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Original Article

The prognostic value of morphologic findings for lung squamous cell carcinoma patients

Duygu Gürel[a,*], Çağnur Ulukuş[a], Volkan Karaçam[b], Hülya Ellidokuz[c], Cenk Umay[d], İlhan Öztop[c], Sülen Sarıoğlu[a]

[a] Department of Pathology, Dokuz Eylül University, Faculty of Medicine, Izmir, Turkey
[b] Department of Thoracic Surgery, Dokuz Eylül University, Faculty of Medicine, Izmir, Turkey
[c] Institute of Oncology, Dokuz Eylül University, Faculty of Medicine, Izmir, Turkey
[d] Department of Radiation Oncology, Dokuz Eylül University, Faculty of Medicine, Izmir, Turkey

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ABSTRACT

Background: Novel histopathological prognostic features for squamous cell carcinoma (SCC) of lung, such as tumor budding, mitotic rate, tumor stroma ratio, stroma type, stromal inflammation and necrosis, have been evaluated in the literature. In this study, the prognostic value of multiple morphological features is assessed in lung SCC.

Materials and methods: This study reports on seventy-six patients with lung SCC treated with complete surgical excision. Tumor size, tumor stage, lymph node status, lymphovascular invasion, histopathologic grade, mitotic count, necrosis, tumor budding, tumor stroma ratio, stroma type, stromal lymphoplasmacytic reaction and ratios of stromal plasma cells and their relationship with the prognosis were evaluated. Univariate and multivariate analyses were performed for histopathological markers for local disease free survival (LDFS), distant disease free survival (DDFS), overall disease free survival (ODFS) and overall survival (OS).

Results: The univariate prognostic analysis of the pathological factors revealed that the pathological stage (OS: $p = 0.001$, DDFS: $p = 0.040$), lymph node metastases (OS: $p = 0.013$), mitotic index (OS: $p = 0.026$), tumor necrosis (DDFS: $p = 0.013$, ODFS: $p = 0.021$) and tumor size (OS: $p = 0.002$) had a prognostic significance. The multivariate analysis demonstrated that the pathological stage (OS: $p = 0.021$), tumor size (OS: $p = 0.044$), lymph node status (DDFS: $p = 0.019$, ODFS; $p = 0.041$) and necrosis (ODFS: $p = 0.048$) were independent prognostic factors.

Conclusions: Although many histopathological factors have recently been proposed as important prognostic markers, we only found significant results for mitotic index and tumor necrosis, as well as the well known parameters such as tumor stage and lymph node status. To the best of our knowledge, this is the first study evaluating such a wide range of morphological prognostic factors in lung SCC.

1. Introduction

Non-small cell lung cancer (NSCLC) is one of the primary causes of cancer-related deaths throughout the world. At present, the majority of NSCLC patients present with the advanced stages of the disease, which are not amenable to curative treatment [1–3]. Even in pathologic stage I disease, approximately 30% of all patients die due to recurrence within five years after curative resection [1]. Therefore, it is necessary to examine the histopathological features to clarify the NSCLC cases with poor prognosis. Furthermore, since currently there is no targeted therapy for squamous cell carcinoma (SCC) of lung, prognostic markers for this group may be more valuable [4].

In the literature, many histopathological features have been described as prognostic markers for lung SCC, including tumor size [5–7], tumor stage [5], pleural invasion [5,8], lymph node status [5–7,9], lymphovascular invasion [5–7,9,10], histopathologic grade [6], mitotic count [11,12], necrosis [13], tumor budding [5–7,9,10,12], tumor stroma ratio and stroma type [6,10,14],

* Corresponding author.
E-mail addresses: duygu.gurel@deu.edu.tr (D. Gürel), cagnur.ulukus@deu.edu.tr (Ç. Ulukuş), volkan.karacam@deu.edu.tr (V. Karaçam), hulya.ellidokuz@deu.edu.tr (H. Ellidokuz), cenk.umay@deu.edu.tr (C. Umay), ilhan.oztop@deu.edu.tr (İ. Öztop), sulen.sarioglu@deu.edu.tr (S. Sarıoğlu).

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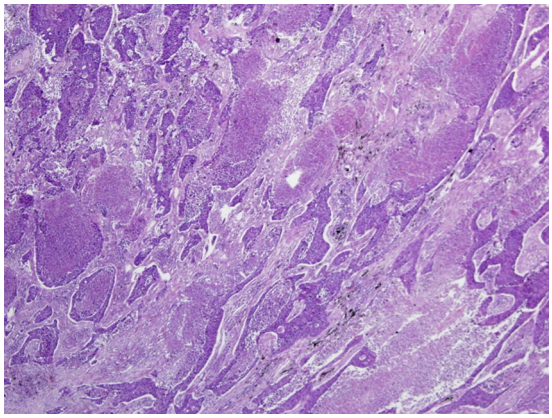

Fig. 1. Lung squamous cell carcinoma with tumor necrosis (H&E staining; 40×).

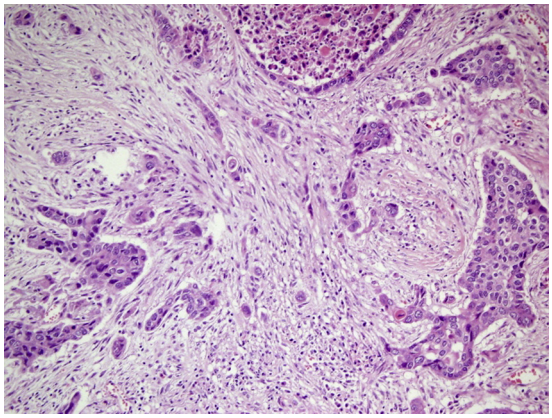

Fig. 2. Tumor budding in the fibrotic areas of lung squamous cell carcinoma (H&E staining; 200×).

stromal lymphoplasmacytic reaction [10,15,16] and the ratios of stromal plasma cells [15]. However, they were not evaluated in a single series.

None of the markers given above have been evaluated in a single study. Therefore we decided to select the morphological features that can easily be evaluated even in Hematoxylein & Eosin (H& E)-stained tissue sections.

2. Material and methods

For the analysis, archival materials from 76 lungs with SCC were used. Demographical and clinical features of the patients were obtained from hospital charts. The following histopathological and clinical data was recorded: patient's age and sex, pathological tumor and lymph node stage, locoregional and distant recurrence of the tumor and fatality. Locoregional recurrence was defined as tumor occurring at the resection site. Distant recurrence was defined as tumors outside the site of resection including the liver, adrenals or bones. Recurrence was diagnosed by radiologic imaging.

2.1. Histological examination

Differentiation: Tumors were graded as well, moderately and poorly differentiated in accordance with the 2004 WHO classification of lung carcinomas [17].

Mitotic count: Mitoses were evaluated in the 50 HPF areas that had the highest mitotic activity and then were calculated as an average of mitotic figures per 10 HPF [18].

Necrosis: The presence of tumor necrosis was defined where necrotic areas were observed in the tumor mass at low magnification (40×) [19] (Fig. 1).

Tumor budding: Isolated single cells and clusters composed of fewer than five cancer cells were defined as budding as previously described [20]. In a slide sample to semiquantify budding, a field in which budding intensity seemed to be maximal was selected, and the number of buds in that field was counted using a 20× objective lens (Fig. 2). Budding counts of 1–4 were graded as 1; 5–10 as 2 and more than 10 as 3; as previously described by Ueno et al. for colorectal carcinoma [21]. We divided the tumors into two groups; budding positive (bud+) and negative (bud−). Furthermore, we categorized the tumors according to budding intensity as low budding index (LBI) and high budding index (HBI). Tumors with budding counts equal to or greater than 5 were included in the HBI group.

Tumor stroma: We categorized stroma as fibrous, thin and intermediate type, as previously described [14]: when stroma had a width larger than some cancer nests and intermingled with plump fibroblast and/or collagen fibers, it was defined as "fibrous stroma";

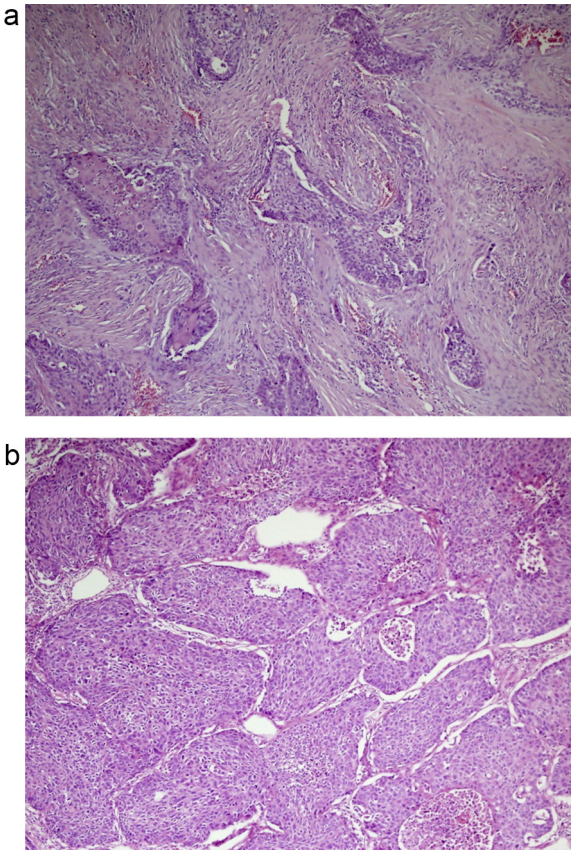

Fig. 3. (a and b) Squamous cell carcinoma that have fibrous (a) and thin (b) stromal type.

when most cancer cell nests were separated from each other by a narrow stroma composed of thin collagen fiber lamellae or stroma consisted of infiltrative lymphocytes as "thin stroma". Since, some of the tumors possessed the characteristics of both stromal types, we defined these cases as "intermediate stromal type", in which the predominant cancer nests were not surrounded by fibrous stroma (Fig. 3a and b).

Tumor stroma ratio: The percentages of tumor fibrosis were recorded semi quantitatively [12]. For statistical purposes, tumors were limited to two groups: greater than or equal to 25% and less than 25%.

Stromal lymphoplasmacytic reaction and ratios of plasma cells: The stromal lymphoplasmacytic inflammation was scored semi