Oesophagectomy is the mainstay of treatment of patients with oesophageal cancer without local invasion into the surrounding organs and without distant metastases. In patients with locally advanced tumours, multimodal protocols including chemotherapy, radiotherapy and surgery may improve survival, whereas, in those with metastatic disease, primary radiochemotherapy and/or interventional endoscopic techniques provide symptomatic improvement and, possibly, longer survival. As a result of these therapeutic advances, the approach taken in a patient with oesophageal cancer is changing. Accurate staging is critical to the identification of those patients most likely to benefit from primary surgery and those for whom multimodal or nonsurgical therapy is indicated [1–3].

The advantages of fiberoptic bronchoscopy in the assessment of possible airway invasion by oesophageal cancer located above the level of the tracheal bifurcation (so called suprafubrical oesophageal cancer) are well documented [4–8]. It is less clear, however, whether bronchoscopy is indicated as a part of routine preoperative staging in patients with oesophageal cancer located below the level of the tracheal bifurcation (so called infrabifurcal oesophageal cancer).

Theoretically, central airway invasion from an infrabifurcal cancer could occur through extraoesophageal spread of the tumour to higher levels of the mediastinum or through tumour invasion from the mediastinal lymph nodes involved. The cancer may also directly invade the lower lung lobes from the surrounding areas. Further, patients with squamous cell oesophageal cancers develop second primary tumours in the aerodigestive tract at a rate of 4% per year [9, 10]. Although curative resection of an associated oesophageal and lung cancer can be performed in approximately half of all patients [11] and direct pulmonary invasion might be easier to resect than involvement of the major airways or aorta [7, 10–12], the long-term survival of such patients is poor [13]. Bronchoscopy may provide valuable information not only in patients with suprabifurcal cancer but also in patients with potentially resectable oesophageal cancer located below the level of the tracheal bifurcation.

The aim of this study was to prospectively evaluate the benefits of bronchoscopy in such patients.

**Patients and methods**

In a prospective protocol, patients with untreated biopsy-proven carcinoma of the oesophagus diagnosed between February 1, 1995 and October 31, 1998 underwent preoperative staging by means of swallow oesophagography,
posteroanterior and lateral chest radiography, computed tomographic scanning of the chest and abdomen, percutaneous sonography, oesophageal endoscopic ultrasound (EUS) and fibreoptic bronchoscopy. The tumour was considered "infrabifurcal" if its proximal end was below the level of the tracheal bifurcation on radiography [1]. A questionnaire was designed that asked prospectively for detailed information about the tumour invasion of the airways from the bronchoscopist preoperatively, and the surgeon and pathologist postoperatively.

Of the 316 patients presenting in the bronchoscopy department with oesophageal cancer during the study period, 51 had the proximal extent of their cancer below the level of the tracheal bifurcation. They form the basis of this report. Sixteen of these patients have been briefly reported on previously [4], but because of the small numbers involved they were not analysed with respect to the validity of bronchoscopy. It is therefore considered justifiable to include these 16 patients in the present analysis dealing exclusively with patients with infrabifurcal oesophageal cancer.

The basic characteristics of the patients are given in table 1. Their mean age was 59 yrs (range 33–79 yrs). There was a male predominance of 49:2. Twenty-six of them had squamous cell cancer and 21 adenocarcinoma. Twenty-two were current smokers, 17 past smokers and 12 nonsmokers. Eighty-eight per cent of the patients with squamous cell cancer were current smokers or past smokers as compared to 57% of those with adenocarcinoma. The mean time lapse between the onset of symptoms of oesophageal cancer (mainly dysphagia and/or odynophagia) and bronchoscopy was 8.8±4.7 weeks (range 3–24 weeks). Forty-four patients had no pulmonary symptoms, four dyspnoea, two dry cough and one hoarseness.

After obtaining informed consent, fibreoptic bronchoscopy was performed as previously reported [4]. First, each mainstem bronchus was irrigated with physiological saline, and washings for cytological examination were obtained by suction from all lung lobes. The whole tracheobronchial tree was examined, and, if an endobronchial lesion was noted, biopsy and brush cytology specimens were taken. All direct (exophytic intraluminal growth or infiltration of the airway wall) and indirect tumour signs (distortion or compression of normal structures, altered structure of the mucosa, increased vascularity, focal thickening, protrusion at the posterior wall of the trachea or a major bronchus, widened and immobile bifurcation, rigid and fixed tracheobronchial structures on breathing or coughing manoeuvres) were recorded and three or four forceps biopsy specimens as well as a brush cytology sample taken from these areas. This was also done in cases of protrusion of the airway wall with a macroscopically normal appearance of the mucosa. If no abnormalities were seen on bronchoscopy, brush cytology and three or four biopsy specimens were routinely taken from the pars membranacea of the right main bronchus, left main bronchus and the distal half of the trachea. The quality of the biopsy specimens as assessed by the pathologist was considered optimal when at least two pieces of >2 mm were obtained from the region of interest, and adequate when at least two specimens were >1 mm. The brush and washing samples for cytology were considered adequate when at least 4 cell-rich slides, consisting predominantly of columnar epithelial cells, could be analysed microscopically.

After the staging, potentially operable patients either proceeded directly to oesophageal resection or received 5-fluorouracil-based neoadjuvant polychemotherapy preoperatively [14]. All patients staged as having tumours potentially resectable for cure were offered surgery. The resectability criteria were established prior to the commencement of the study and included exclusion of distant metastases and of airway invasion by bronchoscopy with cancer-positive microscopic examination. Either subtotal transthoracic en bloc oesophagectomy with extended two-field lymphadenectomy or transmediastinal resection was the procedure of choice [15, 16]. Reconstruction was performed with a gastric tube anastomosed to the cervical oesophagus via a left cervical incision. Tumour extent and tracheobronchial invasion were determined intraoperatively and by histopathological examination of the resection specimens. Pathological stage was determined on the basis of the Union Internacional Contra la Cancrum primary tumour, regional nodes, metastasis classification guidelines [17].

### Follow-up

Patients who had been operated on were followed-up every 3 months for the first year and at 6-month intervals thereafter. Episodes suggestive of cancer invasion of the airways were specifically looked for. Extensive evaluation of tumour recurrence was initiated only if the patient had symptoms suggestive of recurrence. Patient death records were obtained from the hospital or through the authors' tumour registry. The outcome in all patients was ascertained by June 30, 1999 through telephone calls with the patients, their relatives or their primary physicians.

### Diagnostic criteria

For the therapeutic decision, the results of bronchoscopy were reported and the patients classified into three groups: 1) no invasion: no macroscopic abnormality and

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**Table 1.** Characteristics of the study population

<table>
<thead>
<tr>
<th>All patients</th>
<th>Patients operated on</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients n</td>
<td>51</td>
</tr>
<tr>
<td>Sex Male/Female</td>
<td>49/2</td>
</tr>
<tr>
<td>Age yrs</td>
<td>59±11</td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
</tr>
<tr>
<td>Squamous cell cancer</td>
<td>26</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>21</td>
</tr>
<tr>
<td>Small cell cancer</td>
<td>3</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Tumour stage (uT, EUS)</td>
<td></td>
</tr>
<tr>
<td>uT1</td>
<td>1</td>
</tr>
<tr>
<td>uT2</td>
<td>6</td>
</tr>
<tr>
<td>uT3</td>
<td>38</td>
</tr>
<tr>
<td>uT4</td>
<td>2</td>
</tr>
<tr>
<td>EUS not possible</td>
<td>4</td>
</tr>
<tr>
<td>Tumour length cm</td>
<td></td>
</tr>
<tr>
<td>Swallow contrast</td>
<td>6.2±2.9</td>
</tr>
<tr>
<td>Oesophagoscopy</td>
<td>5.8±2.8</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. *: n=38; #: n=21. EUS: endoscopic ultrasound; uT: tumour stage as assessed by EUS.
no malignancy on routine biopsy or washing and brush cytology; 2) possible invasion: macroscopic abnormality without microscopic proof of malignancy from samples taken from the macroscopically suspect areas as well as routine biopsy and washing and brush cytology; 3) proven invasion: histological or cytological proof of malignancy. For the assessment of the validity of bronchoscopy in the diagnosis of tracheobronchial invasion, a complete (R0) tumour resection [17] with regard to the airways and survival >6 months without any pulmonary problems was considered the gold standard for the absence of tracheobronchial invasion.

Statistical analysis

Descriptive information is summarized as mean ± SD for continuous variables and as frequencies or percentages for categorical variables. Standard methods for proportions were used. A binomial distribution was used to compute the 95% confidence intervals (CIs) for the frequency of bronchoscopic abnormalities and for their validity indices.

Results

Bronchoscopy

There were no complications due to bronchoscopy. The biopsy specimen quality was considered by the pathologist to be optimal in 74% of cases and adequate in 26%. Adequate brush samples for cytological examination were obtained in 39 (75%) cases and adequate washings on bronchoscopy in 40 (77%).

Table 2 lists the macroscopic findings in the trachea and main bronchi on bronchoscopy. One smoking patient with squamous cell oesophageal cancer showed a direct tumour sign (an endoluminal mass in the ostium of the left upper lobe) which proved to be an asymptomatic primary bronchial cancer (squamous cell type) not seen on computed tomography (CT) or plain chest radiography. Because of previous contralateral pulmonary segment resection and the need for pneumonectomy on the left side, and because of the locally advanced oesophageal cancer, this patient was excluded from curative resection. The patient received laser treatment and brachyradiotherapy of the bronchial cancer, and primary radiochemotherapy of the oesophageal cancer.

Of the indirect tumour signs, mobile protrusion of the pars membranacea was the most frequent, occurring in four (7.8%) of the patients. In one nonsmoking patient, the macroscopically suspect mucosa of left 9 (S9) bronchus was histologically proved to be infiltrated by the adenocarcinoma of the distal oesophagus. This locally advanced situation was considered by the surgeon to be surgically incurable and the patient received primary polychemotherapy.

On bronchoscopy, 15.7% of patients showed some abnormality, whereas in 84.3% the airways were macroscopically normal. None of the routine biopsy specimens taken from macroscopically normal areas of the trachea and main bronchi were cancer-positive. Taking bronchoscopic biopsy as gold standard, the positive predictive value for all abnormalities (i.e. the probability that a given macroscopic abnormality was due to cancer) was 25% (95% CI 3.2–65.1%).

None of the tracheal brush cytology samples from 34 patients with normal macroscopic appearance were cancer-positive; none of the samples from the five patients with some macroscopic abnormality were cancer positive. None of the 40 pairs of bronchial washings (34 from patients showing a normal macroscopic appearance and six from those with some macroscopic abnormality), taken separately from the left and the right lung, were cancer-positive.

Altogether, in two of the 51 (4%) patients, airway infiltration of the oesophageal cancer or a coexistent bronchial cancer was diagnosed on bronchoscopy and confirmed by biopsy. In these two patients, bronchoscopy was decisive for the exclusion from surgery.

Course after bronchoscopy

After the staging, 26 patients proceeded directly to oesophageal resection, 15.6±13.1 (range 2–70) days after bronchoscopy. Five patients with locally advanced cancer (all of them without any macroscopic abnormality and with normal histological and cytological samples on bronchoscopy) received neoadjuvant chemotherapy after bronchoscopy and were operated on thereafter (137±64 days, range 66–240 days, after bronchoscopy). In addition to the two patients with airway invasion by the oesophageal cancer or coexistent bronchial cancer described above, 18 others were rejected from surgery. Of these 18 palliatively treated patients, three were rejected from surgery because of an extensive local tumour mass, four due to general inoperability, six due to distant metastases and five for other reasons. Of these 18 patients, 16 showed normal bronchoscopic findings and two some macroscopic abnormalities (widened carina in one and mobile protrusion of the posterior wall of the left main bronchus in the other) with normal microscopy results in samples taken from these areas.

Oesophageal resection

All 31 patients who underwent oesophagectomy were operated on with curative intent. The surgical approach was transthoracic in 23 patients and transmediastinal in eight. The complete resection rate was 26 of 31 (84%). In five patients, complete tumour resection could not be achieved due to infiltration of structures other than the airways. No airway infiltration was found on surgery or by histological examination of the resected specimen.

Four of the patients operated on showed some macroscopic abnormality (mobile protrusion in three patients,
suspect mucosa in one, widened carina in one and rigid pars membranacea in one) but yielded normal histological and cytological samples on bronchoscopy. Regarding the macroscopic abnormalities without microscopic proof of cancer as indices of airway involvement, both the specificity and accuracy of bronchoscopy were 87.1% (95% CI 70.2–96.4%). When only microscopic proof of cancer on bronchoscopy was taken as evidence of airway involvement, both the specificity and accuracy of bronchoscopy increased to 100% (95% CI 88.8–100%).

Overall validity of bronchoscopy

Table 3 summarizes the results of bronchoscopy in the 33 patients for whom a definitive diagnosis was obtained. Included are all 31 surgically treated patients and the two palliatively treated patients with airway infiltration or a second primary bronchial cancer diagnosed by bronchoscopically and confirmed microscopically. Excluded are the 18 patients rejected for surgery for reasons other than airway infiltration and discovered by examinations other than bronchoscopy, i.e., patients in whom the bronchoscopy could have been omitted had it been performed as the last procedure in the staging process. The gold standard for the presence of airway invasion was positive microscopy at bronchoscopy or surgery, and, for the absence of invasion, an R0-resection with regards the airway. The overall accuracy of bronchoscopy in proving or excluding tracheobronchial invasion in these potentially operable patients was 100% (95% CI 89.4–100%). By excluding from surgery patients in whom curative resection was not possible, bronchoscopy was the sole decisive staging investigation in two patients (6.5% of potentially operable patients and 3.9% of all patients).

Follow-up

Follow-up was complete in 50 patients. One patient who had been operated on was lost after 9 months. Of the 31 patients operated on, 13 have been alive >6 months after surgery without any pulmonary problems. Eighteen patients died 8.6±8.9 (range 0.1–32) months after surgery, seventeen of them of causes unrelated to the tracheobronchial tree. One patient, the cause of death 8 months after surgery was unknown.

The two patients with airway invasion by the oesophageal cancer and with coexistent bronchial cancer diagnosed on bronchoscopy died 11 and 12 months after bronchoscopy, respectively. Of the 18 palliatively treated patients, excluded from surgery for reasons other than airway infiltration, 10 died 6.5±4.9 (range 0.5–16) months after bronchoscopy. Of these ten patients, eight died of causes unrelated to the tracheobronchial tree and, in two, airway invasion could neither be proved nor excluded. Eight patients survive 13.8±9.0 (range 5.5–31) months after bronchoscopy. Four are living without any pulmonary problems, in one airway invasion of the tumour is possible and, in the other three, airway invasion could neither be proved nor excluded.

Correlations with other staging procedures

Most patients gave either a normal chest radiograph or a radiograph consistent with an obstructed oesophagus, i.e. an abnormal air/ fluid level in the oesophagus as the only abnormality. Specifically, no patient had a mediastinal tumour mass in the area of the oesophageal cancer, compression of the trachea, atelectasis, pulmonary nodules or pleural effusion. Only one patient (with both normal macroscopic and microscopic results on bronchoscopy) showed mediastinal lymphadenopathy.

No patient showed compression of the trachea or an oesophagotracheal fistula on swallow oesophagography. Endosonography showed invasion outside the oesophagus (tumour stage 4 as assessed by EUS (uT4)) in two of 47 patients (of the diaphragm in both). In neither of them was direct airway infiltration suspected. Both patients gave normal bronchoscopic results with negative microscopic examination of the routine biopitic and cytological samples.

Forty-nine of the 50 patients showed no airway or lung parenchymal abnormalities on thoracic CT; one scan was not available. By definition, no computed tomographic scan showed the tumour mass abutting the trachea or main bronchus. In the patient with coexistent bronchial cancer diagnosed on bronchoscopy, CT did not show these abnormalities. In the patient with airway invasion of the oesophageal adenocarcinoma into the left lower lobe, the computed tomographic finding in this area was interpreted as consistent with discrete postinflammatory changes, but not with tumour infiltration.

Discussion

The most important finding in this study was that, even in patients with infra-bifurcal oesophageal tumour, the addition of bronchoscopy to the staging work-up improved the ability to classify patients as having either resectable or unresectable disease and therefore facilitated selection of patients for operation. The study showed a high overall accuracy (100%) of bronchoscopy with biopsy and brush and washing cytology in proving or excluding airway invasion by oesophageal cancer in potentially operable patients. Bronchoscopy also identified unsuspected coexistent bronchial cancer that was not recognized by other staging procedures. Of the 20 patients eventually classified as having unresectable disease, bronchoscopy was the decisive staging procedure, enabling exclusion from surgery because of airway tumours in two patients, in 3.9% of the overall study population and 6.5% of otherwise potentially operable patients. For these patients, bronchoscopy clearly altered the course of therapy, as they otherwise would have undergone oesophagectomy in the presence of a probably unresectable tumour. Although extended resection is technically possible in locally advanced cancer infiltrating
neighbouring organs, the long-term results are very poor [13]. The authors felt, therefore, that, if bronchoscopy spares only four unwarranted attempts at resection in 100 patients, it is worth performing.

The incidence of bronchoscopically detected airway invasion of infrabifurcal oesophageal cancer in this study (one patient, i.e. 3.2% of potentially operable and 2% of all patients) was, as expected, much lower than in patients with suprabifurcal cancer (6–15%) [4] or in other studies in which patients were not clearly differentiated between with regard to the site of the tumour [6–8]. Another reason for the low incidence is the thorough prescreening of the patients, aimed at evaluating bronchoscopically only those who were potentially operable.

Although the oesophageal tumours were situated distant from the central airways, suspect macroscopic abnormalities were observed in 16% (eight of 51) of patients on bronchoscopy. However, microscopic proof of cancer through histology could be obtained in only 25% of these abnormalities. Brush and washing cytology results were negative in all patients, with and without macroscopic abnormalities. Four patients with macroscopic abnormalities and without microscopic proof of cancer eventually underwent an R0 resection; they would have been rejected for curative surgery if the diagnosis of airway invasion had been based on macroscopic findings only. Because the assessment of indirect tumour signs is subjective, the diagnosis of airway invasion must be based on microscopic proof of cancer from the suspected areas. In infrabifurcal oesophageal cancer, the microscopic proof of malignancy may be even more important than in suprabifurcal tumours for the exclusion of false positive results. Because the primary tumour is not in close contact with the central airways, the possibility of overestimation of indirect tumour signs is greater.

None of the routine biopsy specimens taken from patients with no macroscopic abnormality were cancer-positive. It is difficult to assess from the present results the value of routine biopsy specimens from macroscopically normal areas of the main stem bronchi and distal trachea. The taking of three or four biopsy specimens from each of the three regions in the absence of visible abnormalities represents more sampling than usual in the normal clinical setting. Thus the applicability of the current data to the normal clinical setting may be limited.

Melissas et al. [8] reported bronchoscopic signs of early airway invasion in 38.4% of their 39 patients with cancer located in the lower third of the oesophagus. Choi et al. [7] reported impingement of the central airway wall in 7.1% and macroscopic signs of invasion in 5.4% of their 112 patients with cancer located in the lower third of the oesophagus. They hypothesized that these changes were due to local infiltration of the tumour. Although no attempt was made in either study to validate the nature of these macroscopic abnormalities by taking samples for histology, the authors concluded that bronchoscopy should be performed regardless of the size and location of the tumour in oesophagus.

One case of unsuspected synchronous bronchial cancer was found. In this patient, curative resection of both cancers was considered unlikely and accompanied by a very high operative risk, and palliative therapy was instituted. The incidence of bronchial cancer in the present study (one of 26, i.e. 4% of patients with squamous cell oesophageal cancer) was comparable with that in previous studies (5.3% [18], 4.6% [5] and 3.2% [11]). These data suggest that bronchoscopy should be performed in all patients with squamous cell oesophageal cancer to exclude unsuspected bronchial cancer, irrespective of the tumour site. In contrast, it is unlikely that in nonsmoking patients with infrabifurcal adenocarcinoma and normal chest radiography and CT results, the yield of bronchial cancers would be great enough to justify bronchoscopy.

The postoperative survival of >6 months without any pulmonary problems is further proof of a R0 resection with regard to the airways, making the “gold standard” with which the present bronchoscopic findings were correlated sufficiently reliable. It is impossible to ascertain whether the exclusion of airway invasion by bronchoscopy was correct in the patients treated palliatively for other reasons. Natural tumour growth and the palliative radiotherapy and/or chemotherapy in these patients could have influenced tumour invasion in the airways, making any later evaluation of the accuracy of the bronchoscopy worthless.

In this study, 35.3% of patients (18 of 51) were excluded from resection because of systemic metastases, an extensive local tumour mass or poor physiological status documented only after bronchoscopy was performed. If this information had been available prior to bronchoscopy, the procedure could have been avoided. Bronchoscopy should be performed as the last investigation in the staging work-up, after inoperability has been excluded by chest radiography, CT, swallow oesophagography, EUS and assessment of physiological status [19]. The results of bronchoscopy in inoperable patients without pulmonary symptoms does not substantially modify their palliative treatment.

Perhaps newer techniques used in the detection of early lung cancer, such as fluorescence bronchoscopy or endobronchial ultrasonography, could further improve the validity of bronchoscopic diagnosis of airway invasion by oesophageal cancer. Endobronchial ultrasonography allows investigation of various layers of the airway wall and can be used in the determination of the depth of penetration of the tumour. However, in the trachea, the naked ultrasonic probe gives only a restricted sectorial image at the site of direct contact, and the investigation time is limited to the duration of apnoea tolerated by the patient. The principle underlying fluorescence bronchoscopy is based on a difference in fluorescence between normal and malignant tissue made visible by the use of stimulating light of a specific wavelength. It remains to be seen whether this technique will also be useful in the detection of tumours invading the airway wall from the outside.

The chest radiography, swallow oesophagography and EUS did not indicate airway involvement in any of the present patients. These investigations are not useful in assessing airway invasion in cases of infrabifurcal oesophageal cancer. CT is valuable in the assessment of cancer invasion of the mediastinal structures [3, 20] and in revealing the tumour’s relation to the tracheobronchial tree [4]. The authors feel that the bronchoscopist should have a computed tomographic scan available for review before the procedure in order to be able to take the biopsy specimens from the areas most suspicious with regard to tumour invasion. In this study, CT did not detect either the secondary bronchial cancer or the airway invasion by the oesophageal cancer.
The best design of a study to assess the value of bronchoscopy in determining the resectability of infra-bifurcal oesophageal cancer would have been a prospective randomized trial in which patients staged with standard methods were compared with those staged using bronchoscopy in addition to these methods. However, because bronchoscopy is already considered a standard procedure by the present surgeons [1, 4] and elsewhere [3, 5, 7–9], it would be unethical not to perform bronchoscopy. The results of this study (exclusion from surgery of 6.5% of patients with otherwise operable conditions based the results of bronchoscopy) underline this point of view. Therefore, the next best approach was conducted in a prospective series of patients undergoing staging in order to decide on the possibility of radical curative resection. However, contrary to in patients with suprabifurcal oesophageal cancer [4], in whom bronchoscopy is a mandatory part of their preoperative staging, not all patients with infrabifurcal oesophageal cancer were referred for bronchoscopy. Patients with small (uT1–2) adenocarcinomas in the gastro-oesophageal junction were staged without bronchoscopy, because cancer invasion of the tracheobronchial system or a concurrent bronchial cancer were considered highly unlikely in these patients.

In conclusion, the present study shows that bronchoscopy is a useful procedure in the preoperative staging of infrabifurcal squamous cell oesophageal cancer, since it may detect invasion of the lower lobes of the lungs or synchronous lung cancer in a substantial proportion of such patients. Whether routine bronchoscopy should be recommended in the staging of nonsmokers with adenocarcinoma of the distal oesophagus requires clarification in a larger patient population.

Acknowledgements. The authors thank R.W. Hauck for performing some of the bronchoscopy in this study, and E. Amaseder, O. Felbermayr, E. Hopp and I. Reinheimer for excellent technical assistance with the bronchoscopy.

References