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Repeat Mediastinoscopy as a Restaging Procedure

Die Re-Mediastinoskopie als diagnostisches Verfahren zur Restadiierung des Bronchialkarzinoms

Abstract

Background: Repeat cervical mediastinoscopy is a diagnostic surgical procedure for preoperative nodal staging in patients with insufficient first mediastinoscopy, with recurrent or second primary lung neoplasms, and following induction chemotherapy or chemo-/radiotherapy for locally advanced lung cancer. The aim of this study was to critically analyse indications, technical characteristics, intra- and postoperative complications, also to define selection criteria for patients with a higher probability of successful complete resection. **Material and methods:** 279 patients with lung cancer (66 female and 213 male patients, mean age 58 years, range 28 to 78 years) underwent repeat mediastinoscopy from 1968 to 2004, 12 because of inadequate first procedure (group A), 67 because of recurrent lung cancer (group B) 35 because of second primary lung cancer (group C), and 165 following induction chemo-/radiotherapy for IIIa and IIIb disease (group D). The interval between first and second procedure was 17 days (range, 12 – 38) in group A, 14 months (range, 5 – 29) in group B, 27 months (range, 19 – 124) in group C, and 132 days (range, 113 – 145) in group D. **Results:** No intra- or postoperative deaths were observed, 7 patients developed minor complications. N2 or N3 disease was found in 3/12 patients of group A (25 %), in 17/67 patients of group B (25.4 %) and in 6/35 patients of group C (17.1 %). Of the 116 patients with N2, and 49 with N3 disease before induction treatment (group D), repeat mediastinoscopy showed 126 N0, 20 N2 and 14 N3 status. Because of the presence of inseparable adhesions repeat mediastinoscopy was not possible in 5 cases. Five-year survival for patients with per-

Zusammenfassung

Einleitung: Die kollare Remediastinoskopie stellt ein diagnostisches Verfahren zur Klärung des Lymphknotenstatus bei Patienten mit Bronchialkarzinom und einer insuffizienten ersten Mediastinoskopie, beim Lokalrezidiv, beim Zweittumor und schließlich nach neoadjuvanter Chemotherapie oder Chemo-/Radiotherapie beim lokal fortgeschrittenen Bronchialkarzinom dar. Ziel dieser aggressiven erneuten Untersuchung des oberen Mediastinums ist die Selektion von Patienten mit einer höheren Wahrscheinlichkeit einer kurativen Resektion. **Krankengut:** Von 1968 – 2004 wurde bei 279 Patienten mit einem Bronchialkarzinom eine Remediastinoskopie vorgenommen, 12 wegen einer nicht aussagereichenden ersten Mediastinoskopie (Gruppe A), 67 wegen eines Lokalrezidivs nach vorausgegangener Resektion (Gruppe B), 35 wegen eines Zweittumors (Gruppe C) und schließlich 165 nach induktiver Chemo-/Radiotherapie für Bronchialkarzinom im Stadium IIIA und IIIB (Gruppe D). Es handelte sich um 66 Frauen und 213 Männer mit einem Durchschnittsalter von 58 Jahren (28 – 78 Jahre). Das Zeitintervall zwischen der ersten und zweiten Untersuchung betrug für die Gruppe A 17 Tage (12 – 38), die Gruppe B 14 Monate (5 – 29), die Gruppe C 27 Monate (19 – 124) und die Gruppe D 132 Tage (113 – 145). **Ergebnisse:** Die intra- oder postoperative Letalität betrug 0 %. Bei 7 Patienten konnten leichte Komplikationen festgestellt werden. Bei der Remediastinoskopie fand sich in 3/12 Fällen der Gruppe A (25 %), in 17/67 der Gruppe B (25,4 %) und in 6/35 der Gruppe C (17,1 %) eine N2- bzw. N3-Situation. In der Gruppe D hatten vor der Induktionstherapie 116 Patienten eine N2- und 49 eine

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Dedication
Dedicated to Professor W. Maaßen for his 85th anniversary

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sistent N2 in repeat mediastinoscopy was despite surgery only 5%. **Conclusion:** Repeat mediastinoscopy is a safe explorative procedure for the restaging of patients with primary locally advanced, recurrent or second primary lung cancer. In patients after induction treatment it is, however, less sensitive than the primary mediastinoscopy because of adhesions and fibrotic tissue. Patients with persistent N2 or N3 disease in repeat mediastinoscopy have a poor survival so that the indication for surgery has to be taken into consideration very carefully.

N3-Erkrankung: Die histomorphologischen Ergebnisse der Präparate bei der Remediastinoskopie zeigten in 126 Fällen eine N0, in 20 eine N2- und in 14 eine N3-Situation. Bei 5 Patienten konnte die Remediastinoskopie wegen starker Verwachsungen bzw. Fibrose des Gewebes nicht durchgeführt werden. Die 5-Jahres Überlebenszeit bei Patienten mit persistierendem Lympknotenbefall in der Remediastinoskopie (N2) betrug trotz Resektion nur 5%. **Zusammenfassung:** Die Remediastinoskopie ist ein sicheres diagnostisches Verfahren zur Restadiierung von Patienten mit einem lokal fortgeschrittenen Bronchialkarzinom, mit einem Rezidiv eines Bronchialkarzinoms oder mit einem Zweittumor. Nach Induktionstherapie ist die Remediastinoskopie wegen der Verwachsungen und des fibrotischen Gewebes weniger sensitiv als das erste Verfahren. Patienten mit persistierenter N2- oder N3-Erkrankung in der Remediastinoskopie haben eine schlechte Prognose, so dass die Operationsindikation sehr genau überdacht werden sollte.

Introduction

Preoperative evaluation of the mediastinal lymph nodes is important in patients with lung cancer in order to determine local operabiliy and/or need for neoadjuvant treatment. Cervical mediastinoscopy (CM) is generally accepted as a safe and highly accurate procedure in the staging of lung cancer. Nodes accessible to CM are those of the superior (level 2R and 2L) and inferior (level 4R and 4L) paratracheal and subcarinal (level 7) nodal stations. Additionally, extended CM and left parasternal mediastinotomy allow exploration of the aortopulmonary window (level 5) and anterior mediastinal nodes (level 6). Until the early nineties, repeat mediastinoscopy (RM) was considered contraindicated because of fibrosis due to the first procedure and the associated risk of injury to vital structures [1–3]. Neoadjuvant clinical trials with induction chemotherapy or chemoradiation, however, necessitated agressive re-exploration of the upper mediastinum. Prognostically, it seemed important to select therapy-responsive patients with high probability of complete resectability, thereby reducing the number of futile thoracotomies in patients with locally advanced lung cancer [4–6]. Early studies included small numbers of patients, but demonstrated technical feasibility and high diagnostic accuracy. Further indications were reported in patients after insufficient first mediastinoscopy and for staging of recurrent or second primary lung neoplasms [7–10].

The aim of this study was to present the large experience of our institution with this method, and to critically analyse indications, technical characteristics, intra- and postoperative complications, finally to define groups with high probability of complete resectability after multimodal treatment and prognostically higher survival.

Material and methods

From 1961 to 2004 we performed more than 22 800 CM in all patients with suspected or previously diagnosed lung cancer. 279 patients (66 female and 213 male patients, mean age 58 years, range, 28–78 years) underwent RM (1.17%). The indication for RM were inadequate first procedure (group A), defined as complete absence of lymphatic tissue on biopsies or biopsies that had not sampled contralateral nodal stations, recurrent disease following prior resection for non small cell carcinoma (group B), preoperative staging for second primary lung cancer, defined as second malignancy with a different histologic type, different anatomic site and occurrence after more than 2 years from the first malignancy (group C), and RM following induction chemo-/radiotherapy for NSCLC IIIa-IIIb and SCLC IIb-IIIb disease (group D). There were 12 patients in group A, 67 in group B (16 with prior stage IB, 12 stage IIA, 32 stage IIB and 7 IIIA disease, they had resulted in 47 lobectomies, 8 bilobectomies and 12 sleeve lobectomies), 35 patients in group C (prior resection included 28 lobectomies, 3 bilobectomies and 4 sleeve lobectomies), and 165 in group D (N2, 165 patients and N3, 49 patients). Neoadjuvant treatment in group D consisted of 3 courses of chemotherapy (three cycles of split-dose cisplatin 60 mg/m^2 days 1,7 and etoposide 150 mg/m^2 days 3, 4, 5) followed by concurrent chemoradiotherapy (one cycle cisplatin 50 mg/m^2 days 2, 9 and etoposide 100 mg/m^2 days 4, 5, 6 combined with 45 Gy hyperfractionated accelerated radiotherapy to primary tumor and mediastinal nodes) and restaging with CT scan of the chest and upper abdomen, CT of the brain, bone scan and bronchoscopy. Patients with radiological evidence of tumor remission or stable disease and Karnowsky index of more than 70% underwent RM.

The interval between first and second procedure is demonstrated in table **1**. RM was performed with resection of the scar of the first operation and preparation to the pretracheal fascia. Digital dissection and/or sharp preparation was followed by removal of adhesions along the “mediastinoscopic route”. In case of severe fibrosis, the left paratracheal route was taken, an area generally relatively spared by the first mediastinoscopy. All accessible lymph nodes were sampled and mapped according to the revised regional lymph node classification for lung cancer by Mountain [11]. A RM was considered complete if bilateral inferior paratracheal (level 4R and 4L) and subcarinal (level 7) nodal stations were included.

Results

No intra- or postoperative deaths were observed, average blood loss amounted to 26 ml (range 10 – 160 ml) and was not different from first operation. Three patients developed postoperative recurrens nerve palsy, two had wound infection, two cardiac arrhythmia. RM was incomplete (14 patients, 5.2 %) or not possible (5 patients, 1.8 %) because of diffuse inseparable adhesions. Data of all patients with RM are demonstrated in the table **1**. Differences in each group are described separately.

Group A. One patient with solitary nodal involvement (nodal station 4R) and all 9 patients with negative histology underwent resective surgery (7 lobectomies and 3 pneumonectomies). Resection confirmed the results of RM in all cases. Final histopathological stages were Ia in 2, Ib in 3, IIb in 4 and IIIa in 1 case.

Group B. 41 patients underwent lung resections, 3 of them despite N2 positive nodal station: 29 pneumonectomies, 4 lobectomies, 6 anatomical segmentectomies and 2 wedge resections. 3 patients refused operative treatment, 5 proved inoperable because cardiopulmonary limitation, 4 had were irresectabel tumors at thoracotomy. All accessible lymph nodes were removed during thoracotomy, which confirmed the 3 cases of RM positive nodal involvement and disclosed additional N2 disease in 6 patients (3 at the levels of nodal stations 5, 6 and 8 which were inaccessible to RM).

Group C. Because of routine oncological follow up after the first operation, most of the patients had lesions less than 3 cm at the time of diagnosis. This explains the comparatively small numbers of positive mediastinal nodes at RM. Seven patients were excluded from sugery because of multiple positive mediastinal nodal stations at RM (4 patients) or functional inoperability (3 patients). 28 patients underwent resection: 17 lobectomies (15 involving the contralateral lung compared to the first operation), 7 anatomical segmentectomies and 4 wedge resections. At thoracotomy 2 additional patients proved to have positive N2 nodes, 1 of them in stations not reached by RM.

Group D. 116 patients had N2 and 49 N3 disease before induction treatment. The most frequent histological types were squamous cell carcinoma (59 patients) and adenocarcinoma (55 patients). They were followed by large cell carcinoma (19 patients), small cell carcinoma (28 patients) and mixed type of lung cancer (4 patients) cases. RM was not possible in 5 cases because of the difuse inseparable adhesions. A total of 528 lymph node stations (mean, 3.3) were sampled during 160 RM (compared to 672 nodal stations at first mediastinoscopy, mean 4.2). The histological findings of RM demonstrated 126 N0, 20 N2 and in 14 N3 status. 27 patients with N3 and multilocular N2 disease, 2 patients with limited cardiopulmonary reserve, and one patient with cerebral metastasis were excluded from resection. One patient refused operative treatment. Resection in the remaining 129 patients yielded N0/N1 in 110 and N2/N3 in 19 cases status. 12 patients demonstrated N2 nodal involvement at thoracotomy that had not been evident at RM (false negative RM). For the group IV sensivity was 74 %, specifity 100 %, PPV 100 %, NPV 86 % and accuracy 92.5 %. Median survival rates in patients with persistent N2/N3 disease in RM was 17.8 months, in responders without nodal involvement 55.6 months. The five years survival was 5 % and 36.6 % respectively.

Discussion

46 years after its introduction by Carlens in 1959 [12], mediastinoscopy continues to be an important step in the evaluation of the mediastinal lymph node status and selection of patients with lung cancer for surgery. Depending on surgical technique, mediastinal exploration is varably described as cervical mediastinoscopy, parasternal mediastinotomy, extended cervical mediastinoscopy and thoracoscopy. The results of prior studies support routine use of mediastinoscopy in the preoperative staging of patients with lung cancer [13,14]. RM, by contrast, was rare in the era before neoadjuvant treatment protocols of locally advanced lung cancer. Patient numbers reported were small and outcome data was insufficient [1 – 3]. RM was considered technically difficult due to commonly encountered tissue adhesions and fibrosis, particularly between trachea and innominate artery. Maaßen in 1968 performed the first RM at our institution in a patient with recurrent lung cancer. Meersschaut et al. was the first to employ RM as a routine staging procedure [7]. In his series of 140 RMs he observed no procedural deaths and no complications necessitating surgical revision. Indications for RM have since expanded to include incomplete primary mediastinoscopy [9], assessment of locoregional extent of recurrent [2,7,9] and second primary cancer [8], and re-staging after neoadjuvant chemotherapy [4 – 6]. The present study, in addition, includes for the first time a large group of 165 patients post neoadjuvant chemoradiation therapy.

The technical aspects of RM have been described in previous reports [4,7]. The presence of peritracheal adhesions makes the exploration more complex than at initial mediastinoscopy. We found that preparetion along the left lateral tracheal wall was

Table **1** Results of 279 patients with RM

Group	*n patients*	*Time to RM*	*N2/N3 in RM*	*n Resection*	*RM Not possible*	*RM Incomplete*
A (insufficient first mediastinoscopy)	12	17 (11 – 38)d	3 (25 %)	10	0	0
B (recurrent lung cancer)	67	14 (5 – 29)mo	17 (25.4 %)	41	0	3
C (second primary lung cancer)	35	27 (19 – 124)mo	6 (17.1 %)	28	0	2
D (after neoadjuvant treatment)	165	132 (113 – 145)d	34 (21.4 %)	129	5	9

simpler, possibly because of relative sparing during the first procedure, and helped avoid the critical innominate-tracheal area. Digital dissection and direct sharp dissection or electrocautery was used for mediastinal exploration. Only 5 patients proved inoperable due to inseperable adhesions, beginning by the separation of the strap neck muscles. In our opinion the feasibility of RM depends on exploration standards by the initial mediastinoscopy and the experience of the surgeon. If possible, biopsies have to be taken from the same nodal stations as at the first procedure and RM has to be done by the same surgeon. RM was performed 3 to 4 weeks after radiation therapy and was no more difficult than for other indications. Patients, however, were excluded from RM if radiation dose exceeded 45 Gy or if primary mediastinoscopy was performed at another institution. Although our experience with videoscopic RM is very limited, we think that the magnification of the optical field and the simultaneously use of more than one instrument may contribute to facilitate the preparation.

The advent of new imaging techniques such computed tomography (CT scan) and magnetic resonance imaging (MRI) warrant a critical appraisal of mediastinoscopy today [15,16]. Neither CT scan nor MRI are able to distinguish malignant from hyperplastic, anthracotic, granulomatous or fibrotic leasions, more so after induction treatment. With reported sensitivities and specificities of 69%, respective 71% for CT scan and 45%, respective 65% for MRI, both techniques prove too inaccurate for reliable locoregional staging. Other newer techniques such as positron emission tomography (FDG-PET or FDG-PET/CT) and endobronchial (EBUS) or endoscopic (EUS) ultrasound guided fine-needle aspiration (FNA) are also used for mediastinal staging. In a prospective study involving 202 patients with NSCLC, Gonzalez-Strawinski et al. found that current FDG-PET technology alone was not sufficiently reliable to warrant treatment changes or omission of mediastinoscopy [17,18]. FDG-PET results have been shown to be difficult to interpret after radiotherapy. An inherent problem of the FDG contrast is that inflamed tissue will absorb it, so that granulomatous or inflammatory mediastinal disease or cases of obstructive malignant processes result in difficulty to identify mediastinal malignancy. Radiated mediastinal tissue shows intense FDG uptake, accounting for 20% false positive results [19]. Only low uptake values, therefore, because of good negative predictive accuracy, may obviate the need for RM [20]. The best time of study nevertheless remains undetermined.

EBUS and EUS guided FNA are additional new techniques employed in the staging of solid tumors. They target lesions and lymph nodes adjacent to trachea, main bronchi and esophagus. Results, however, are not comparable to those of mediastinoscopy or RM [21,22], Selection of the patients for EUS or EBUS-FNA is based on computed tomographic scanning and with that done only in patients with pathological radiological findings [23]. Both techniques are used to assess the entire mediastinum or to stage predominantly only one nodal station, but they are not used for the systematical standarized exploration of individual nodes as performed by mediastinoscopy [24]. Moreover, the echogenic characteristics alone of a node might not be as reliable after radiation as they are before. In our experience it is difficult to obtain representative material from scarred lymph nodes after chemoradiotherapy and the false positive results on cytologic examination of FNA must be considered. The representative histological tissue, however, is because of the prognostic value paramount in the assessment of locally advanced disease following induction therapy, so that it is unlikely that the addition of transtracheal, transbronchial, and endoscopic ultrasonographically guided FNA will sufficiently rule out disease relative to the histologic results achieved from mediastinoscopy. EBUS and EUS are supplementary diagnostical tools and may contribute to improve staging, especially in cases with metastasis in the hilar nodes or the mediastinal nodes which could not be reached by CM or RM.

Insufficient primary mediastinoscopy is uncommon today because of better education of thoracic surgeons and introduction of procedural standards in departments with high activity in thoracic surgery. Indeed, our study included only 12 cases of negative primary mediastinoscopies, which, because of CT criteria or absence of bioptic lymph node tissue underwent RM at our institution. RM was technically unproblematic, yielded 3 cases of N2 /N3 disease, and resulted in exclusion from surgery of 2 patients. In patients with recurrent or second primary cancer mediastinal lymph nodes sampling and not a systematic lymphadenectomy including the surrounding fat tissue was performed at the first operation. Despite considerable scarring, RM achieved acceptable sampling of nodal stations and directly contributed to successful resection in 41 patients with recurrent and 28 patients with second primary lung cancer. Futile thoracotomy was thus avoided in 14 cases of recurrent and 4 cases of second primary lung cancer, particularly when extracapsular or multilocal nodal involvement was detected.

Inclusion of systemic treatment as early as possible into the management of locally advanced non small cell lung cancer has proved feasible and effective, resulting in increased survival of stage IIIa and IIIb lung cancer patients in prospectively randomised trials [25,26]. Several investigators have focused on early intensification of preoperative downstaging by bimodality induction including chemotherapy as well as radiation before surgery [27 – 29]. In these patients clinical assessment especially of the mediastinal stage after induction treatment requires maximal accuracy. Bueno et al. [30] and Voltolini et al. [31] pointed out in two separate reports that nodal stage after induction therapy for stage IIIA lung cancer determined patient survival. Patients downstaged to N0 status survived 59% at 3 years and 35.8% at 5 years, respectively. Persistence of lymph node metastasis after induction treatment, by contrast, had a discouraging prognosis with 0% 3-year survival [30] and 9% 5-year survival [31]. These data support surgical resection only for downstaged patients, mandating that every effort be made to improve the accuracy of restaging procedures. Indeed, both phase II and phase III trials completed by our oncology group [32,33] included RM in their standard post-induction and pre-resective re-staging protocol. The total number of sampled stations at RM was slightly less compared to that at first mediastinoscopy (528 versus 672), indicating that not all lymph nodes were re-explored, mostly because of adhesions or fibrosis following the induction treatment. RM proved highly sensitive in identification of patients with persistent N3 or multilocular N2 disease and thus was decisive in excluding prognostically inoperable patients from resective surgery. Incomplete eradication of mediastinal cancer post induction chemoradiation, however, was found in

26% of patients. This resulted in a significant difference in median survival and in 5 years survival between patients with positive and negative RM. Because of the poor survival we decided to exclude patients with persistent N2/N3 disease at the RM from surgery.

We also found a small group of patients with N2 disease on primary mediastinoscopy but negative cancer histology on RM that proved to have residual cancer on mediastinal lymphadectomy obtained during resective surgery. Such patients have previously been thought to have an inherently better prognosis [4], an assumption not born out in our patient's series.

We conclude that RM is a feasible and safe surgical procedure for the restaging of patients with primary locally advanced, recurrent or second primary lung cancer. Mortality is nil and perioperative complications are rare. Diagnostic accuracy outweighs that of radiological staging studies (including chest CT scan and MRI), FDG-PET and ultrasound guided FNA, and remains high even in the setting of tissue fibrosis post induction radio-chemotherapy. RM, therefore, must be considered despite the technical complexity as criterion standard for mediastinal restaging in patients with locally advanced lung cancer and following neoadjuvant induction treatment.

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