

Ultrasound guided fine-needle aspiration biopsy of metastases in nonpalpable supraclavicular lymph nodes in lung cancer patients

Agobiopsia ecoguidata delle metastasi nei linfonodi sopraclavicolari non palpabili in pazienti affetti da tumore polmonare

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ABSTRACT

Background and objectives: To assess frequency and significance of enlarged nonpalpable supraclavicular lymph nodes with routine ultrasound (US) evaluation and US-guided fine-needle aspiration biopsy (FNAB) for the diagnosis and staging of patients with lung cancer.

Materials and methods: 106 consecutive patients with lung cancer and nonpalpable supraclavicular lymph nodes were evaluated with cervical US for the presence of pathological lymph nodes. FNAB was performed in patients with nodes with short-axis > 5 mm, rounded shape and missing echogenic hilum.

Results: 27 (25.5%) patients had enlarged supraclavicular lymph nodes on US. Fourteen patients (13.2%) had cytologically proven lymph node involvement. Supraclavicular lymph node metastasis was more frequent in patients with mediastinal invasion ($p = 0.0001$) and patients with enlarged lymph nodes on upper paratracheal stations on thorax CT ($p = 0.0001$). No relation was found between supraclavicular lymph node involvement and T stage ($p = 0.27$), distant metastasis ($p = 0.50$) or histological type ($p = 0.80$). Three patients were upstaged from IIIA to IIIB status. US-guided FNAB was the only diagnostic method in 2 patients.

Conclusion: US-guided FNAB is a simple and safe procedure

which can document N3 stage of disease in lung cancer patients. Thereby more invasive and expensive diagnostic procedures can be avoided in selected lung cancer patients.

Keywords: Diagnosis, fine-needle aspiration biopsy, lung cancer, staging, ultrasonography.

RIASSUNTO

Razionale ed obiettivi: Valutare la frequenza e la rilevanza di linfonodi sopraclavari di dimensioni aumentate, ma non palpabili, mediante una valutazione routinaria con ultrasuoni (US) ed una biopsia mediante agoaspirato con ago sottile (FNAB) sotto guida US per la diagnosi e la stadiazione dei pazienti con tumore polmonare.

Materiali e metodi: 106 pazienti consecutivi con cancro del polmone e linfonodi sopraclavari non palpabili sono stati indagati con US cervicali per valutare la presenza di linfonodi patologici. Nei pazienti con linfonodi aventi asse minore > 5 mm, forma arrotondata ed ilo non evidenziabile ecograficamente è stata praticata la FNAB.

Risultati: 27 (25,5%) pazienti avevano linfonodi sopraclavari di dimensioni aumentate all'indagine US. 14 pazienti (13,2%) sono risultati positivi alla citologia sull'agoaspirato. Le metastasi ai linfonodi sopraclavari sono risultate più frequenti nei

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pazienti con interessamento del mediastino ($p = 0,0001$) e nei pazienti che alla TAC torace mostravano un ingrandimento delle stazioni linfonodali paratracheali superiori ($p = 0,0001$). Non sono state riscontrate correlazioni tra l'interessamento dei linfonodi sopraclavari e stadio T ($p = 0,27$), metastasi a distanza ($p = 0,50$) o istotipo ($p = 0,80$). Tre pazienti sono stati allocati ad una stadiazione peggiore, da IIIA a IIIB. In 2 pazienti la FNAB US-guidata è risultata l'unica metodica che ha permesso la diagnosi.

Conclusioni: La FNAB US-guidata è una procedura semplice e sicura che permette di documentare lo stadio N3 in pazienti con cancro polmonare. Quindi procedure diagnostiche più invasive e dispendiose possono essere evitate in pazienti selezionati con tumore polmonare.

Parole chiave: Biopsia mediante agoaspirato, diagnosi, stadiazione, tumore polmonare, ultrasuoni.

INTRODUCTION

It is estimated that about one million people die in the world every year due to lung cancer [1]. Tumor stage is the foremost factor that affects prognosis of lung cancer. About 49% of lung cancer cases have distant metastasis on admission. In a revision of the international system for staging lung cancer it was reported that 86% of lung cancer patients were in the advanced stage [2].

During the last 20 years, the most important development in lung cancer has probably been the determination of cases eligible for surgical treatment by staging systems. In staging, the fundamental strategy is to diagnose and stage cases with a simple and fast method and refer them to appropriate treatment modalities. Detection of lymph node metastasis in the supraclavicular region can guide the treatment by indicating N3 lymph node metastasis (stage IIIB status, i.e. inoperable) and so prevent unnecessary surgery. Since the procedure caters for both diagnosis and staging at the same time, unnecessary invasive diagnostic procedures might be avoided as well.

MATERIALS AND METHODS

This was a prospective study that consecutively enrolled patients with lung cancer, who were recruited from inpatient services and outpatient referrals from non-specialized physicians. The inclusion criteria for the patients were the presence of lung cancer with nonpalpable supraclavicular lymph nodes and no prior diagnosis of malignancy. Patients were excluded before further evaluation with ultrasound-guided fine-needle aspiration biopsy (FNAB) if the diagnosis was not lung cancer. Positron emission tomography (PET) scan was not able to be performed for the purpose of evaluation of mediastinal and supraclavicular lymph nodes. Ultrasound (US) examination was made by the same radiologist. US was performed using a 5-7.5 MHz linear probe on a Shimadzu SDV-450 machine. Examination was limited to a B scan and no Doppler imaging was conducted. Transverse and sagittal images were obtained from the carotid bifurcation to the stern-

oclavicular area inferior and lateral to the acromioclavicular joint. The number and location of the enlarged lymph nodes, including whether they were ipsilateral, contralateral, or bilateral with respect to the dominant lung lesion, and their short- and long-axis were documented. The lymph node was classified as pathological if the short axis was > 5 mm, no echogenicity was detected on the hilus of the lymph node, and the long axis/short axis ratio was < 2 (rounded shape).

US-guided FNAB procedures were performed by 2 pulmonologists. The patients were placed in a supine position with the neck hyperextended. Enlarged nodes were aspirated with fine 20 gauge needles. Cytological examination results were recorded. Since supraclavicular US examination is a non-invasive procedure and FNAB was performed on enlarged lymph nodes, as recommended by guidelines, we asked all patients simply to sign an informed consent before enrolling in the study.

Chi-square and McNemar tests were used for statistical analysis.

RESULTS

A total of 136 patients with suspected lung cancer were recruited for the study. Twenty-eight patients were excluded due to lack of definitive cancer diagnosis or a final diagnosis other than cancer. FNAB was not performed because of close proximity of supraclavicular lymph nodes to the vascular structures in 2 patients; these patients were also excluded from the study. Finally 106 patients were eligible for the study.

Mean age of the patients was 59.4 years. Seven (6.6%) of the patients were female and 99 (93.4%) were male. Demographic and clinical characteristics of the patients are shown in Table I.

Twenty-five (23.6%) patients had morphologically pathological supraclavicular lymph nodes at US. Fourteen patients (13.2%) had cytologically confirmed supraclavicular lymph node metastasis. An association was found between the presence of supraclavicular lymph node invasion and presence of lymph nodes in 2R-2L stations on thorax CT ($p = 0.03$), \geq N2 nodal stage ($p = 0.001$), central location of tumor ($p = 0.03$), and radiological presence of mediastinal invasion ($p = 0.01$). There was no relation between the supraclavicular lymph node invasion and histological type of tumor ($p = 0.80$), T stage ($p = 0.27$) or M stage ($p = 0.50$) (Table II).

There was no correlation between the number and size of supraclavicular lymph nodes at US and lymph node involvement (Table III). Three patients (2.8%) were upstaged to inoperable stage IIIB from operable stage IIIA by US-guided supraclavicular lymph node FNAB. Before US-guided FNAB, 37 patients were considered as surgery candidates, 69 patients were considered for chemotherapy and/or radiotherapy. After US-guided FNAB examination the number of surgery candidates decreased to 34 patients. But statistically no significant difference was found between 'before FNAB' and 'after FNAB'

TABLE I: CLINICAL CHARACTERISTICS OF THE PATIENTS

| | Supraclavicular lymph node metastasis (+) (n = 14) | Supraclavicular lymph node metastasis (-) (n = 92) | Total (n = 106) |
|-------------------|---|---|--------------------|
| Age (years) | 56.1 ± 6 | 59.8 ± 10 | 59.4 ± 11 |
| Sex (male/female) | 13/1 | 86/6 | 99/7 |
| Stage | | | |
| I | - | 2 | 2 |
| II | - | 28 | 28 |
| III | 8 | 31 | 39 |
| IV | 6 | 31 | 37 |

in regard to treatment ($p = 0.25$).

US-guided FNAB was the sole diagnostic method in 2 patients (1.9%) with distant metastasis. One of these 2 patients' diagnosis was a challenge, since no diagnosis could be established despite the use of various invasive diagnostic procedures. The other patient was in a poor health status, and no invasive procedure could be performed.

DISCUSSION

Currently, there exist many invasive and non-invasive diagnostic modalities for the diagnosis of lung cancer. Since staging is the most important prognostic factor in lung cancer, it would be appropriate to say that diagnostic methods which also provide staging simultaneously will have an increasing importance in the future. The most important advantage of US-guided FNAB of supraclavicular lymph nodes is that it allows both diagnosis and staging to be performed by a single procedure.

Until recently, supraclavicular lymph nodes were evaluated by palpation and patients without palpable lymph nodes were considered as not having malignant disease. However, during the last 20 years, studies focused on head-neck carcinomas, esophageal carcinomas, and melanomas have found palpation of supraclavicular and head regions to be not very reliable for detection of lymph node metastasis, while noninvasive imaging modalities such as CT and US have been reported to be more sensitive than palpation [5-8].

Surgical biopsy results of nonpalpable supraclavicular lymph nodes are not very sensitive and only 8.9% of them are reported to detect metastasis [9]. Haber et al. reported the sensitivity and specificity of palpation as 64% and 85% respectively, whereas sensitivity and specificity of supraclavicular ultrasound was reported to be higher (72% and 96%, respectively) in head and neck cancer patients [10]. Sensitivity and specificity could not be evaluated in the present study since no lymph node

TABLE II: FACTORS ASSOCIATED WITH SUPRACLAVICULAR LYMPH NODE METASTASIS

| | | Supraclavicular lymph node metastasis (+) (n = 14) | Supraclavicular lymph node metastasis (-) (n = 92) | p |
|--|-------------|---|---|------|
| T Status | cT1 | - | 3 | 0.27 |
| | cT2 | 3 | 42 | |
| | cT3 | 2 | 12 | |
| | cT4 | 9 | 35 | |
| Mediastinal invasion | Present | 10 | 33 | 0.01 |
| | Absent | 4 | 59 | |
| Nodal staging | cN (0 or 1) | 0 | 42 | 0.00 |
| | cN (2 or 3) | 14 | 50 | |
| Distant Metastasis | Absent | 8 | 61 | 0.50 |
| | Present | 6 | 31 | |
| Type of tumor | NSCLC | 12 | 81 | 0.80 |
| | SCLC | 2 | 11 | |
| Localization of primary tumor | Central | 13 | 60 | 0.03 |
| | Peripheral | 1 | 32 | |
| Enlarged lymph nodes in 2R-2L stations | Present | 12 | 16 | 0.00 |
| | Absent | 2 | 76 | |

Definition of abbreviations: cN, clinical nodal staging; cT, clinical tumoral staging; 2L, left upper paratracheal lymph node; 2R, right upper paratracheal lymph node; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

TABLE III: RELATIONSHIP BETWEEN SUPRACLAVICULAR LYMPH NODE INVOLVEMENT AND SUPRACLAVICULAR LYMPH NODE SIZE AND NUMBER

| | | Supraclavicular lymph node metastasis (+) | Supraclavicular lymph node metastasis (-) | p |
|-----------------------------------|----------|---|---|------|
| Supraclavicular lymph node size | ≥ 1 cm | 10 | 5 | 0.24 |
| | < 1 cm | 4 | 6 | |
| Supraclavicular lymph node number | single | 13 | 7 | 0.13 |
| | multiple | 1 | 4 | |

biopsy was performed in our study. Kumaran et al. found the rate of nonpalpable supraclavicular lymph node metastasis higher in cases with N3 or multiple N2 on thorax CT. Sixty-one (60%) of their 101 examined cases were subjected to FNAB with supraclavicular US, and lymph node metastasis was detected in a total of 46 (45.5%) patients (at first examination in 44 cases and at second examination in 2 more cases). Since each patient first underwent supraclavicular US, unnecessary invasive procedures were eliminated in 43 cases (42.6%) [11]. Ohno et al. recently published a study in which they performed mediastinoscopy and supraclavicular lymph node biopsy on 123 non-small cell lung carcinoma patients with nonpalpable supraclavicular LAM, and found supraclavicular metastasis in 5 (4.1%) and mediastinal involvement in 23 (18.7%) cases, while reporting a high rate of supraclavicular metastasis among patients with bulky N2 involvement [12]. Ohno et al. and Kumaran et al. noted a higher likelihood of supraclavicular lymph node metastasis among patients with multiple N2 than others [11,12]. Similarly, in our study, supraclavicular lymph node invasion prevalence was higher among those who had enlarged N2 and N3 on thorax CT ($p < 0.001$). Sihoe et al. analyzed 50 cases suspected of potentially resectable lung cancer. Supraclavicular US revealed lymph nodes suggestive of malignancy in 10 (20%) of 50 cases, cervical lymph node metastasis was determined in 4 (8%), and further invasive diagnostic methods were deemed unnecessary because 2 of those cases advanced to stage IIIB. The authors advocated use of this technique in routine preoperative evaluation as a cost-effective treatment management due to the possibility it allows to avoid unnecessary surgery [9].

In our study, the cases in the supraclavicular lymph node metastasis group were generally at advanced stages; at the time of diagnosis, 3 (21.4%) cases were at stage IIIA and the remaining 11 (78.6%) were at stage IIIB or IV. Three of those patients advanced to stage IIIB from IIIA. Change from stage IIIA to IIIB may appear to be minimal, but costly imaging modalities to evaluate surgical respectability, including fluorodeoxyglucose positron emission tomography (FDG-PET) and magnetic resonance (MR) as well as invasive diagnostic and staging techniques including mediastinoscopy, video-assisted thoracic surgery (VATS), and mediastinotomy were avoided.

Overhagen et al. compared palpation, cervical CT, thoracic CT and supraclavicular US in 117 lung cancer patients and showed supraclavicular metastasis in 30 (26%) patients. They determined supraclavicular lymph node metastasis in 8 (31%) of 26 SCLC cases and in 22 (24%) of 91 NSCLC cases. Sensitivity of supraclavicular US, CT, and palpation in lymph node detection were 100%, 83%, and 33% respectively; supraclavicular US and CT modalities were found to be significantly more sensitive than palpation [5].

Fultz et al. compared CT and supraclavicular US in potentially operable lung cancer cases without palpable supraclavicular lymph node, and determined supraclavicular lymph node metastasis in 17 (31%) of 55 cases. While supraclavicular US demonstrated lymph node in 22 (40%) of the cases, CT revealed lymph nodes only in 18 (33%) cases. Supraclavicular US may display some supraclavicular lymph nodes that do not appear distinct on CT. They reported supraclavicular lymph node metastasis in 46% of cases with enlarged mediastinal lymph nodes and 48% of cases with suspected distant metastasis. Thus they suggested that supraclavicular lymph node metastasis could be as frequent as distant extrapulmonary metastases [13].

Chang et al. determined the prevalence of SC lymph node metastasis as 12% in 51 patients and the majority of the cases had centrally located tumors [15]. In the current study, 68.5% of the cases had centrally located tumor, and the frequency of supraclavicular lymph node involvement was higher in those cases ($p < 0.05$). Similarly patients with mediastinal invasion on CT had a higher rate of supraclavicular lymph node involvement ($p < 0.05$).

Ozkan et al. performed a similar study on 40 lung cancer patients who had multiple mediastinal lymphadenomegaly on thorax CT, and detected supraclavicular lymph node invasion in 16 (40%) patients [16]. In this study, supraclavicular lymph node invasion was more frequent among patients with enlarged upper paratracheal lymph nodes on CT. US-guided FNAB was the sole diagnostic method in 2 patients and 3 patients advanced to stage IIIB. US-guided FNAB did not change the therapeutic approach of the study population. In the present study, 28 (26%) of the cases had enlarged lymph nodes in 2R-2L stations on CT. Twelve patients (86%) with supraclavicular lymph node metastasis had lymph nodes of pathological size in 2R-2L stations. Among those cases, the frequency of

lymph node detection and positivity of FNAB were found to be higher ($p = 0.0001$).

In our study, 37 (35%) patients had clinical and radiological finding of metastasis, 30% of those were extrapulmonary distant organ metastasis. Six of 37 stage IV patients (16%) had supraclavicular lymph node metastasis. Ozkan et al. reported that 6 of 10 stage IV patients (60%) had supraclavicular lymph node metastasis. While supraclavicular US-guided FNAB does not contribute much to staging in patients with stage IV, it seems valuable in terms of being a simple and less invasive method for diagnosis [14]. US-guided FNAB may rarely lead to some complications such as hemorrhage, infection, pneumothorax, lymph channel damage, air embolism, phrenic nerve damage, and recurrent laryngeal nerve damage [12,17,18]. No complications have been observed in studies involving US-guided FNAB of the supraclavicular region, suggesting US-guided FNAB as a safe method [5,11,13,19].

Limitations of our study

US examination was limited to B-mode. The US device we used had no Doppler option. Doppler allows a better distinction of lesions of vascular origin and enables visualization of the blood flow pattern in lymph nodes suspected of malignancy. Although supraclavicular pathological lymph nodes were observed in 25 patients by US, cytological verification was achieved in 14 patients by performing FNAB

once. Among those patients, the lymph nodes detected by US may be mistaken as being benign. A second FNAB performed on morphologically pathological but cytologically negative supraclavicular lymph nodes might provide more reliable results. Moreover, the "gold standard" lymph node excision was not applied; thus sensitivity, specificity, true positivity, and true negativity rates could not be calculated.

CONCLUSION

We believe that using supraclavicular US-guided FNAB as a routine initial screening and diagnosis test on admission of all cases of suspected lung cancer may not be very helpful. Nonetheless, it may be performed as the initial examination method in cases with: advanced stage of lung cancer; problematic diagnosis; limited respiratory function and/or poor overall health status; presence of mediastinal lymph nodes, particularly the upper paratracheal lymph node, on thorax CT; and centrally located tumors invading the mediastinum. In cases where malignancy is diagnosed by US-guided FNAB, unnecessary invasive diagnostic methods can be avoided. It is a safe and simple method for selected patients which allows diagnosis and staging in a single step.

CONFLICT OF INTEREST STATEMENT: None of the authors has any conflict of interest to declare in relation to the subject matter of this manuscript.

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