The validity of preoperative lymph node staging guidelines of European Society of Thoracic Surgeons in non-small-cell lung cancer patients

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Abstract

Objective: The European Society of Thoracic Surgeons (ESTS) has proposed preoperative lymph-node staging guidelines (LNSGs) for non-small-cell lung cancer (NSCLC) based on the introduction of new staging modalities into clinical practice. The validity of these guidelines was assessed.

Methods: Among the patients (n = 185) with histologically confirmed NSCLC diagnosed between 2007 and 2009, who were suitable for thoracotomy, the 168 who underwent computed tomography (CT) of the chest and CT-integrated positron emission tomography (PET-CT) were included in the study. The preoperative mediastinal stage was confirmed by mediastinoscopy in all patients. A thoracotomy was done for mediastinoscopy-negative patients. The mediastinal staging results were adapted to the ESTS-LNSG (direct thoracotomy for T1—2 N0 tumour according to CT and PET-CT and invasive staging for others) and the validity of the guidelines was tested.

Results: In this series, the overall mediastinal lymph-node metastasis (MLNM) prevalence was 29.2%. If the guidelines had been applied, thoracotomy without invasive mediastinal staging would have been done in only 11 (6.5%) patients, and no MLNM would have been detected. Mediastinoscopy would have been performed in 157 patients and MLNM would have been found in 41 (26%). In the 116 mediastinoscopy-negative patients, MLNM would have been detected after thoracotomy in an additional eight patients. Thus, the sensitivity, specificity, and positive and negative predictive values of the guidelines were calculated as 84%, 100%, 100% and 94%, respectively.

Conclusions: The preoperative LNSGs for NSCLC proposed by the ESTS are effective.

Keywords: Non-small-cell lung cancer; Mediastinal staging

1. Introduction

Mediastinal lymph node (MLN) metastasis (MLNM) is the most important factor determining both the treatment method and the prognosis in non-small-cell lung carcinoma (NSCLC) patients, who have no distant metastasis [1,2]. Many invasive and non-invasive methods are used to detect MLNM before a lung resection with curative intent. Thus, the European Society of Thoracic Surgeons (ESTS) issued a preoperative mediastinal staging algorithm for NSCLC patients in 2007. According to these guidelines, due to the low positive predictive value (PPV) of positron emission tomography (PET) in mediastinal staging, additional histopathological confirmation by mediastinoscopy is recommended in patients in whom PET studies show mediastinal 18F-fluorodeoxyglucose (FDG) uptake. No mediastinoscopy is suggested in cases in whom PET shows no mediastinal metastasis, while mediastinoscopy is still indicated due to the high risk of mediastinal metastasis if the tumour is located centrally or an enlarged MLN with a short axis greater than 1.5 cm is seen on computed tomography (CT) of the thorax, or a tumour with a low standard uptake value (SUV) or FDG uptake in the hilar lymph nodes (N1) is seen on PET [3]. This study examined the accuracy of the ESTS preoperative mediastinal staging guidelines.

2. Materials and methods

All NSCLC patients, who were referred to our clinic for surgery between 2007 and 2009 (n = 185), were enrolled. In all patients, the diagnosis of NSCLC was confirmed preoperatively by a biopsy obtained via bronchoscopy or transthoracic needle aspiration. Patient and tumour variables were entered in a database.

Each patient underwent thoracic CT. The patients were split into central or peripheral tumour groups according to either the CT localization of the tumour in the central third of the chest or to bronchoscopic involvement of the tumour in lobe-segment bronchi. A radiologist re-examined the CT...
images and, if an MLN with a diameter longer than 1.5 cm in its short axis was seen, the CT was accepted as showing mediastinal metastasis.

PET had been obtained from all patients and no distant metastasis had been seen. Fourteen patients, in whom PET was obtained with a PET-fusion CT scanner, were excluded. In the remaining 171 patients, the scanner was a multidetector CT-integrated high-resolution PET-CT scanner (Siemens Biograph LSO HI-RES PET/CT). When a focus showing elevated FDG uptake in the mediastinum compared with the mediastinal background and adjacent tissues was seen in the PET-CT images, the result was recorded as mediastinal metastasis.

One patient who refused surgery and one high-risk patient who could not undergo surgical lung resection were excluded from the study. As part of a complete preoperative mediastinal evaluation, all the remaining patients underwent standard cervical mediastinoscopy under general anaesthesia. An informed consent was obtained from the patients. One patient in whom the interval between PET and mediastinoscopy was more than 1 month was also excluded. The remaining 168 patients constituted the study group. At mediastinoscopy, samples were routinely obtained from the bilateral upper—lower paratracheal and subcarinal stations. When the pathologist detected MLNM, the patient was referred to the oncology clinic for neo-adjuvant or definitive chemo-/radiotherapy. Patients who had no metastasis at mediastinoscopy underwent lung resection via a thoracotomy, after providing informed consent. A pathologist evaluated the specimens and the exact mediastinal stage was determined after the surgical and pathological evaluations (Fig. 1).

After determining the final mediastinal staging, the results were adapted to the preoperative lymph-node staging guidelines of the ESTS. The guidelines can be summarized as follows:

- direct thoracotomy without invasive staging in patients, who are evaluated to have peripheral, clinical stage I (T1–2 and N0) tumours on CT and PET;
- mediastinoscopy in patients who have central tumours, or are clinical T3–4 stage NSCLC cases, or have an MLN larger than 1.5 cm on thorax CT images; and
- mediastinoscopy where PET reveals a tumour with low FDG uptake, or mediastinal or hilar lymph nodes showing FDG uptake.

The sensitivity, specificity, and positive and negative predictive values (PPV and NPV) were calculated using standard formulae. Frequencies were compared using chi-square or Fisher’s exact test.

The data were collected prospectively and analysed retrospectively. The Internal Review Board approved the study.

3. Results

Overall, 149 patients were males and 19 were females. Eighty (48%) patients had a tumour in the right lung, 88 (52%) in the left lung and 55 (32.7%) in a central location. The mean age was 60 years (range 30–84).

Seventy-eight (46.4%) patients had squamous cell carcinoma, 57 (34%) had adenocarcinoma, nine (5.4%) had adenosquamous cell carcinoma, seven (4.2%) had pleomorphic carcinoma, one (0.5%) had large cell carcinoma and 16 (9.5%) had NSCLC without further specification.

In the PET studies, no mediastinal uptake was seen in 103 patients, although 14 had MLNM (number of false-negative (FN) cases for mediastinal staging = 14/103, 13.6%). The negative result was not true in 12% of peripheral versus 17% of central tumour patients (p = 0.3). Of the 103 patients in whom no mediastinal uptake was reported, hilar lymph node uptake (N1) was observed in 20 and MLNM was discovered in six (at mediastinoscopy in five and at thoracotomy in one). In the patients who had neither mediastinal nor hilar uptake (n = 83), MLNM was found in eight (discovered at mediastinoscopy and at thoracotomy in four each). The MLNM rate was lower, when hilar FDG uptake was not reported, compared with the presenting patients (p = 0.03).

Of the patients, 65 had mediastinal uptake on PET. In 35 of these, MLNM was confirmed (at mediastinoscopy in 32 patients and at thoracotomy in three; number of true-positive (TP) cases for mediastinal staging = 35/65). No MLNM was found in the other 30 patients (number of false-positive (FP) cases = 30/65).

The sensitivity and specificity of PET at mediastinal staging were 71 (95% confidence interval; CI: 57–83%) and 75% (CI: 66–82%), respectively, and the PPV, NPV and accuracy were 54 (CI: 41–66%), 87 (CI: 78–92%) and 74% (CI: 67–81%), respectively (Table 1; Fig. 1).

The mean number of stations sampled at mediastinoscopy was 3.98 (range 2–7). Mediastinoscopy demonstrated the presence of mediastinal metastasis (N2 or N3) in 41 patients, whereas 127 patients in whom MLNM was not demonstrated underwent lung resection via thoracotomy and mediastinal lymphatic dissection. Eight of these patients exhibited MLNM at thoracotomy (number of FN cases for mediastinal staging = 8/127).
The sensitivity, specificity, PPV, NPV and accuracy of our routine mediastinoscopy strategy in mediastinal staging were 84 (CI: 70—92%), 100 (CI: 96—100%), 100 (CI: 89—100%), 94 (CI: 88—97%) and 95 (CI: 92—99%), respectively (Table 1, Fig. 1). The prevalence of MLNM in this series was 29.2% (49/168 of NSCLC patients).

Our surgical-pathological lymph-node staging results were adapted to the preoperative lymph-node staging guidelines of the ESTS. If the guidelines had been followed, no mediastinoscopy would have been done in 11 patients (those with peripheral, T1-2, NO tumours according CT and NO disease according to PET) and no MLNM would have been discovered at thoracotomy. According to the guidelines, mediastinoscopy would have been indicated in the remaining 157 patients, and MLNM would have been seen in 41 patients. Mediastinoscopy would have been FN in eight patients (number of FN cases for mediastinal staging = 8/116; Table 1; Fig. 1).

The sensitivity, specificity, PPV, NPV and accuracy of the ESTS guidelines in mediastinal staging would have been 84 (CI: 70—92%), 100 (CI: 96—100%), 100 (CI: 89—100%), 94 (CI: 88—97%) and 95 (CI: 92—99%), respectively.

4. Discussion

Mediastinoscopy remains the gold standard for mediastinal staging of NSCLC [4]. Although PET may yet prove to be an accurate non-invasive method of mediastinal staging, the results regarding PET and mediastinal staging are currently inconsistent [5,6]. Thus, we prefer routine mediastinoscopy for preoperative mediastinal staging. The major difference between our routine mediastinoscopy strategy and the new preoperative mediastinal staging guidelines proposed by the ESTS is the selective use of PET. However, before adopting the new ESTS guidelines, we wanted to validate them with our mediastinal staging results, obtained using a more aggressive strategy.

For mediastinal staging, the PPV of PET is only approximately 50% [6,7], and if positive results are accepted as true, the half of the PET-positive patients who do not have MLNM will forego the chance of potentially curative surgery. Consequently, the preoperative ESTS staging guidelines recommend histopathological confirmation of mediastinal metastasis using an invasive method, if PET demonstrates mediastinal FDG uptake [3]. Our results support this argument because 30 of the 65 patients in whom mediastinal uptake was seen had no MLNM. Invasive staging restored their chance for surgical treatment.

According to the ESTS guidelines, invasive staging is avoidable for peripheral, clinical stage I tumours with no mediastinal or hilar FDG uptake on PET images [3]. Our results also show that this strategy is appropriate. Although only a few patients in our series met these criteria (6.5%), the guidelines would have saved those patients from unnecessary mediastinoscopy.

The ESTS recommends invasive mediastinal staging, if PET is negative for mediastinal metastasis, but an enlarged mediastinal lymph node is seen on CT. In meta-analyses, the reported prevalence of MLNM was 17—21% in PET-negative patients with an MLN of pathological size or larger than 1.6 cm on CT [8,9]. In our series, this rate was 33%. In light of these results, as recommended by others and the ESTS, we conclude that histopathological staging should be performed in patients with a mediastinal lymph node with a diameter exceeding 1.5 cm on CT despite negative PET findings for mediastinal FDG uptake.

Among the patients with negative PET for mediastinal metastasis, if the tumour is located centrally according to CT and bronchoscopy, or if hilar lymph-node metastasis is suspected on PET, the ESTS also recommend mediastinoscopy. The mediastinal lymphatic metastasis rate can reach 83% in patients with a centrally located tumour or no mediastinal uptake, but uptake in hilar lymph nodes [10]. Cerfolio reported MLNM in 23.5% of the patients with hilar nodes, but no mediastinal FDG uptake [11]. These results may be associated with the failure of PET in distinguishing hilar from mediastinal lymph nodes, or in detecting lymph-node micrometastases [12—14]. In our study, PET was more frequently falsely negative for mediastinal metastasis in central tumours than in peripheral tumours, and in patients in whom hilar FDG uptake was reported. In agreement with the ESTS recommendations, despite the absence of mediastinal uptake on PET, invasive staging is necessary in cases with central tumours or if PET showed hilar lymph-node metastasis.

In our series, all patients underwent mediastinoscopy. If we had followed the ESTS guidelines, we would have performed mediastinoscopy on the patients with central or T3-4 tumours and in those with enlarged mediastinal lymph nodes; these constituted 42.8% of our patients. In these patients, PET would not have been indicated for mediastinal staging. The rate of patients requiring mediastinoscopy would have been 93.5%, if we had added the patients in whom PET showed mediastinal and hilar FDG uptake. Ultimately, when compared with our routine mediastinoscopy strategy, the number of patients undergoing mediastinoscopy would have been reduced (in 6.5% of the patients), but the accuracy rates would not have been different.

In conclusion, when compared with routine invasive staging, although it does not reduce the need for invasive staging considerably, the preoperative lymphatic staging guidelines of the ESTS can be used effectively in the mediastinal staging of NSCLC. The guidelines should be
adopted in those medical settings where both PET and mediastinoscopy are available.

References


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