

## Editorials

## Palliative care for patients with non-malignant end stage respiratory disease

K M Hill, M F Muers

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality in the United Kingdom; 28 000 people in England and Wales died of the disease in 1999, a figure comparable with lung cancer which killed 29 000 people in the same year.<sup>1</sup> Equal numbers of patients with COPD and lung cancer are therefore experiencing preterminal disease and are likely to require similar medical and social services. The UK Department of Health's expert report published in 1992<sup>2</sup> advocated the extension of palliative care services to all who need them, whatever their diagnosis. Since then, the availability and provision of holistic supportive care to patients dying from non-malignant disease has become a topical issue for palliative medicine.<sup>3</sup> However, while countries such as the USA admit a high proportion of non-cancer patients to hospice inpatient units (30% in 1994-5),<sup>4</sup> the UK lags far behind, concentrating these services mainly on cancer patients with only a small proportion of hospice inpatients (4% in 1995) suffering from diseases other than cancer.<sup>5</sup>

Severe COPD and advanced lung cancer are both progressive diseases which are often managed by the same health care professionals such as primary care teams. However, the palliative care needs of patients with these two diseases have never previously been compared. The publication of the paper by Gore *et al* in this issue of *Thorax* is therefore of interest because it provides further evidence that the care needs of patients with severe COPD should be considered in the same way as those with lung cancer.<sup>6</sup> This is an important message for medical practice where the relevance of palliative care skills to patients with terminal non-malignant conditions is recognised but where the framework for extending these services beyond cancer patients is still in need of development.<sup>7</sup>

The aim of palliative care is the achievement of the best quality of life for patients and their families.<sup>8</sup> This aim is often assessed by measures of quality of life. The concept of quality of life, however, is complex and difficult to define, being both individual and multidimensional and, although many instruments exist which attempt to quantify it, measurement is difficult. In the medical context, quality of life is usually measured in terms of physical symptoms, psychological well being, and limitations on physical and social functioning. Thus, the majority of instruments in common use are health related quality of life (HRQoL) measures. Generic measures, which are applicable to anyone including those in good health, are useful for comparing diseases or for measuring disease related impairment by comparisons with data from "normal" populations. There is still some debate, however, about the applicability of generic instruments in chronic disease and the Medical Outcomes Study Short Form 36 (MOS SF-36), for example, has been shown to have limitations in some groups of

patients.<sup>9</sup> Disease specific instruments, by comparison, have items relevant to the condition being studied. They are therefore more sensitive to change and can be used to measure outcomes and evaluate the effects of treatment or other interventions. The St George's Respiratory Questionnaire (SGRQ)<sup>10</sup> and the Chronic Respiratory Disease Questionnaire (CRDQ)<sup>11</sup> are examples of questionnaires frequently used in studies of respiratory patients to measure HRQoL. In studies of COPD these instruments have shown how interventions such as rehabilitation programmes and inhaled corticosteroids can improve quality of life for patients.<sup>12 13</sup> They have also provided evidence that, as the disease progresses, quality of life declines but, in common with generic measures, they do not always correlate strongly with objective measures of physical function such as forced expiratory volume in one second (FEV<sub>1</sub>) in patients with COPD.<sup>14</sup> This reflects the fact that quality of life is not only a highly personal concept but also a dynamic one, changing as individuals adjust to changes in their health status and react to experience, interpersonal relationships, and altering roles.

In cancer studies the European Organisation for the Research and Treatment of Cancer Core questionnaire (EORTC QLQ-C30) and the site specific module LC-17 for lung cancer is a well validated and widely used outcome measure.<sup>15</sup> Many cancer studies now include HRQoL as an end point but sequential data for lung cancer are less common than for COPD as worsening symptoms and shorter survival times mean that drop out from studies is high. Some studies have reported longitudinal quality of life data for lung cancer patients using various instruments but these have mainly been concerned with demonstrating differences between treatment modalities.<sup>16</sup>

Gore *et al* propose that patients with COPD experience worse quality of life than those with lung cancer and that COPD care is less well resourced in the UK, despite the similar patterns of morbidity and mortality that both diseases produce. However, readers should be aware of the methodological limitations of this study which, while not entirely negating the conclusion, mean that some caution is needed in the interpretation of the results.

The sampling method used by the authors produced two study populations which are atypical in sex distribution and disease severity, and in length of survival in the lung cancer group. Of the 28 000 deaths from COPD in England and Wales in 1999, 56% were men and 44% were women. The male:female proportions were reversed in the study sample which, while it may be explained by local variations in the prevalence of COPD in men and women, is relevant here because the lung cancer group studied was biased toward male sex: 72% men/28% women compared with national figures of 62% and 38%, respectively. Health

surveys in random samples of the general population consistently report sex differences in physical symptom reporting, and female sex is associated with higher levels of symptomatology and lower self-reported health status.<sup>17</sup> Although this effect is not always seen in specific groups of cancer patients, it is relevant to the generic assessment of HRQoL. Women, both in cancer studies and in other diseases, also report higher anxiety levels measured by the Hospital Anxiety and Depression Scale (HADS).<sup>18</sup>

The medical criteria used for the selection of patients also have implications for the generalisability of the results. By selecting only COPD patients who had had at least one admission for hypercapnic respiratory failure, the authors may have excluded many more stable emphysematous patients with severe disease and an FEV<sub>1</sub> of less than 0.75 l. By intentionally identifying end stage COPD, they selected a group of very severely impaired patients whereas, in the cancer group, the median interval between diagnosis and interview of one year was twice the median survival time of about six months for patients with non-small cell lung cancer (NSCLC) in the UK. Thus, while not explicitly excluding patients with a poorer prognosis, failing to study a representative number of them has resulted in an atypical sample of patients with NSCLC.

The health related quality of life data presented in this paper gave generic and disease specific scores for two sample groups which showed the COPD group to be reporting worse quality of life on comparable dimensions. This is an important result, notwithstanding any reservations related to the study populations used, but the levels of impairment need to be placed in context in order to fully understand their meaning.

It is difficult to compare different studies of quality of life in lung cancer patients because of the large number of cancer specific instruments available to researchers and the various methods used to present the results. Gore *et al* commented that their patients reported disease specific scores comparable to those studied by Aaronson *et al* in 1993.<sup>19</sup> However, 90% of the patients in the study by Aaronson and coworkers had a good performance status (WHO grade 0–2) which is probably not typical of NSCLC overall. In comparison, a recent study of 65 patients in the Netherlands with a poorer performance status receiving palliative radiotherapy for previously untreated, locally advanced, or metastatic NSCLC reported lower EORTC scores for emotional function.<sup>20</sup> Similarly, the mean HADS scores are not easily comparable with other groups of NSCLC patients. Many authors opt for categorising HADS scores on the basis of “normal”, “borderline”, or “significant anxiety and depression” rather than quoting actual scores, while others present median scores and ranges which are appropriate summary statistics for this type of data.<sup>21 22</sup> However, we are aware of one paper which reported mean HADS scores for a random sample of 751 Norwegian inoperable or relapsed patients with a variety of cancers including lung cancer. Compared with this study, the patients studied by Gore *et al* appeared to score much better on the HADS scale. Although not directly comparable, the Norwegian patients are representative of those who would require palliative care services at some stage.<sup>18</sup>

Scores for the SGRQ range from 0 to 100 with higher scores representing a worse level of functioning. The mean (SD) total scores of 72 (14)% for the SGRQ support the view that these patients with COPD were experiencing very severe disease compared with those in other studies using the same instrument. The ISOLDE study<sup>12</sup> examined the effect of inhaled corticosteroids in 751 patients with moderate to severe COPD (FEV<sub>1</sub> 50% of predicted normal and at least 0.8 l after bronchodilator) and reported baseline mean (SD) total scores of just under

50% for the SGRQ (placebo group, n = 375: 49.9 (17.4)%; treatment group, n = 376: 47.7 (17.6)%).

Effectively, Gore *et al* have compared long term survivors with long term sufferers; as not enough is known about the way individuals value the many aspects of quality of life—particularly in relation to illness—this comparison is not straightforward. The diagnosis of cancer is a devastating and emotive one but not all its impacts are persistently negative. Cancer patients have been shown, for example, to report more positive social experiences than a random sample of the population, possibly as a result of relatives and friends being brought closer together in a time of crisis.<sup>23</sup> Depression measured on the HADS scale has also been shown to lessen as the interval from the diagnosis of cancer increases.<sup>18 24</sup> In COPD the pattern is different; social isolation is common, as in many chronic and progressive diseases, as dependency increases and the burden of caring becomes harder for relatives and friends to cope with. HADS depression scores for patients with COPD mirror this, worsening as the disease progresses.<sup>25</sup> Gore *et al* may indeed have identified a real and important difference in the overall quality of life in these two patient groups, but their findings need to be confirmed in further studies, ideally including NSCLC patients undergoing active treatment or those who have been diagnosed with more advanced disease.

The proposal that patients with COPD are less well served by the UK health care system than those suffering from lung cancer is one that respiratory health care professionals would intuitively accept. However, a survey by the British Thoracic Society in 1997<sup>26</sup> showed that fewer than 30% of lung cancer units then had access to a specialist cancer nurse. The assumption that there are more specialist cancer nurses than respiratory nurse specialists with an interest in COPD may therefore be flawed. Cancer is a high profile disease associated with death, pain, and suffering which touches the lives of many and is perceived as being worse than most other diseases by the general population. There is no doubt that more counselling and palliative care services are available for cancer patients, many funded by charitable organisations and staffed by volunteers. Patients with severe COPD are often disabled by their disease for longer, and have a mortality rate comparable to that of many common cancers. COPD should therefore be viewed as a disease with similarities to cancer and there is no moral reason to exclude this group of patients from a palliative care approach including access to inpatient facilities and outreach services. There is already good evidence to show that outreach support such as local rehabilitation programmes for patients with COPD improves quality of life and that the benefits are sustained.<sup>13</sup> Palliative care professionals are already extending their services to patients with motor neurone disease and HIV/AIDS. Although further comparisons would be useful, this paper adds to the evidence that palliative care has a role in chronic and debilitating non-malignant diseases. As Archie Cochrane wrote in 1972: “Cure is rare but the need for care is widespread . . .”.<sup>27</sup> In the case of chronic irreversible conditions like COPD this remains very true today.

K M HILL  
M F MUERS

Department of Respiratory Medicine,  
Leeds General Infirmary,  
Great George Street,  
Leeds LS1 3EX, UK  
[amajones@ulth.northy.nhs.uk](mailto:amajones@ulth.northy.nhs.uk)

1 Office of Population and National Statistics. *Annual report*. London: HMSO, 1999.

2 NHSE. *A policy framework for commissioning cancer services: palliative care services*. EL96. London: NHS Executive, 1996: 85.

- 3 Addington-Hall JM, Karlsen S. Age is not the crucial factor in determining how the palliative care needs of people who die from cancer differ from those of people who die from other causes. *J Palliat Care* 1999;15:13-9.
- 4 Lupu D. Hospice inpatient care: an overview of NHO's 1995 inpatient survey results. *Hospice J* 1996;11:21-39.
- 5 Eye A, Smith AM, Tebbitt P. Hospice and palliative care in the UK 1994-5, including a summary of trends 1990-5. *Palliat Med* 1997;11:31-43.
- 6 Gore JM, Brophy CJ, Greenstone MA. How well do we care for patients with end stage chronic obstructive pulmonary disease (COPD)? A comparison of palliative care and quality of life in COPD and lung cancer. *Thorax* 2000;55:1000-6.
- 7 Saunders C, Baines M. *Living with dying: the management of terminal disease*. Oxford: Oxford University Press, 1983.
- 8 Johnston G, Abraham C. The WHO objectives for palliative care: to what extent are we achieving them? *Palliat Med* 1995;9:123-37.
- 9 McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993;31:247-63.
- 10 Jones PW, Quirk FH, Baveystock CM. A self-complete measure of health status for chronic airflow limitation. *Am Rev Respir Dis* 1992;144:1321-7.
- 11 Guyatt GH, Berman LB, Townshend M, et al. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;42:773-8.
- 12 Burge PS, Calverley PMA, Jones PW, et al on behalf of the ISOLDE study investigators. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000;320:1297-303.
- 13 Lacasse Y, Wong E, Guyatt GH, et al. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. *Lancet* 1996;348:1115-9.
- 14 Bestall JC, Paul EA, Garrod R, et al. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54:581-6.
- 15 Bergman B, Aaronson NK, Ahmedzai S, et al. for the European Organisation for Research and Treatment of Cancer (EORTC) Study Group on Quality of Life. The EORTC QLQ LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. *Eur J Cancer* 1994;30A: 635-42.
- 16 Helsing M, Bergman B, Thaning L, et al. Quality of life and survival in patients with advanced non-small cell lung cancer receiving supportive care plus chemotherapy with carboplatin and etoposide or supportive care only: a multi-centre randomised phase III trial. Joint Lung Cancer Study Group. *Eur J Cancer* 1998;34:1036-44.
- 17 Van Wijk CM, Kolk AM. Sex differences in physical symptoms: the contribution of symptom perception theory. *Soc Sci Med* 1997;45:231-46.
- 18 Aass N, Fossa SD, Dahl AA, et al. Prevalence of anxiety and depression in cancer patients seen at the Norwegian Radium Hospital. *Eur J Cancer* 1997;33:1597-604.
- 19 Aaronson NK, Ahmedzai S, Bergman B, et al. The EORTC QLQ-C30: a quality of life instrument for use in clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365-75.
- 20 Langendijk JA, ten Velde GP, Aaronson NK, et al. Quality of life after palliative radiotherapy in non-small cell lung cancer: a prospective study. *Int J Radiat Oncol Biol Phys* 2000;47:149-55.
- 21 Bailey AJ, Parmar MK, Stephens RJ. Patient-reported short-term and long-term physical and psychological symptoms: results of the continuous hyperfractionated accelerated radiotherapy (CHART) randomized trial in non-small-cell lung cancer. CHART Steering Committee. *J Clin Oncol* 1997;16:3082-93.
- 22 Bredin M, Corner J, Krishnasamy M, et al. Multi-centre randomised controlled trial of nursing intervention for breathlessness in patients with lung cancer. *BMJ* 1999;318:901-4.
- 23 Tempelaar R, De Haes JC, De Ruiter JH, et al. The social experiences of cancer patients under treatment: a comparative study. *Soc Sci Med* 1998;29:635-42.
- 24 Ford S, Lewis S, Fallowfield L. Psychological morbidity in newly referred patients with cancer. *J Psychosomatic Res* 1995;39:193-202.
- 25 Williams SJ. *Chronic respiratory illness*. London: Routledge, 1993.
- 26 British Thoracic Society (BTS) Standards of Care Committee. *Survey of resources used by respiratory physicians for the diagnosis and management of lung cancer*. London: BTS, 1997.
- 27 Cochrane A. *Effectiveness and efficiency*. London: Nuffield Provincial Hospitals Trust, 1972.

*Thorax* 2000;55:981-983

## Management of malignant pleural effusions

G Antunes, E Neville

Malignant pleural effusion is a common problem in respiratory medicine and oncology and in some series accounts for up to 50% of all pleural effusions.<sup>1,2</sup> The median survival following diagnosis ranges from three to 12 months and is largely dependent upon the underlying malignancy. Currently, lung cancer is the most common metastatic tumour to the pleura in men and breast cancer in women. Both malignancies account for 50-65% of all malignant effusions while lymphomas, genitourinary, and gastrointestinal tumours account for a further 25%, and 7-15% of all malignant effusions have no identifiable primary.<sup>3-5</sup>

Malignant effusions result predominantly from obstruction and disruption of lymphatic channels by malignant cells. However, vascular endothelial growth factor (VEGF), a potent angiogenic mediator and promoter of endothelial permeability, is produced in significant amounts by diseased pleural tissue and is thought to play a part in the formation of malignant effusions and local tumour growth.<sup>6,7</sup>

The general approach to managing malignant effusions is determined by symptoms (dyspnoea, exercise tolerance limitation, and chest discomfort), performance status of the patient, expected survival, and response of the known primary tumour to systemic treatment. Intervention options range from observation in the case of asymptomatic effusions through simple thoracentesis to more invasive methods such as thoracoscopy, pleuroperitoneal shunting, and pleurectomy. Repeated aspiration is favoured in patients with limited survival and poor performance status and obviates lengthy hospitalisation. In the patient with reasonable survival expectancy and good per-

formance status, every attempt should be made to prevent recurrence of the effusion. Intercostal tube drainage with instillation of a sclerosing agent, resulting in the obliteration of the pleural space, is the most widely used and cost effective method to control recurrent symptomatic malignant effusions.

### Size of drainage tube

Over the last two decades several new developments have modified the method originally described by Adler and Sayek.<sup>8</sup> By convention, large bore intercostal tubes (size 24-32 F) have been used for drainage of malignant effusions and intrapleural administration of sclerosing agents. These large tubes are frequently associated with significant discomfort to patients and restrict mobility. Studies using small bore catheters (8-14 F) have reported similar success rates to those using large bore tubes, and small bore catheters are better tolerated and associated with less discomfort.<sup>9-12</sup> In the only controlled randomised study published to date, no significant difference was seen in the pleurodesis success rate but larger randomised studies are required to confirm these results.<sup>13</sup> A further potential advantage of the small bore catheter is in the area of ambulatory treatment of malignant effusions. Patz *et al*, using small bore catheters (10 F) and bleomycin as a sclerosing agent, achieved a modest pleurodesis success rate of 79% in outpatients.<sup>14</sup>

### When to sclerose

Lung re-expansion remains the most important requisite for successful pleural symphysis and sclerotherapy failures usually occur when complete lung re-expansion is not

achieved. The minimum amount of pleural fluid drainage (normally taken to be less than 150 ml/day) before sclerotherapy appears to be less relevant for successful pleurodesis than confirmation of lung re-expansion radiologically.<sup>15</sup> The role of intrapleural fibrinolytic agents in the management of malignant effusions is in its infancy and remains controversial.<sup>16 17</sup>

### Patient rotation and tube clamping

Rotation of the patient following intrapleural administration of a sclerosing agent is no longer thought to be critical to achieve distribution of the agent throughout the pleural space. Recent evidence using radiolabelled tetracycline revealed that the agent is dispersed throughout the pleural space within seconds in a fairly uniform fashion.<sup>18</sup> A subsequent clinical randomised trial found no significant difference in the success rate or duration of fluid drainage between the rotated and non-rotated patients.<sup>19</sup>

The practice of clamping of intercostal tubes or catheters following instillation of a sclerosing agent is to be discouraged. The reasons for this are based on the rapid dispersion of the sclerosing agent, potential complications such as tension pneumothorax in the presence of an unsuspected persistent air leak, and a lack of good evidence for its use. Removal of the intercostal tube or catheter should occur within 72 hours of sclerotherapy provided the lung remains fully expanded and there is a reduction in the rate of fluid drainage.

### Sclerosing agents

The ideal sclerosing agent will have a high molecular weight, low regional and rapid systemic clearance, a steep dose/response curve, and be well tolerated with minimal side effects. Despite the evaluation of a large number of agents, no ideal sclerosing agent exists. Poor study design and disparate criteria for measuring response hamper proper comparison of these agents. The choice of a sclerosing agent is thus largely dependent on the success rate or efficacy, accessibility, safety, ease of administration, and cost.

Tetracycline was, until 1998, the most popular and widely used sclerosing agent via an intercostal tube in the UK when its production was discontinued by the manufacturer following its discontinuation in the USA in 1992.<sup>20</sup> Tetracycline may still be imported from Europe (Germany) at present but this supply may also cease in the near future. Tetracycline has a modest efficacy (average success rate 65%), an excellent safety profile, and it is relatively inexpensive. It is well tolerated and side effects are infrequent, mild, and transient.<sup>21</sup> Other tetracycline derivatives such as doxycycline and minocycline have only been evaluated in small uncontrolled trials and neither is available in the UK.<sup>22 23</sup>

Bleomycin is the most widely used antineoplastic agent for sclerotherapy. Its mechanism of action is predominantly as a chemical sclerosing agent similar to tetracycline and sterile talc. It is an effective sclerosant with an average success rate of 60% and has an acceptable side effect profile. However, its major limitation is the cost per treatment.<sup>21</sup>

Sterile talc is a trilayered magnesium silicate sheet and was first used as a sclerosing agent in 1935.<sup>24</sup> The modern preparation is asbestos-free and is administered either as talc poudrage at the time of thoracoscopy using an atomiser or as talc slurry via an intercostal tube. Success rates for talc poudrage and slurry range from 80% to 100%.<sup>25-28</sup> Earlier studies quoted higher success rates for talc poudrage than for talc slurry but Yim *et al* recently found no significant difference between the two methods with respect to success rate, duration of chest drainage,

hospital stay, and complications.<sup>29</sup> Talc is usually well tolerated and the most common side effects reported are pleuritic chest pain and fever.

Adult respiratory distress syndrome (ARDS) or acute talc pneumonitis is a rare and occasionally fatal complication of intrapleural administration of talc. The precise mechanism leading to acute pneumonitis is unclear and has been reported with both talc poudrage and slurry.<sup>25 30</sup> ARDS or talc pneumonitis appears to be dose related, most cases having been associated with doses in excess of 5 g. In a recent study by York *et al* talc pneumonitis was reported in eight cases of a series of 125 patients who underwent talc slurry pleurodesis with a dose of 5 g.<sup>31</sup> Closer scrutiny of the study shows that five patients had radiological features consistent with ARDS and only two patients required mechanical ventilation. All eight cases received high dose corticosteroids and survived to hospital discharge.

Recent data in lower mammal studies using equivalent doses of talc per kg have shown distribution of talc particles beyond the lung to distant organs such as the kidneys and brain.<sup>32-34</sup> In the rat model absorption through the pleura was not dose related.<sup>32</sup> Distribution of talc particles and its clinical relevance in humans with diseased pleura has not yet been studied. The findings in lower mammals should be interpreted with caution as there are significant anatomical and physiological differences and all the studies were carried out in animals with normal pleura.

Forthcoming guidelines will recommend either talc slurry, tetracycline, or talc poudrage depending on local availability both of agents and thoracoscopy service.<sup>35</sup>

### Surgical options

Pleuroperitoneal shunting is an acceptable palliative option in patients with trapped lung and large refractory malignant effusions. Insertion of the shunt is facilitated by thoracoscopy or mini-thoracotomy and is usually well tolerated.<sup>36</sup> Complications such as shunt occlusion, infection, and tumour seeding are not infrequent and have contributed to its low popularity. Although open pleurectomy is a very effective method of achieving pleurodesis, it has an unacceptable morbidity and mortality rate.<sup>37</sup> Video-assisted thoracoscopic pleurectomy appears to be a promising and much safer technique although experience is limited and it is not widely available.<sup>38</sup>

Video-assisted thoracoscopic surgery (VATS) and medical thoracoscopy are widely used in continental Europe and North America for both diagnostic and therapeutic purposes in malignant effusions.<sup>39 40</sup> Malignant effusions are the leading indication for such procedures with a high diagnostic yield of more than 90%. Their therapeutic role is well studied with pleurodesis success rates (talc poudrage) of over 90%.<sup>28</sup> The main indications for referral are pleural effusions of undetermined aetiology after repeated pleural fluid analysis and refractory malignant effusions unresponsive to pleurodesis via an intercostal tube.

### Conclusions

There have been several advancements in the management of malignant pleural effusions over the last two decades, but further research is required. The exact mechanisms involved in the formation of malignant effusions have yet to be fully elucidated. Technical aspects such as the most appropriate intercostal tube or catheter size need to be established. Although sterile talc is the most effective sclerosing agent available at present, it is associated with a potentially life threatening—albeit rare—complication and further efforts should be made to find an alternative agent. The potential role of thoracoscopy is yet to be fully realised in both the diagnosis and treatment of malignant pleural

effusions. Only by answering some of these remaining questions will we improve the prognosis and outlook of this subgroup of patients with malignant disease.

G ANTUNES  
E NEVILLE

Respiratory Centre,  
St Mary's Hospital,  
Portsmouth PO3 6AD, UK

- Leuallen EC, Carr DT. Pleural effusion. A statistical study of 436 patients. *N Engl J Med* 1955;252:79–83.
- Storey DD, Dines DE, Coles DT. Pleural effusion: a diagnostic dilemma. *JAMA* 1976;236:2183–6.
- Chernow B, Sahn SA. Carcinomatous involvement of the pleura. *Am J Med* 1977;63:695–702.
- Molengraaf van de FJMM, Vooijs GP. Survival of patients with malignancy-associated effusions. *Acta Cytol* 1989;33:911–6.
- Abbruzzese JL, Abbruzzese MC, Hess KR, et al. Unknown primary carcinoma: natural history and prognostic factors in 657 consecutive patients. *J Clin Oncol* 1994;12:1272–80.
- Cheng D, Rodriguez RM, Perrett EA, et al. Vascular endothelial growth factor in pleural fluid. *Chest* 1999;116:760–5.
- Kraft A, Weindel K, Ochs A, et al. Vascular endothelial growth factor in the sera and effusions with malignant and nonmalignant disease. *Cancer* 1999;85:178–87.
- Adler RH, Sayek I. Treatment of malignant pleural effusion: a method using tube thoracostomy and talc. *Ann Thorac Surg* 1976;22:8–15.
- Parker LA, Charnock GC, Delany DJ. Small bore catheter drainage and sclerotherapy for malignant effusions. *Cancer* 1989;64:1218–21.
- Morrison MC, Mueller PR, Lee MJ, et al. Sclerotherapy of malignant pleural effusion through sonographically placed small-bore catheters. *AJR* 1992;158:41–3.
- Seaton KG, Patz EF Jr, Goodman PC. Palliative treatment of malignant pleural effusions: value of small-bore catheter thoracostomy and doxycycline sclerotherapy. *AJR* 1995;164:589–91.
- Patz EF Jr, McAdams HP, Erasmus JJ, et al. Sclerotherapy for malignant pleural effusions: a prospective randomized trial of bleomycin vs doxycycline with small-bore catheter drainage. *Chest* 1998;113:1305–11.
- Clements P, Ewald T, Grode G, et al. Treatment of malignant pleural effusion: pleurodesis using a small percutaneous catheter. A prospective randomized study. *Respir Med* 1998;92:593–6.
- Patz EF Jr, McAdams HP, Goodman PC, et al. Ambulatory sclerotherapy for malignant pleural effusions. *Radiology* 1996;199:133–5.
- Villanueva AG, Gray AW Jr, Shahian DM, et al. Efficacy of short term versus long term thoracostomy drainage before tetracycline pleurodesis in the treatment of malignant pleural effusions. *Thorax* 1994;49:23–5.
- Davies CWH, Traill ZC, Gleeson FV, Davies RJO. Intrapleural streptokinase in the management of malignant multiloculated pleural effusions. *Chest* 1999;115:729–33.
- Gilkeson RC, Silverman P, Haaga JR. Using urokinase to treat malignant pleural effusions. *AJR* 1999;173:781–3.
- Lorch DG, Gordon L, Wooten S, et al. Effect of patient positioning on distribution of tetracycline in the pleural space during pleurodesis. *Chest* 1988;93:527–9.
- Dryzer SR, Allen ML, Strange C, et al. A comparison of rotation and non-rotation in tetracycline pleurodesis. *Chest* 1993;104:1763–6.
- Hefner JE, Unruh LC. Tetracycline pleurodesis: adios, farewell, adieu. *Chest* 1992;101:64–6.
- Walker-Renard PB, Vaughan LM, Sahn SA. Chemical pleurodesis for malignant pleural effusions. *Ann Intern Med* 1994;120:56–64.
- Hefner JE, Standerfer RJ, Torstveit J, et al. Clinical efficacy of doxycycline for pleurodesis. *Chest* 1994;105:1743–7.
- Hatta T, Tsubuota N, Yoshimura M, et al. Effect of intrapleural administration of minocycline on postoperative air leakage and malignant pleural effusions. *Kyobu Geka* 1990;43:283–6.
- Bethune N. Pleural poudrage: new technique for deliberate production of pleural adhesions as a preliminary to lobectomy. *J Thorac Surg* 1935;4:251–61.
- Kennedy L, Rusch VW, Strange C, et al. Pleurodesis using talc slurry. *Chest* 1994;106:342–6.
- Webb WR, Ozmen V, Moulder PV, et al. Iodized talc pleurodesis for the treatment of pleural effusions. *J Thorac Cardiovasc Surg* 1992;103:881–5.
- Yim AP, Chung SS, Lee TW, et al. Thoracoscopic management of malignant pleural effusions. *Chest* 1996;109:1234–8.
- Viallat J-R, Rey F, Astoul P, et al. Thoracoscopic talc poudrage pleurodesis for malignant effusions. A review of 360 cases. *Chest* 1996;110:1387–93.
- Yim AP, Chan ATC, Lee TW, et al. Thoracoscopic talc insufflation versus talc slurry for symptomatic malignant pleural effusion. *Ann Thorac Surg* 1996;62:1655–8.
- Bouchama A, Chastre J, Gaudichet A, et al. Acute pneumonitis with bilateral pleural effusion after talc pleurodesis. *Chest* 1984;86:795–7.
- York A, Bondoc P, Bach P, et al. Talc pneumonitis: incidence, clinical features and outcome. *Chest* 1999;116(Suppl):358–9S.
- Werebe EC, Pazetti R, Milanez de Campos JR, et al. Systemic distribution of talc after intrapleural administration in rats. *Chest* 1999;115:190–3.
- Light RW, Wang N-S, Sassoon CSH, et al. Talc slurry is an effective pleural sclerosant in rabbits. *Chest* 1995;107:1702–6.
- Kennedy L, Harley RA, Sahn SA, et al. Talc slurry pleurodesis. Pleural fluid and histologic analysis. *Chest* 1995;107:1707–12.
- Antunes G, Neville E, Duffy J, et al. British Thoracic Society guidelines: management of malignant pleural effusions. 2000 (in preparation).
- Petrou M, Kaplan D, Goldstraw P. Management of recurrent malignant pleural effusions. The complementary role of talc pleurodesis and pleuroperitoneal shunting. *Cancer* 1995;75:801–5.
- Martini N, Bains MS, Beattie EJ Jr. Indications for pleurectomy in malignant effusion. *Cancer* 1975;35:734–8.
- Waller DA, Morritt GN, Forty J. Video-assisted thoracoscopic pleurectomy in the management of malignant pleural effusion. *Chest* 1995;107:1454–6.
- Menzies R, Charbonneau M. Thoracoscopy for the diagnosis of pleural disease. *Ann Intern Med* 1991;114:271–6.
- Loddenkemper R. Thoracoscopy: state of the art. *Eur Respir J* 1998;11:213–21.

*Thorax* 2000;55:983–985

## Obtaining tissue from the mediastinum: endoscopic ultrasound guided transoesophageal biopsy

S A Roberts

Endoluminal or endoscopic ultrasound (EUS) was first attempted in 1957 by Wild and Reid who placed a mechanical ultrasound transducer in the rectum.<sup>1</sup> It was not until 1975 that the upper gastrointestinal tract was examined when Rasmussen *et al*<sup>2</sup> measured the stomach wall thickness with a 6 MHz transducer passed through the biopsy channel of a gastrocope. In the 1980s, with the development of a dedicated endoscope incorporating a mechanical ultrasound transducer, EUS became important in clinical practice. Accurate local and nodal staging of oesophageal, gastric, and pancreatic tumours<sup>3–6</sup> and assessment of stone disease in the biliary tract<sup>7</sup> established EUS in the investigation of gastrointestinal disease. The accurate detection of mediastinal lymph nodes in oesophageal cancer had obvious implications for patients with lung cancer, and the role of EUS in lung cancer was first described in Japan in 1988.<sup>8</sup> Further work confirmed the

superior accuracy of EUS in the nodal staging of lung cancer compared with computed tomographic (CT) scanning,<sup>9</sup> although EUS is not yet used routinely in the preoperative staging of lung cancer in the UK.

Further technical advancement led to the development of the linear EUS probe. This allows passage of a needle down the biopsy channel of the endoscope, through the wall of the gastrointestinal tract, and into adjacent structures such as lymph nodes. The orientation of the ultrasound beam, parallel rather than perpendicular to the long axis of the endoscope, allows continuous ultrasound monitoring of the needle tip. Several studies have shown that transoesophageal EUS guided fine needle aspiration (EUS-FNA) is a simple, relatively non-invasive method of obtaining tissue from various nodal stations in the mediastinum.<sup>10–12</sup> Only the anterior mediastinum is off limits because of air in the trachea. It is performed as a day

case in most patients, it is safe, and requires only conscious sedation. Complications related to EUS-FNA reported by Wiersema *et al* in 457 patients with 554 lesions occurred in only three patients who underwent aspiration of cystic pancreatic lesions (haemorrhage and fever). This series included 192 peri-intestinal lymph node biopsies with no complications.<sup>13</sup>

Does the technique have a role? Sensitivities of 85–92%<sup>13 14</sup> for malignancy in lymph nodes suggest that EUS-FNA is worth considering before more invasive techniques. For example, EUS-FNA can be used before mediastinoscopy where bronchoscopic biopsy specimens have failed to provide a tissue diagnosis. Fritscher-Ravens *et al* describe 16 patients with an intrapulmonary lesion on the chest radiograph or CT scan who had inconclusive pathology results obtained at bronchoscopy with forceps biopsy and/or brush cytology.<sup>15</sup> Of the 10 patients with a final diagnosis of malignancy, this was established with EUS-FNA in nine. Transcarinal needle aspiration was not performed in this study which might have obviated the need for EUS-FNA in some of these patients.

A more systematic approach to the role of EUS-FNA has been explored as part of a routine staging protocol for patients with known or presumed lung cancer.<sup>10 12</sup> Gress *et al*<sup>12</sup> reported that EUS-FNA avoided unnecessary surgery in 14 of 24 patients, confirming N2 disease in two and N3 disease in 12 patients. Mediastinoscopy, altogether more invasive and expensive than EUS-FNA, was avoided in all 24 patients with only one false negative result. Aabakken *et al* have also shown that EUS-FNA is a cost effective alternative to mediastinoscopy/mediastinotomy in a comparison using a cost effectiveness model.<sup>16</sup> However, there are few proper comparative data between the techniques. Despite small patient numbers, in the only comparative study of EUS-FNA with mediastinoscopy to date Serna *et al* reasonably concluded that the techniques may be complementary, mediastinoscopy targeting the upper and anterior mediastinum and EUS-FNA targeting subcarinal and posterior mediastinal lesions.<sup>17</sup> Further comparative data are required to assess properly its role as part of formal lung cancer staging protocols but the initial pointers are favourable.

Let us briefly consider some of the other relatively non-invasive techniques for obtaining tissue. Percutaneous needle biopsy with CT guidance is an alternative which was reported to have a remarkably high sensitivity of 98% (40 of 41) for diagnosing carcinoma in one series,<sup>18</sup> although this was in a selected population thought to have lung cancer. In the same series, however, pneumothorax occurred in 34% of patients with a chest tube being required in 14%. Another limiting factor in this study was that biopsy samples were only taken from nodes with a diameter greater than 1.5 cm, although biopsy samples were successfully taken from nodes with a diameter of 1.2 cm in another series<sup>19</sup> which again had a significant pneumothorax rate of 22%. In our experience nodes of less than 1 cm in diameter can be aspirated relatively easily and without complication with EUS-FNA.<sup>20</sup> Although there are disadvantages to the percutaneous approach, particularly the higher complication rate, a major advantage is that no specialist equipment is necessary as virtually all district hospitals have a CT scanner. This, of course, assumes that the radiological skill, inclination, and time to take biopsy samples is available.

Transbronchial/carinal needle aspiration (TCNA) performed at the time of flexible bronchoscopy has a variable yield and sensitivities ranging from 34% to 89%.<sup>21–23</sup> More recently there have been preliminary reports of the procedure being assisted by CT scanning or endobronchial ultrasound. With CT guidance the sensitivity increased from 20% to 60%<sup>24</sup> and, on a per node basis, a sensitivity

of 88% was achieved when guided by virtual bronchoscopy.<sup>25</sup> Shannon *et al* reported that EUS guidance reduces the number of passes required, but does not increase the already high yield without guidance.<sup>26</sup> The sensitivities with and without EUS guidance were 82% and 90%, respectively, in this series with on site cytopathology. One of the problems with TCNA is that the promising results obtained in academic centres have not necessarily been repeated in smaller units. This variability in yield may have prevented the more widespread use of the technique. When used for staging lung cancer, concerns about TCNA have also been raised regarding false positive results caused by contamination of the specimen with malignant cells from the lumen.<sup>27 28</sup> This should not be a problem with the transoesophageal approach.

In conclusion, the role of EUS-FNA in assessing mediastinal pathology needs greater attention. It is clearly a useful technique and the tissue obtained safely and relatively non-invasively will influence patient management in the majority of cases. There are no more than five centres performing this procedure in the UK; three years ago there was only one. For a proper assessment of its role in preoperative staging of lung cancer, more centres need to perform the technique which is relatively simple to learn and appropriate comparative studies could then be set up. EUS-FNA was primarily developed with gastrointestinal disease in mind, particularly staging and obtaining tissue from pancreatic cancer. Biopsy specimens can also be taken from lymph nodes adjacent to the gastrointestinal tract below the diaphragm. The indications have expanded further with EUS guided pancreatic pseudocyst drainage and coeliac plexus neurolysis for pain relief. The ultrasound machine required (Hitachi) can be used for general ultrasound work and the cost of setting up this service may be spread by consultation with gastrointestinal and radiological colleagues. EUS has moved on considerably from the rectum since 1957 and there is now adequate evidence for an increased role in the management of a number of diseases across several specialities.

S A ROBERTS

Singleton Hospital,  
Swansea SA2 8QA, UK  
[ashley.roberts@swansea-tr.wales.nhs.uk](mailto:ashley.roberts@swansea-tr.wales.nhs.uk)

- 1 Wild JJ, Reid JM. In: Kelly E, ed. *Ultrasound in biology and medicine*. Volume 1. American Institute of Biological Sciences, 1957: 30–45.
- 2 Rasmussen SN, Riis P, Northeved A, *et al*. Ultrasonographic measurements of the rectal and gastric wall thickness. *Scand J Gastroenterol* 1975; **10**(Suppl 34):25.
- 3 Tio TL, Cohen P, Cohen PP, *et al*. Endosonography and computed tomography of esophageal carcinoma. *Gastroenterology* 1989;**96**:1478–86.
- 4 Botet JF, Lightdale CJ, Zaubler AG, *et al*. Preoperative staging of esophageal cancer: comparison of endoscopic us and dynamic CT. *Radiology* 1991;**181**:419–25.
- 5 Ziegler K, Sanft C, Zimmer T, *et al*. Comparison of computed tomography, endosonography and intraoperative assessment in TN staging of gastric carcinoma. *Gut* 1993;**34**:604–10.
- 6 Muller F, Meyenberger C, Bertschinger P, *et al*. Pancreatic tumours: evaluation with endoscopic US, CT and MR imaging. *Radiology* 1994;**190**:745–51.
- 7 Amouyal P, Amouyal G, Levy P, *et al*. Diagnosis of choledocholithiasis by endoscopic ultrasonography. *Gastroenterology* 1994;**106**:1062–7.
- 8 Kobayashi H, Danbara T, Tamaki S, *et al*. Detection of the mediastinal lymph node metastasis in lung cancer by endoscopic ultrasonography. *Japan J Med* 1988;**27**:17–22.
- 9 Hawes RH, Gress F, Kesler KA, *et al*. Endoscopic ultrasound versus computed tomography in the evaluation of the mediastinum in patients with non-small cell lung cancer. *Endoscopy* 1994;**26**:784–7.
- 10 Silvestri GA, Hoffman BJ, Bhutani MS, *et al*. Endoscopic ultrasound with fine-needle aspiration in the diagnosis and staging of lung cancer. *Ann Thorac Surg* 1996;**61**:1441–6.
- 11 Wiersema M, Kochman M, Cramer H, *et al*. Preoperative staging of non-small cell lung cancer: transoesophageal US-guided fine needle aspiration biopsy of mediastinal lymph nodes. *Radiology* 1994;**190**:239–42.
- 12 Gress FG, Savides TJ, Sandler A, *et al*. Endoscopic ultrasonography, fine-needle aspiration biopsy guided by endoscopic ultrasonography, and computed tomography in the preoperative staging of non-small-cell lung cancer: a comparison study. *Ann Intern Med* 1997;**127**:604–12.
- 13 Wiersema MJ, Vilmann P, Giovannini M, *et al*. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology* 1997;**112**:1087–95.

- 14 Williams DB, Sahai AV, Aabakken L, *et al*. Endoscopic ultrasound guided fine needle aspiration biopsy: a large single centre experience. *Gut* 1999;**44**:720–6.
- 15 Fritscher-Ravens A, Petrasch S, Reinacher-Schick A, *et al*. Diagnostic value of endoscopic ultrasonography-guided fine-needle aspiration cytology of mediastinal masses in patients with intrapulmonary lesions and nondiagnostic bronchoscopy. *Respiration* 1999;**66**:150–5.
- 16 Aabakken L, Silvestri GA, Hawes R, *et al*. Cost-efficacy of endoscopic ultrasonography with fine-needle aspiration vs. mediastinotomy in patients with lung cancer and suspected mediastinal adenopathy. *Endoscopy* 1999;**31**:707–11.
- 17 Serna DL, Aryan HE, Chang KJ, *et al*. An early comparison between endoscopic ultrasound guided fine needle aspiration and mediastinoscopy for diagnosis of mediastinal malignancy. *The American Surgeon* 1998;**64**:1014–8.
- 18 Protopapas Z, Westcott JL. Transthoracic needle biopsy of mediastinal lymph nodes for staging lung cancer. *Radiology* 1996;**199**:489–96.
- 19 Akamatsu H, Terashima M, Koike T, *et al*. Staging of primary lung cancer by computed tomography-guided percutaneous needle cytology of mediastinal lymph nodes. *Ann Thorac Surg* 1996;**62**:352–5.
- 20 Roberts SA, Davies G, Howell S, *et al*. Endoscopic ultrasound guided biopsy of sub-carinal lymph nodes. *Clin Radiol* 2000 (in press).
- 21 Gay P, Brutinel W. Transbronchial needle aspiration in the practice of bronchoscopy. *Mayo Clin Proc* 1989;**64**:158–62.
- 22 Wang K, Brower R, Haponik E, *et al*. Flexible transbronchial needle aspiration for staging bronchogenic carcinoma. *Chest* 1983;**84**:571–6.
- 23 Harrow E, Oldenburg FA Jr, Lingenfelter MA, *et al*. Transbronchial needle aspiration in clinical practice. *Chest* 1989;**96**:1268–72.
- 24 Rong F, Cui B. CT scan directed transbronchial needle aspiration biopsy for mediastinal nodes. *Chest* 1998;**114**:36–9.
- 25 Ewert R, Dorffel W, Rogalla P, Mutze S. Computed tomography guided transtracheal needle aspiration of paratracheal lymphadenopathy in endoscopically normal patients. *Invest Radiol* 1997;**32**:667–70.
- 26 McAdams HP, Goodman PC, Kussin P. Virtual bronchoscopy for directing transbronchial needle aspiration of hilar and mediastinal lymph nodes: a pilot study. *AJR* 1998;**170**:1361–4.
- 27 Cropp AJ, DiMarco AF, Lankerani M. False-positive transbronchial needle aspiration in bronchogenic carcinoma. *Chest* 1984;**85**:696–7.
- 28 Schenk DA, Bower JH, Bryan CL, *et al*. Transbronchial needle aspiration staging of bronchogenic carcinoma. *Am Rev Respir Dis* 1986;**134**:146–8.



## Palliative care for patients with non-malignant end stage respiratory disease

K M HILL and M F MUERS

*Thorax* 2000 55: 979-981

doi: 10.1136/thorax.55.12.979

---

Updated information and services can be found at:

<http://thorax.bmj.com/content/55/12/979.full.html>

---

*These include:*

### References

This article cites 16 articles, 9 of which can be accessed free at:

<http://thorax.bmj.com/content/55/12/979.full.html#ref-list-1>

Article cited in:

<http://thorax.bmj.com/content/55/12/979.full.html#related-urls>

### Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

---

### Topic Collections

Articles on similar topics can be found in the following collections

- [Hospice](#) (49 articles)
- [Lung cancer \(oncology\)](#) (374 articles)
- [Lung cancer \(respiratory medicine\)](#) (374 articles)
- [Lung neoplasms](#) (336 articles)
- [Epidemiologic studies](#) (1094 articles)
- [Airway biology](#) (855 articles)
- [Drugs: respiratory system](#) (363 articles)
- [General practice / family medicine](#) (198 articles)
- [Lung function](#) (638 articles)

---

### Notes

---

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>