Intraoperative sentinel lymph node mapping in stage I non-small cell lung cancer: detection of micrometastases by polymerase chain reaction

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Abstract

Objective: We previously reported the results achieved in detecting sentinel lymph nodes (SLN). We applied the molecular techniques (RT-PCR) to improve the detection of micrometastasis in order to evaluate an improvement of staging in early non-small cell lung cancer (NSCLC) patients (pts). Methods: This study was carried out on 22 consecutive NSCLC pts with stage I disease. A dose of 37 MBq (1 ml 99mTc-nanocolloid suspension) was administered. The intralesional injection was performed under CT-guidance (7 pts), by using bronchoscopy (5 pts), VATS (2 pts) and at time of the thoracotomy (8 pts). RT-PCR analysis for cytokeratin 7 and 19 (CK7–CK19) was used to identify tumour-derived material in lymph nodes (LN). Each SLN was bisected: half was used for conventional examination (H&E staining/ by immunohistochemistry (IHC), half was snap-frozen to –80 °C for RNA-detection of CK7 and CK19. Results: SLN was detected in 16 out of 19 pts. In three pts SLN was not identified (due to an incorrect technique). Conventional pathologic examination showed stage I disease in 13 pts, T3N0 disease in 1 pt, N2 in 5 pts. The IHC analysis identified micrometastasis in seven pts (two evaluated N0 according to H&E staining). RT-PCR analysis, performed in 10/16 pts, identified micrometastasis in 6 pts (3 pts evaluated N0 disease by H&E; 1 of these evaluated N0 even by IHC). All N2 patients relapsed. One patient (N0 pts after H&E and IHC analysis) with positive CK7 and CK19 expression by RT-PCR analysis relapsed (systemic relapse) 3 months after surgery. Conclusions: SLN technique could provide a subgroup of patients in which the use of RT-PCR could be applied on a well-focused target. This approach may be useful for stratifying histologically N0 patients into higher risk and lower risk groups.

Keywords: Lung cancer; Sentinel lymph node; Molecular staging; Cytokeratin 7 and 19

1. Introduction

The prognosis of patients with non-small cell lung cancer (NSCLC) is closely related to the pathologic stage of the disease, with the pattern of regional lymph node (LN) involvement as a major determinant [1]. Although surgical treatment represents the best chance in 30% of patients with early stage cancer, a high relapse rate (40%) is recorded within 24 months after complete resection (surgery and complete lymphadenectomy) [2–4].

Undetected metastatic disease is the cause of these recurrences, which may remain undetected for three reasons: (1) an inadequacy of the lymph-adenectomy (the lymph nodes draining the tumour are either not or incompletely removed), (2) inadequacy of pathologic examinations (methods used to detect tumour-derived material in LNs are insensitive) and finally, (3) the lymphatic drainage does not always follow the predicted pattern.

Previous studies sought to improve LN micrometastases identification during surgery through sentinel lymph node (SLN) mapping, or to improve the sensitivity of detecting tumour cells within the resection. Experience with melanoma [5] and breast cancer [6] demonstrated that SLNs were diagnostically accurate, in predicting the status of more distant lymph node stations.

In NSCLC, a few studies identified SLN in >80% of patients and the SLN status was predictive in 80–100% of patients [7–9]. We previously reported the positive results achieved in detecting SLN with a 99mTc-nanocolloid suspension and micrometastasis by immunohistochemistry (IHC) in NSCLC-stage I patients [9]. However, standard detection methods have a low sensitivity, reverse transcriptase-polymerase chain reaction (RT-PCR), which was developed to detect transcripts of genes expressed by tumour cells, is a tool for detecting LN-micrometastasis that is more sensitive than IHC [10–12]. Micrometastasis detected by RT-PCR has been associated with a worse...
prognosis in patients with melanoma and prostate carcinoma [13—15]. In lung cancer few reports exist in this field [16,17]. Our previous study on intraoperative SLN mapping established the feasibility of this technique and formed the basis of this progress report on the evolving utility of this technique in lung cancer [9]. Thus, since January 2005, we combined the SLN mapping technique with molecular staging using cytokeratin 7 and 19 (CK7-CK19), which are markers of epithelial cells. We hypothesised that the RT-PCR for RNA-detection of CK7 and CK19 would accurately detect micrometastases and define an improvement of staging in patients with early lung cancer (stage I disease). The preliminary results show that this technique could provide a sub-group of patients in which the use of RT-PCR could be applied on a well-focused target. This approach may be useful for stratifying histologically N0 patients into higher risk and lower risk groups.

2. Materials and methods

From May 2001 to June 2006, 51 consecutive patients with NSCLC (stage IA—IB) were enrolled. The first 29 pts were included in the first step of our study (validation phase). All resected lymph nodes were analysed by conventional pathologic methods (haematoxylin and eosin staining (H&E) and immunohistochemistry (IHC). Since January 2005, 22 consecutive pts (11 female; median age 69 years, range: 56—78) were selected for SNL mapping by using a new protocol. SLNs were analysed in 16 out of 19 pts by using conventional pathologic examination (H&E/IHC), and molecular analysis by RNA transcriptase-polymerase chain reaction (RT-PCR).

The study was approved by the local ethics committee and informed consent was obtained from each patient.

2.1. Eligibility

Only patients able to tolerate anatomic resection and complete mediastinal node dissection were included in this study. Routine preoperative staging was performed including: clinical examination, blood chemistry analysis, chest X-ray, thoracic computed tomography (CT) scanning and positron emission tomography (PET) scanning, abdominal ultrasonography and bronchoscopy. Furthermore, bone scintigraphy and brain CT scan were performed in patients with suspected distant metastases. The tumour stage was classified according to the Revisions in the International System for Staging Lung Cancer [18].

Selection criteria were: (a) over 18 years of age (legal majority), (b) clinical stage I NSCLC (stage IA—IB), (c) absence of intra-thoracic adenopathy with normal bronchoscopic appearance. Patients with pulmonary metastasis, previous thoracic surgery/adjuvant therapy, enlarged mediastinal lymph nodes more than 1.0 cm in short axis diameter on CT/PET scan or with primary tumour larger than 3 cm in size were excluded. In accordance with our then normal practice for small lesions without mediastinal lymphadenopathy (on the CT/PET scan), mediastinoscopy was not undertaken. These patients were judged to have clinical stage I (NSCLC).

Standard lobectomy combined with systematic lymph node dissection was performed to achieve anatomic resection of the tumour.

2.2. Technique

The SLN technique previously described in our paper was similar to that of other authors [7—9].

The radiotracer was administered on the basis of the tumour’s location: the medium-parenchyma tumours were injected by bronchoscopy or at the time of thoracotomy; those located at periphery were injected under CT-guidance or by thoracoscopy. The molecular analysis (RT-PCR) was added at conventional pathologic SNL examination (H&E and IHC).

2.3. Peripheral tumours

The tumours were localised by means of 5 mm thick high resolution axial computed tomographic sections or by 7 mm endoscopic camera usually at sixth/seventh intercostal space along the midaxillary line. A 22G needle was introduced at the peripheral margins of the tumour through which was injected the radiotracer (Fig. 1).

2.4. Medium-parenchyma tumours

The radioisotope suspension was administered by a fibre-optic bronchoscope or directly during thoracotomy if the technique using bronchoscope was not applicable. This procedure was performed under fluoroscopic guidance by using an endoscopic-needle inserted at the carina of the
most distal pulmonary sub-segment closed to the tumour (Fig. 2).

The intraoperative radioactivity counting at the nodal stations started an average of 1 h (range 50—70 min) after the injection. The radiolabelled tumour and lymph node stations were examined in vivo and ex vivo. The migration of the 99mTc-nanocolloid suspension was considered successful if a specific nodal station measured greater than three times the background. The sentinel node was classified as the node(s) with the highest count rate.

At the end of the operation (after lobectomy and excision of the sentinel lymph node) the mediastinal stations were also examined before performing a complete lymph node dissection. On completion of the procedure a repeated examination with gamma probe was performed to check the residual activity. If indicated by the gamma counter, we completed the re-resections of the nodal stations.

Mediastinal nodal dissection was performed in all eligible patients. Mediastinal metastasis was considered skipping if any one of the mediastinal lymph nodes was involved by the tumour, without hilar or intrapulmonary node metastases. Reassessment of the mediastinum with gamma probe after dissection was routinely performed.

The locations of the lymph nodes were defined according to Naruke’s map.

2.5. Pathologic evaluation

The pathological analysis was not employed intraoperatively. One-half of the SNL was fixed in formalin and was embedded in paraffin for histological analysis and immunohistochemical staining. The other half of the resected node was snap-frozen in liquid nitrogen and stored at —80 °C until the time of RNA isolation for the analysis of cytokeratin 7 (CK7) and cytokeratin 19 (CK19), as markers of epithelial differentiation.

After formalin fixation and embedding in paraffin, sections (2 or 3) were cut and stained with haematoxylin and eosin. Sentinel and non-sentinel nodes were subsequently examined by IHC for pankeratin CK, CK7 and CK19 (Ventana Medical System).

Molecular analysis (RT-PCR) was applied in our second series (our present study). The presence of mRNA for cytokeratin (CK7 and CK19) within the sentinel lymph nodes was accepted as evidence of micrometastatic tumour cells.

2.5.1. Technical details

The RNA was extracted by a standard method, assessed by electrophoresis on a 0.8% agarose gel to determine its integrity and was quantified spectrophotometrically. Using two rounds of amplifications (RT-PCR) and serial dilutions of RNA it was possible to detect down to one tumoural cell in 10⁶. The primer sequences for CK7 were as follows: A: 5'-TGAAAATACGCGGACACAG-3' and B: 5'-TGGAGCTGTCCTACAGTGAC-3'; and C: 5'-CCAGGGAGCCGATGTGTG-3' for the second PCR. First round amplification started with a ‘hot start’ of 100 °C for 10 min. Thirty-five cycles were performed consisting of 1 min denaturation at 94 °C, annealing at 65 °C for 1 min, and extension for 2 min at 72 °C. The PCR reaction was terminated with a 10 min extension. This set of primers produced, after the two rounds of amplification, three bands: 163, 220, and 277 bp. The primer sequences for CK19 were as follows: A: 5'-AAGCATACCATGCAGAACACACAACCAGC-3' and B: 5'-TTATGGCAGGTCAAGGAGAACCC-3' for the first PCR, and C: 5'-AAGGATGATCTGCTCCCGGCG-3' and D: 5'-CGCGACTTGATGTTCTGAGCGCGTTGAC-3' for the second PCR. The cycling conditions were as follows: 94 °C for 1 min, 68 °C for 2 min for 20 cycles for the first PCR and 20 cycles for the second PCR. All PCR reactions were preceded by a denaturation step at 94 °C for 3 min, and terminated by a 10 min extension at 72 °C. The expected size for CK19 amplification band was 409 bp.

All frozen specimens were held until the final pathology report was issued in case the tissue was needed for routine analysis.

3. Results

Positive results in detecting micrometastasis (by IHC) on the first series (29 pts) were previously published [Eur. J. Cardiothorac. Surg., Feb 2003;23:214—20]. Briefly, SLNs were identified in 96.1% of patients, with a total of 31 SLNs detected. Seven out of 31 SLNs (22.5%) were positive for metastatic involvement after full histo-pathologic evaluation (including IHC). In 2/7 of these positive SLNs (positive SLN in level 10) IHC revealed an additional positive N2 station. Two positive SLN (28.5%) were skipping metastases (levels 6 and 7). Step sections and IHC examination revealed micrometastases in 5 (20%) out of 25 patients without metastasis in the routine haematoxylin and eosin-stained sections. Overall Kaplan—Meier survival at 3 years was 78.1 ± 11 months for p-stage I pts vs 50 ± 12.3 months for overstaged pts (with IHC). No significant difference (p = 0.1) was observed.

In the present series, 22 patients were selected for SLN mapping. Three patients with benign lesions were excluded from further analysis. All patients underwent major lung resections (lobectomy was the only procedure performed) and complete lymphadenectomy. The mean tumour size was 2.5 ± 0.7 cm (range 0.8—3.5 cm).

SLNs were detected in 16/19 patients. In 3 out of the 19 patients (#17, #18, #19) SLN was not identified due to
incorrect technique in which the radiotracer injected into the tumour had a poor migration, due to the fact that the tracer was not administered at periphery. Patient’s data are summarised in Table 1.

A single SLN was identified in each patient (total number of SLNs were 16). Among the 16 SLNs, 5 were noted to be mediastinal LN (25%), of which 2 were level 7 and 2 were level 4; 1 was level 8. Five SLNs were found at level 10, 4 at level 11, and 2 at level 12.

H&E revealed 15 adenocarcinomas, 2 squamous cell carcinomas, 1 large cell carcinoma, and 1 bronchoalveolar carcinoma. According to TNM classification, pathologic staging identified: 10 patients with stage I disease; 1 patients with stage IIB; 4 patients with stage IIIA disease; and 1 patient with stage IIIB disease (Table 1).

IHC examination revealed micrometastases in 7 out of 16 (43.75%) patients; 2 of them evaluated N0 by H&E staining. RT-PCR analysis was applied in 10 out of 16 pts (in the remaining six samples, the frozen half of each SLN was insufficient). Micrometastases were detected in six patients; four of these evaluated N0 according to conventional examination (three N0 by H&E, one N0 by IHC).

3.1. Upstaging by conventional and molecular analysis

All SLNs tested by RT-PCR, were analysed also by H&E and IHC. In 9 out of 10 patients, RT-PCR confirmed the IHC staging in all SNLs that could be evaluated. Three patients (#9, #14, #15) who had stage I disease according to routine pathological examination, were upstaged from stage I to stage II (from N0 to N1). Two of them (#9, #15) with positive IHC for pankeratin were evaluated stage II also by RT-PCR. In the 3rd patient (#14) with negative IHC, micrometastasis were identified only by RT-PCR analysis. The presence of cytokeratin 19 (CK19) as markers of epithelial differentiation was accepted as evidence of micrometastasis (Fig. 4). This patient had a systemic relapse 3 months after surgery and died 4 months later. Any patients with N0 or N1 disease by RT-PCR staging had recurrences. Of the five patients with N2 disease according to the RT-PCR analysis, three (#1, #4, #8) patients developed recurrent disease 3, 13, and 14 month after surgery, respectively.

During the follow-up of 9–24 months, three patients died (#1, #8, #14) due to recurrent disease. Of the patients who remained alive, one pt with N2 disease (#4) has recurrence.

Summarizing our data: No complications were observed during the sentinel lymph node mapping procedure. Successful radio nuclide migration was 84.21% (with 0 out of 16 false negative patients). Regarding the pathologic methods, one false negative was noticed by IHC technique, and none by RT-PCR analysis. In this series no skipping was observed.

4. Comment

Lymph node metastasis is the most important prognostic factor in localised and resectable NSCLC. Patients with N0

<table>
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<td>T1N0</td>
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*a Upstaged pts.*

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Fig. 3. Results differences in detecting micrometastases by H&E/IHC/RT-PCR.
disease have favourable survival rates. However, up to 40% of these patients have a recurrence of the tumour and subsequently die, despite complete surgical resection [18]. This suggests that occult micrometastasis tumour cells, undetected by clinical staging examinations and routine histo-pathological methods, have already spread to the regional nodes at the time of surgery [1—4]. Therefore, a plausible explanation could be an inadequate nodal dissection or inadequate pathological analysis [19,20].

SLN is commonly defined as first lymph node that receives afferent lymphatic drainage from a primary tumour [5—11]; therefore, this node is the first site of lymphatic involvement if metastasis has occurred. If this concept is correct, when metastasis is not found in a SLN, it most likely will not be present in the more distal nodes. As shown, for early stages in malignant melanoma and breast cancer, the SLN allowed selective sensitive pathologic analysis to assess micrometastases [5,6]. In NSCLC a few studies identified SLN in >80% of patients, and found that the SLN status was predictive of the status of all other LNs in 80—100% of patients [7—9,21]. However, standard detection methods have a low sensitivity. Better methods for detecting SLN involvement would improve the ability to determine the risk of recurrence, which may affect patient treatment. The staining of serial sections of SLNs by IHC has been the most reported method of identifying micrometastases.

However, the molecular analysis of cytokeratin 7 and 19 by RT-PCR offers a sensitive tool for the detection of micrometastasis [10—12]; this takes advantage of the development of a variety of probes for genes that may be over-expressed in certain tumours. For melanoma, this includes tyrosinase-related proteins (TRP-1, TRP-2), microphthalmia-associated transcription factor (MITF), MAGE-3, gp100, and MART-1; for breast cancer, cytokeratin 19, 12 MUC-1, 13 mammaglobin B, 14 and MAGE-A3 15 have been identified as potential markers, among others. Carcinoembryonic antigen (CEA) and MAGE-A are the most frequently used in colon cancer [22].

In lung cancer few studies exist in this field [16]. We previously reported the positive results achieved in detecting SLN by IHC in early stage patients [9]. Our present protocol includes the application of molecular analysis (RT-PCR for CK7-CK19) in addition to conventional methods (H&E/IHC). Moreover, radiotracer injection has been performed by various procedures (bronchoscopy, thoracotomy, CT-guidance or thoracoscopy) in order to avoid prolonged anaesthesia, and to obtain a tracer migration-time compatible with the course of the nodal dissection. Our preliminary data found RT-PCR evidence of micrometastasis in 6 out of 10 SLNs that could be evaluated. An interesting result was the presence of cytokeratin 19 (CK19) as a marker of epithelial differentiation in one patient (#14) who was evaluated N0 by IHC, and who was upstaged from SI (T1N0) to SII (T1N1) only by molecular analysis. In this case the presence of cytokeratin was accepted as evidence of micrometastasis. However, because the prognostic significance of molecular upstaging in NSCLC is not yet known, this patient was considered as a stage IA, and thus no adjuvant chemotherapy was administered. On the other hand, although adjuvant chemotherapy is becoming the standard of care for most NSCLC patients, and recent studies have demonstrated its benefits in early staging [23], the real advantage in lung cancer patients remains unclear. Intraoperative SLN mapping, in this field could be useful for stratifying histologically N0 patients into higher risk groups.

Regarding the role of radical lymph-adenectomy in lung cancer stage I patients (especially those who have undergone SLN mapping), it is still considered a critical point. Some randomised trials (Izbicki and colleagues) showed no survival benefit [4]; others stressed the therapeutic value of radical systematic lymph-adenectomy [1,24,25].

Sentinel lymph node biopsy was initially developed as a minimally invasive surgical alternative to routine (elective) complete lymph-adenectomy. However, lymph-adenectomy for staging and therapeutic benefit in lung cancer still remains the gold standard for lung cancer staging. Furthermore, trials such as ACOSOG Z0030l will likely define the best procedure in the near future. Taking all of this into consideration, we hypothesised that SLN mapping in lung cancer should be used to improve staging in patients with stage I disease. Therefore, in contrast to other solid tumours, in which this technique has been applied to minimise lymph-adenectomy, in lung cancer this method should be considered as a new technique for stratifying N0 patients. This approach could be a useful way to enable pathologists to identify with higher sensitivity, micrometastasis. Despite the small number of patients in our series, our preliminary data are encouraging and show a sensitivity up to 84.21%, which was similar to other studies [7—9] (the undetected SLNs in the present series (due to a technical error) explain the low detection rate compared to the higher detection rate (96%) found in our first study.) In any cases, it is noteworthy that none of the patients with NO disease according to the RT-PCR analysis developed recurrent disease by the time of last follow-up.

<table>
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<td>IHC</td>
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Fig. 4. Patient (#14): pathologic profile.
In conclusion, the current study confirmed the feasibility of SLN mapping in NSCLC, and demonstrated that SLN molecular studies could improve greatly the detection of micro-metastases in patients with N0 disease. Thus, with increased experience this technique may become a standard practice in the management of early stage NSCLC. Just as micrometastases are codified as N0 sub-stages in breast and colon cancers (American Joint Committee on Cancer (AJCC) staging systems) [24], a similar sub-stage could be applied in lung cancer stage I patients.

However, the actual clinical impact of SLN mapping in lung cancer remains to be elucidated through further studies; moreover, molecular analysis needs to be performed largely in research settings (since the prognostic significance of positive RT-PCR is still unclear). Nevertheless, in the near future, this technique may be useful in selecting a subset of NSCLC N0 patients who are most likely to be cured by surgery alone, as well as those patients who are more likely to benefit from adjuvant therapy.

References