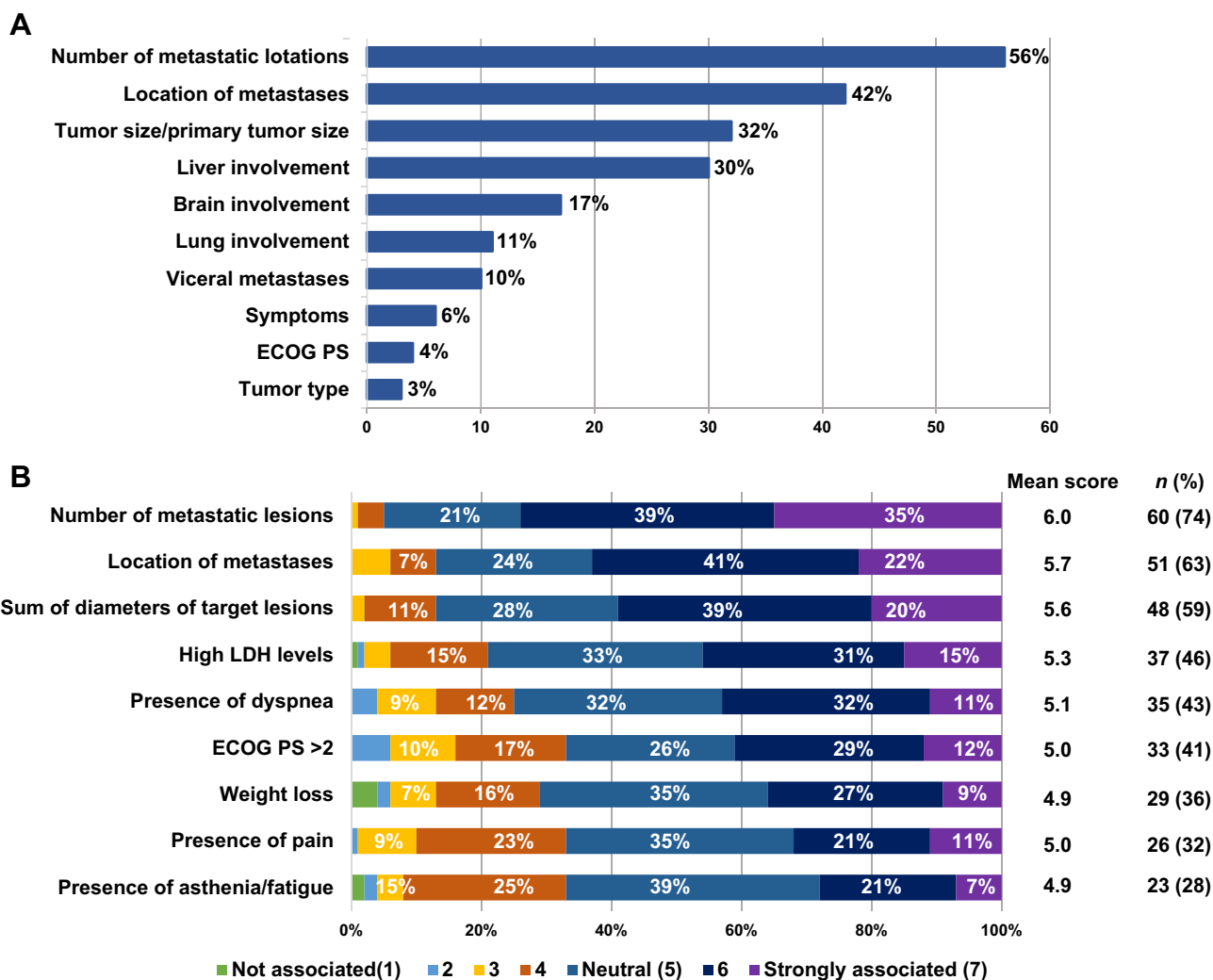
A

Number of metastatic lotations	56%
Location of metastases	42%
Tumor size/primary tumor size	32%
Liver involvement	30%
Brain involvement	17%
Lung involvement	11%
Viceral metastases	10%
Symptoms	6%
ECOG PS	4%
Tumor type	3%

B

	Mean score	n (%)
Number of metastatic lesions	6.0	60 (74)
Location of metastases	5.7	51 (63)
Sum of diameters of target lesions	5.6	48 (59)
High LDH levels	5.3	37 (46)
Presence of dyspnea	5.1	35 (43)
ECOG PS >2	5.0	33 (41)
Weight loss	4.9	29 (36)
Presence of pain	5.0	26 (32)
Presence of asthenia/fatigue	4.9	23 (28)

■ Not associated(1) ■ 2 ■ 3 ■ 4 ■ Neutral (5) ■ 6 ■ Strongly associated (7)

Figure 2 Factors defining "high tumor burden" (**A**) and degree of association of those factors with this concept evaluated through a scoring system (scale from 1 to 7 where 1 is "I do not associate it with 'high tumor burden' at all" and 7 "I strongly associate it with 'high tumor burden'") (**B**).
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase.

lesions, location of metastases, and tumor size; these are factors previously demonstrated to have independent prognostic value in NSCLC.[11–15] According to the experts, high LDH levels, which are associated with poor outcomes in several cancer types and specifically in mNSCLC,[16–18] also allow patients with HTB to be identified.

Interestingly, liver involvement was highly associated with the concept of HTB. This is not surprising considering that, among patients with mNSCLC, those with liver metastases show the lowest median overall survival rates,[12,19–21] and present a 1.55-fold higher mortality risk compared to patients with other distant metastases.[20] The physicians' answers reveal the negative effect associated with the presence of liver metastases, and the relevance of this factor as a poor prognostic factor in NSCLC patients, as previously

reported.[12,22] Given its clear negative impact on survival, therapeutic strategies seeking to improve outcomes in this population are desirable. In this respect, the addition of an antiangiogenic agent in the immunotherapy combination has been especially beneficial for these patients.[23,24]

This analysis has also some limitations. First, our sample only includes a small percentage of Spanish oncologists and, consequently, our findings are limited by the possibility of selection bias. However, it should be taken into account that, as shown, the origin of the participants was well-balanced. Most importantly, we relied on oncologists' opinions for our results. Thus, caution must be exercised when interpreting our findings, bearing in mind that experts' perceptions are not likely to be a completely accurate surrogate for patient disease status. Despite these

limitations, we believe our study is powerful enough to highlight the relevance of HTB as a concept for defining a worse prognosis for mNSCLC patients, although we stress the need for further research to support this notion.

In summary, according to the findings of our survey, HTB, a concept frequently used by oncologists, is mainly defined as having at least two metastatic lesions, mainly liver and brain metastases, a minimum tumor size ranging from 6–10 cm (corresponding to the sum of diameters) and LDH levels ≥2 times the ULN. Given the importance of this concept, efforts should be made to unify its definition and to further explore its potential as a prognostic factor for patients with mNSCLC.

Acknowledgments

Funding

Disclosure

O.H.G. reports advisory and consultancy honoraria from Roche, AstraZeneca, Amgen, Boehringer and Sanofi, speaker honoraria from Roche, Merck, Bristol-Myers Squibb, AstraZeneca, Pfizer and Amgen, as well as travel/accommodation/expenses support from Roche, Merck, and AstraZeneca. A.M.P reports advisory/consultancy, speaker´s honoraria, and/or travel/accommodation expenses from Roche, MSD, and BMS. A-L.O.G. reports advisory and consultancy honoraria from Roche, Merck, Bristol-Myers Squibb and Boehringer, speaker honoraria from Roche, Merck, Bristol-Myers Squibb and Boehringer, as well as travel/accommodation/expenses support from Roche, Merck, and Bristol-Myers Squibb. L.V. reports advisory and consultancy honoraria from Roche, speaker honoraria from Roche and Bristol-Myers Squibb, research grant funding from AstraZeneca, as well as travel/accommodation/expenses support from Merck, Pfizer and Boehringer. D.P.P., P.R-G. and L.S.C-A. were full-time employees of Roche Farma S.A. at the time the survey was conducted. The authors report no other conflicts of interest in this work.

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