Should pulmonary rehabilitation be a standard of care in lung cancer?

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There are few therapeutic interventions as effective as pulmonary rehabilitation (PR) in the management of the chronic respiratory disease. The scientific evidence base demonstrating the clinical benefit of PR is incontestable, indeed the most recent iteration of the Cochrane systematic review summarising clinical trials of PR in chronic obstructive pulmonary disease (COPD) concluded that no further clinical trials testing effectiveness were needed.[1] The gains in physical capacity and health-related quality of life conferred by PR in routine clinical practice are comparable to those seen in clinical trials[2] and the available evidence suggests that completion of PR reduces subsequent healthcare costs through a reduction in the number of days spent in the hospital.[3] This substantial body of evidence is derived largely from studies in people with COPD but, perhaps unsurprisingly, PR is also effective in other chronic respiratory diseases characterised by exercise limitation due to dyspnoea and muscle fatigue such as bronchiectasis, interstitial lung disease and pulmonary hypertension. This benefit, long understood by rehabilitation practitioners in the field, is increasingly now backed up by clinical trials of PR in these specific patient populations.[4–6]

In this issue of the journal, Edbrooke and colleagues further extend our understanding of the broader role of PR in respiratory disease by undertaking a clinical trial of a home-based rehabilitation intervention in patients receiving non-surgical therapy for lung cancer.[7] The trial aimed to encourage participation in an 8-week programme of structured, progressive physical activity and exercise while volunteers were also attending medical centres for active cancer treatment (chemotherapy or radiotherapy, commenced no more than 4 weeks prior to enrolment). On the face of it, there is a strong rationale for such an intervention; patients presenting with inoperable lung cancer frequently have low-performance status, poor exercise capacity and are physically inactive.[8] Rehabilitation has the potential to improve quality of life by modifying these deficits and could theoretically increase the likelihood of successful completion of active cancer therapy. However, the trial did not show a statistically significant between-group difference in 6 min walking distance (6MWD) at 9 weeks (the primary endpoint) although there were significant differences in health status in favour of the rehabilitation group after 6 months. The authors considered adherence to the exercise component of the intervention to be sub-optimal with only around half the participants in the rehabilitation group maintaining adherence to the prescribed training component, speculating that this was the explanation for the lack of efficacy.

The authors can be congratulated on successfully conducting a detailed and well-designed trial in a group of patients likely to have a significant rehabilitation need. The study was adequately assessor blinded and the sample size sufficient to detect the *a priori* defined meaningful treatment effect for the primary endpoint. The lack of efficacy (at least for the primary outcome measure) might also have been explained by the outcome measure chosen and the setting of the rehabilitation intervention. Patients could be included if they reported not achieving guideline prescribed levels of physical activity in the previous month. However, given that the month in question must have been the immediate aftermath of a diagnosis of lung cancer, this estimate may not have been representative of the subjects normal activity (and thereby fitness). In support of this, values for 6MWD at baseline were not especially low and this might have reduced the sensitivity of the 6MWD to detect an improvement in physical performance because of a ceiling effect. The authors chose to deliver a home-based, rather than directly supervised rehabilitation intervention, presumably because this was felt to be more acceptable/practical for volunteers who were also attending healthcare centres regularly for cancer treatment. There are indications from recent trials in COPD that home or self-managed PR may have equivalent efficacy to conventional supervised programmes, although the magnitude of benefit seen across treatment arms in these trials have not always matched those seen for conventional PR in clinical practice.[9 10] It is possible that the challenge of seeing through active chemotherapy or radiotherapy, combined with rather distant supervision of the programme (mostly by telephone) resulted in an exercise intensity insufficient to translate into a meaningful change in exercise performance.

The study adds to the literature on rehabilitation/exercise interventions in patients with advanced non-resectable lung cancer summarised in a recent Cochrane systematic review.[11] While the authors of this review considered the quality of the evidence to be low and the risk of bias high, the meta-analyses performed did indicate that there were positive effects of exercise-based rehabilitation programmes on walking performance and health-related quality of life for those patients who complete them. It is also clear from the scrutiny of the studies included in this review that participants varied in their receipt of active non-surgical cancer therapy and that the timing and supervision of the rehabilitation intervention were similarly variable.

These findings together with the study by Edbrooke *et al* present a complex evidence landscape framing the provision of rehabilitation in patients with advanced lung cancer in clinical practice. We can simply extrapolate the likely benefit of exercise training in terms of physical performance from trials in other respiratory populations (and indeed healthy, older people), but this would ignore the unique set of circumstances pertaining to patients who have had a recent diagnosis of lung cancer and are faced with the fearfulness of an uncertain prognosis and the prospect of undertaking chemotherapy and/or radiotherapy.

A diagnosis of cancer can be considered as a 'biographically disruptive event', a term first described by Bury[12] in relation to the onset of chronic disease as the disruption to an individual's expectation of life trajectory and personal biography.[13] These circumstances might present a substantial barrier to active engagement in progressive exercise rehabilitation, when attention will be focused on coming to terms with the diagnosis and prospect of undertaking cancer treatment and readiness to engage in PR might be low. In this respect, there is a contrast to the situation in COPD, where the indolent nature of the condition without a clear initiating event has been identified as an indicator of a lack of biographical disruption and a more passive acceptance of the

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constraints of the disease.[14] How these different disease narratives impact readiness to undertake PR, which can only be effective with the active engagement of the recipient, is unknown. In an insightful investigation of the views of patients living with advanced lung cancer about exercise therapy, Cheville *et al* reported that 'highly structured, non-daily activity-oriented exercise programme will be unappealing and poorly accepted by this population without careful planning and implementation'.[15] Some patients, however, were 'robustly, and perhaps defiantly, active' and a common theme was the view that specific exercise recommendations made by their oncologist would carry substantial weight. The timing and source of a rehabilitation offer for lung cancer sufferers will clearly be crucial. In the absence of more robust evidence about the optimal timing of the offer of PR after a diagnosis of lung cancer, referrers and practitioners will need to take a judgement in individual cases whether the intervention might be more effectively initiated after active cancer treatment has been completed because this might be the moment when the patient will be most open to behaviour change with the objective of improving physical activity and health and enhancing survival chances. Interestingly and in support of this, in the study by Edbrooke *et al*, there was a greater increment in 6MWD between the 9-week and 6-month timepoints in the rehabilitation group; the latter presumably after active cancer treatment had been completed. Indeed, the between-group difference in 6MWD at 6 months (in the modified intention to treat analysis) was 41 m which is higher than the recently revised minimum clinically important difference (MCID) but lower than the difference the study was powered to detect. This, married to the gains in health status observed at 6 months, suggests that the intervention might have brought about an important although delayed health benefit.

Perhaps the most tantalising finding of the study by Edbrooke *et al* was the observation of better survival in the active rehabilitation group. The authors rightly do not place too much emphasis on this finding as the study was not powered to investigate mortality and the observed difference was not statistically significant. However, the finding is plausible and in line with epidemiological evidence that higher physical activity and fitness is associated with better long-term cancer survival.[16] This together with robust trial evidence that exercise rehabilitation in other cancer types is effective in improving symptoms and quality of life has prompted the Clinical Oncology Society of Australia to publish a position statement recommending exercise is prescribed to all cancer sufferers as part of their treatment regimen.[17] As developments in targeted biologic therapy advance, the impact and prognosis of lung cancer may improve such that the time course of the condition could become more akin to chronic disease. While there is much to learn about how it should be integrated with active cancer therapy, there is little doubt that exercise-based therapies such as PR will have an important role to play.

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