Physical behavior and associations with health outcomes in operable NSCLC patients: A prospective study


A prospective study with 23 patients (13 female) diagnosed with primary NSCLC and scheduled for curative lung resection was performed. Outcome measures were assessed two weeks preoperative, and one, three and six months postoperative, and included accelerometer-derived physical behavior measures and the following health outcomes: six minute walking distance (6MWD), questionnaires concerning health-related quality of life (HRQOL), fatigue and distress.

Results: On group average, physical behavior showed significant changes over time. Physical behavior worsened following surgery, but improved between one and six months postoperative, almost reaching preoperative levels. However, physical behavior showed high variability between patients in both amount as well as change over time. More time in moderate-to-vigorous physical activity in bouts of 10 min or longer in the first month postoperative was significantly associated with better 6MWD, HRQOL, distress, and fatigue at six months postoperative.

Conclusion: As expected, curative lung resection impacts physical behavior. Patients who were more active in the first month following surgery reported better health outcome six months postoperative. The large variability in activity patterns over time observed between patients, suggests that physical behavior 'profiling' through detailed monitoring of physical behavior could facilitate tailored goal setting in interventions that target change in physical behavior.

1. Introduction

Physical activity (PA) is recognized as an important health-promoting behavior throughout the entire cancer continuum [1]. Higher levels of PA are associated with less negative treatment side effects, improved exercise capacity and patient reported outcomes measures (PROMs), and lower risk of recurrence and mortality in various cancer types [1–4]. Independent of time spent in PA, increased time spent in sedentary behavior (SB) is related to lower health related quality of life (HRQOL), and higher mortality rates for cancer survivors [2,5,6].
Self-reported measures are often used to capture the extent and nature of PA. However, considerable discrepancy between self-reported PA and objectively measured PA is reported in patients in general [7], and those with cancer [8], including non-small cell lung cancer (NSCLC) [9]. Despite this discrepancy, the number of studies in operable NSCLC patients that measure PA using objective measures is limited [9–13]. The few studies available show that lung cancer patients have low levels of PA at diagnosis, which further decline in the first months following surgery.

In these studies, PA was represented by a single measure such as number of steps [9,11,12] or overall physical activity level (PAL) [13], while more and more evidence stresses the importance of including other, additional measures that characterize physical behavior more precisely [10,14]. Especially time spent in SB and moderate to vigorous PA (MVPA) and how this time is accumulated are considered clinically relevant, due to their association with health and PROMs in cancer survivors [14]. So far, pre- to postoperative patterns of physical behavior of operable NSCLC patients and their relation to health and PROMs are lacking from literature. Inclusion of these additional measures will provide a more comprehensive description of physical behavior of operable NSCLC patients and their clinical relevance for recovery following resection, which might reveal new targets for rehabilitation.

Following this, the primary objective of this study was to characterize daily physical behavior of operable NSCLC patients, from preoperative to six months postoperative using accelerometry. Secondary objective was to explore if physical behavior preoperative and in the first month following surgery is associated with better health outcomes at six months postoperative.

2. Methods

2.1. Participants and study design

A prospective study was performed at the Netherlands Cancer Institute (NKI), Amsterdam, the Netherlands from July 2012 to July 2014. Ethical approval was obtained (PTC12.0835/P12RQL) and all participants provided written consent. Eligible participants were Dutch-speaking adults aged 18 years or older, diagnosed with primary non-small lung cancer (NSCLC) and scheduled for curative lung resection. Participants were identified during the multidisciplinary meeting at the NKI. Participants were excluded if they were unable to walk independently (with or without walking aid), exhibited severe cognitive disorders or emotional instability, suffered from uncontrolled comorbidities, received palliative treatment or recurrence of cancer.

A study information letter was sent to eligible patients, after which patients were contacted by the first author. Patients were measured at four time-points: at baseline (2–4 weeks prior to surgery, t0), and one (t1), three (t2) and six months (t3) after surgery. All patients received standard care at the hospital, which included outpatient appointments with the physician (thoracic surgeon or pulmonologists) at (t0, t1 and t3), and the physiotherapist (at t0 and t1). Measurements were synchronized with standard appointments at the hospital. Structured instruction or education about PA or rehabilitation was not part of standard care.

2.2. Primary outcome: physical activity

A waist-worn accelerometer was used to measure physical behaviors (ProMove 3D, 63 × 96 × 16 mm, 67 g, Inertia Technology, Enschede, The Netherlands, output being ‘integral of the modulus of acceleration per minute’ (IMA) comparable to the study of Bouten et al. [15], and referred to as ‘counts’ for detailed description see [16]). Participants were asked to wear the accelerometer prior to each physician appointment (at t0, t1, t2 and t3) for a minimum of three days during waking hours, excluding time spent bathing or participating in water activities. Instructions to patients also included to perform their daily routine, and not change their physical activity pattern.

Several measures were derived from the accelerometer, reflecting characteristics of physical behavior (Fig. 1). Overall physical activity level (PAL) is the average counts per minute (cpm) of all valid days, calculated from total number of counts divided by the time the accelerometer was worn (i.e. wear time).

Intensity levels were divided in sedentary behavior (SB), light PA (LIPA) and moderate-to-vigorous PA (MVPA). Cutoff values for intensity levels were used as described by Wolvers et al. [14] (Fig. 1).

Bout duration is the percentage of wear time spent in uninterrupted bouts of an intensity level. Time in prolonged SB bouts (pSB) is the total SB time accumulated in uninterrupted bouts of 30 min or longer [17]. Time in prolonged LIPA (pLIPA) and prolonged MVPA (pMVPA) is the total time in LIPA or MVPA accumulated in uninterrupted bouts of 10 min or longer [17]. Time in prolonged PA (pPA) is the total time in PA (i.e. LIPA and MVPA) in uninterrupted bouts of 10 min or longer.

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Fig. 1. Physical activity outcome measures calculated from the accelerometer.

Abbreviations: LIPA, low intensity physical activity; MVPA, moderate to vigorous activity; PAL, physical activity level; pLIPA, prolonged LIPA bouts; pMVPA, prolonged MVPA bouts; pPA, prolonged PA bouts; pSB, prolonged SB bouts; SB, sedentary behavior. Cut points intensity levels: sedentary < 1303 cpm; light PA 1303– < 2588 cpm; MVPA ≥ 2588 cpm.
2.2.1. Analysis data accelerometer

Raw IMA-data were processed in Matlab version R2015b (The MathWorks Inc., Boston, MA, USA). Data was scanned for non-wear, using the activity diary if they were available. Non-wear was removed, except when patients reported resting while placing the sensor on the bed or table in their activity diary. For these cases, the data was maintained and treated as sedentary time. Data were analyzed separately per time-point and averaged across valid days. Due to the explorative nature of this study, a minimum of two days (per time-point) with ≥8 h/day of data were required to be included in the analysis.

2.3. Secondary outcomes

We assessed functional capacity using the Six Minute Walking Distance (6MWD), which was performed according to published guidelines [18]. The parcours for the 6MWD measured 10 m x 2.5 m x 10 m x 2.5 m.

With the European Organization for the Research and Treatment of Cancer Questionnaire (EORTC QLQ-C30) we assessed HRQOL over the previous week using the ‘physical functioning’ (5 items), ‘global QOL’ (2 items) and ‘pain’ subscale (2 items) [19]. The EORTC scoring procedures were followed resulting in a composite score ranging from 0 to 100 for each subscale. For the subscales physical functioning and global QOL, higher scores represent higher level of functioning and QOL. For the pain subscale a higher score represents higher level of pain.

Subscales of the Multidimensional Fatigue Inventory (MFI)-20 were used to assess ‘general fatigue’, ‘physical fatigue’ and ‘reduced activity’ [20]. Each subscale contains four items, with scores ranging from 1 to 5 per item. Scores per scale can range from 4 to 20, with higher scores representing higher level of fatigue.

Psychological distress was assessed using the sum score of the Hospital Anxiety and Depression Scale (HADS) [21,22]. The HADS consists of 14 items. Item scores range from 0 to 3, with higher score indicating higher symptom level. Consequently, the sum score of the HADS may range from 0 to 42, with higher scores representing more distress.

At baseline, socio-demographics were obtained including age, gender, smoking status, marital status, and employment status. We extracted the following clinical information from the patient record: extent and technique of resection, body mass index (BMI), pack years, preoperative lung function (percentage of predicted 1 s forced expiratory volume (FEV1%pred), percentage of predicted diffusing capacity for carbon monoxide (DLCO%pred)), cardiorespiratory fitness (VO2peak), presence of COPD and presence of other comorbidities such as cardiovascular disease, diabetes mellitus, and renal insufficiency.

2.4. Statistical analysis

IBM’s Statistical Package for the Social Sciences (SPSS, 23.0) was used for the statistical analyses of all data. Descriptive statistics and graphs (PP-Plots and histograms) were used to assess normality of the outcome measures. Continuous variables were expressed as mean with standard deviation (SD) or median with interquartile range (IQR), categorical variables as counts with corresponding percentages.

To present change in activity behavior over time, a mixed-model analyses for repeated measures (normally distributed or transformed variables) or Friedman’s ANOVA (non-normally distributed; transformation not successful) was performed with time of measurement (t0-t3) as a within-subjects factor for each outcome separately. Mixed models were estimated by maximum likelihood and a heterogenous first-order autoregressive structure variance-covariance matrix was used. If significant, the analyses were followed by a post-hoc pairwise analysis (SIDAK corrected) to test for significant differences between any combination of time of measurement.

To investigate if preoperative and early postoperative physical behavior relates to health outcomes six months postoperative (t3), first Spearman’s correlations were calculated between selected physical behavior measures preoperative and health outcomes at six months postoperative (t3), and between physical behavior measures at one month postoperative (t1) and health outcomes at six months postoperative (t3). To limit the number of tests, we calculated the association between the physical behavior measures PAL, SB, pSB, and MVPa, since their relevance in cancer rehabilitation has previously been reported [14]. Second, for pMVPa, patients were classified into three groups based on the international guidelines for PA in cancer survivors, that is a minimum of 150 min of MVPa per week [6]. This was translated to a daily amount of 150/7 = 21 min per day. Based on the time spent in prolonged bouts in MVPa, patients were classified as ‘no MVPa’ (no min spend in pMVPa); ‘some MVPa’ (> 0 min/day but < 21 min/day in pMVPa) and ‘sufficient MVPa’ (≥ 21 min/day in pMVPa). The Jonckheere-Terpstra test was used to examine the relationship between group category at t0 and health outcomes at t3, and between group category at t1 and health outcomes at t3. For all statistical analyses, a significance level of p < 0.05 was used.

3. Results

During the study, 105 patients underwent lung resection for NSCLC in the NKI. Of these patients, 34 (32%) were approached, and twenty-nine consented to participation (Fig. 2). Reasons for non-consent were ‘feeling too emotional’ (n = 2), ‘it will be too much’ (n = 2), or ‘don’t want to monitor PA at home’ (n = 1).

In total, seven patients dropped out during the course of the study, primarily due to recurrence of cancer. Patients who dropped out during the study had comparable baseline characteristics to those who remained in the study. Table 1 shows the main characteristics of the patients included in at least one of the analyses. Mean age of the patient group was 59 years, and more women than men were included. Most patients lived at home with family, were not employed and ex-smokers. The majority of the group had early stage disease and most underwent lobectomy.

3.1. Physical activity behavior

Twenty-five patients monitored physical behavior at one or more time points during the study, resulting in 256 monitoring days. During analysis, 37 days with less than 480 min of data were removed. Median wear time (per time point) of included days varied between 13 h/day and 14 h/day. Twenty-three patients had valid data for at least one of the time points; 10 (43%), 16 (70%), and 21 (91%) patients had valid physical behavior data at four, three, and two time point(s), respectively.

PAL and time spent in SB, LIPA, MVPa and pPA all showed significant changes over time (Table 2). Overall, patients tended to accumulate more sedentary time and less time being physically active, at one month postoperative (t1) compared to baseline (t0). At one month postoperative, median percentage of time in SB and pSB increased to 80% and 44% respectively (compared to 74% and 37% at t0), while median percentage of time in MVPa and pPA both dropped just to below 5% (compared to 8% and 9% at t0) (see Table 2 and Fig. 3). At three months (t2) and six months (t3) following surgery, PAL and time spent in SB, LIPA, MVPa and pPA gradually improved, almost reaching preoperative levels at t3. Time spent in pSB, pLIPA and pMVPa showed no significant changes over time.

At baseline, four patients (22%) spent more than 21 min per day in pMVPa. Postoperative, four (25%), six (33%) and five patients (28%) spent more than 21 min/day in pMVPa at t1, t2 and t3 respectively.

3.2. Individual patterns of PA

On an individual level, we observed high variability within and between patients regarding the distribution of time spent active and...
sedentary and the patterns of change in physical behavior over time (Fig. 3). That is, at any one time, patients could be in different categories for different physical behavior outcomes. For example, some patients exhibited high levels of sedentary behavior together with low levels of physical activity, while others showed low levels of sedentary behavior but also low physical activity. Moreover, change patterns of physical behavior outcomes over time could occur in different combinations, for example increasing SB in combination with decreasing MVPA, but also less obvious combinations such as increasing SB together with increasing pPA or increase of total sedentary behavior (SB) together with a decrease of time spent in prolonged SB (pSB).

3.3. Relation between physical behavior at t0/t1 and health outcomes at t3

Patients experienced worsening of self-reported physical function, pain and general fatigue between t0 and t1. Postoperative, measures gradually improved again (see Table 3).

The Jonckheere-Terpstra test for ordered alternatives showed no difference in patients in higher pMVPA category (from ‘no pMVPA’, ‘some pMVPA’ to ‘sufficient pMVPA’) at t0 and health outcomes at t3. Contrary, patients in higher pMVPA category at t1 scored significantly better on 6MWD ($T_{JT} = 63.000$, $z = 2.967$, $p = .003$), HRQOL physical function ($T_{JT} = 63.500$, $z = 3.074$, $p = .002$), distress ($T_{JT} = 16.000$, $z = -2.114$, $p = .034$), physical fatigue ($T_{JT} = 15.500$, $z = -2.172$, $p = .030$) and reduced activity ($T_{JT} = 16.000$, $z = -2.118$, $p = .034$), at t3.

For the other physical behavior outcome measures (i.e. PAL, SB, MVPA, pSB and pPA), only pSB at t0 showed moderate correlations with pain score at t3 ($r = 0.47$). At t1, moderate correlations were found between: PAL and HRQOL (physical functioning, $r = 0.50$; general QOL, $r = 0.42$); MVPA and 6MWD ($r = 0.48$) and HRQOL (physical functioning, $r = 0.42$), pSB and HRQOL (physical function ($r = -0.49$). However, none of these correlations were significant (table included in Supplementary Materials).

4. Discussion

This study is the first, to our knowledge, that explored physical behavior patterns in detail from preoperative to six months postoperative in resected primary NSCLC patients. In line with previous research [12], lung resection had significant negative impact on time spent in PA and SB. One month postoperative, patients spent on average more than 80% of the day in sedentary behavior, with almost half of this sedentary time accumulated in bouts with duration longer than 30 min. In the following months, time spent in SB declined, and PA levels recovered almost to preoperative levels. So far, only Granger and colleagues reported longitudinal PA levels (as steps per day) in NSCLC patients from pretreatment (baseline) until six months following...
physical behavior, then when should we intervene and what pattern of physical behavior should we aim for as to promote health? Regarding the timing of intervention, research suggests that pre- and postoperative exercise training both have advantages on health and recovery [24–27]. Preoperative exercise training seems promising to optimize physical fitness prior to surgery, which then might result in better outcomes early following surgery, such as reduced length of stay or decreased chance of complications [27]. However, evidence from a recent RCT demonstrated no long-term beneficial effect of preoperative exercise on recovery and health outcomes following surgery [28]. In contrast, postoperative exercise training may effectively improve postoperative functional recovery [24,25,29]. This supports the findings of our study, which show that physical behavior prior to surgery does not relate with health-related outcomes and PROMs at six months postoperative, while time spent in prolonged bouts of MVPA in the first month postoperative does. Therefore, to improve health-related outcomes and PROMs following resection, promotion of physical behavior in the early period postoperative might be more effective than interventions preoperative. Next to that, feasibility of preoperative interventions might be low due to the often small time window between diagnosis and actual surgery [30].

With regard to the desirable pattern of physical behavior, international guidelines recommend a minimum of 150 min per week of MVPA, preferably in bouts of minimal 10 consecutive minutes, for health promotion [6]. In line with these guidelines, our results show better health outcome at six months postoperative for patients that do perform some or sufficient MVPA in prolonged bouts compared to those patients who spent no time in prolonged MVPA early following surgery. However, only a minority of NSCLC patients meet these guidelines of MVPA postoperative [9,31]. Therefore, instead of using the guideline as a fixed rule, which is possibly unrealistic and demotivating for a majority of NSCLC patients, we advise to tailor physical behavior goals in the early postoperative period based on previous and current physical behavior patterns, preferences, and physical capabilities. Tailoring is especially relevant given the considerable variability in activity patterns between operable NSCLC patients. Some of the patients in our study spent relatively much time in moderate-to-vigorous activity, while at the same time accumulating considerable time in prolonged bouts of sedentary behavior; or vice versa. This supports the notion of individual variability, and emphasizes the need for so-called physical behavior ‘profiling’ to facilitate tailored goal setting in interventions that target change in physical behavior [14].

Tailored goal setting through physical behavior profiling is a promising new approach in cancer rehabilitation that acknowledges the individual variability in physical behavior and actually uses this variability for optimizing behavioral interventions [14,32]. For operable NSCLC patients, this approach will require objective monitoring of physical behavior measures both prior to and postoperative, as to identify patients with disadvantageous physical behavior profiles. The physical behavior profile in combination with factors that cause this physical behavior profile can then form the basis for a tailored approach to improve physical behavior patterns. As a result, the actual intervention might differ between patients, varying from increasing time spent in prolonged bouts of MVPA in one patient, or breaking up prolonged bouts of sedentary behavior in the other, or starting with removing existing barriers for physical behavior change [33]. With increasing awareness of the complexity of physical behavior and how we might exploit this complexity for individual benefit, and given the recent advancements in technology, physical behavior could be a promising functional, patient-centered outcome in the treatment of operable NSCLC patients.

Nevertheless, further research is needed to live up to this promise. The present study was limited by a combination of small sample size and missing values at the different measurement occasions. Non-adherence to study protocols is a well-known problem in patients diagnosed with lung cancer, due to poor prognosis and high symptom
It is possible that patients with worse physical behavior and worse health outcome were not included or non-compliant to the monitoring protocol, resulting in a bias of the results, such as overestimation of physical behavior and health outcomes. Also, because of the explorative nature of the study, we did not control for confounders that might influence both physical behavior early following surgery and better health outcomes at six months postoperative. Possible confounders might include a combination of personal, disease and treatment related factors, such as prior experience with exercising, age, comorbidities, smoking, surgery extent, complications, or (neo-)

<table>
<thead>
<tr>
<th>Physical behavior over time reported as median [interquartile range].</th>
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<tbody>
<tr>
<td>Preoperative (t0)</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>PAL [cpm]</strong></td>
</tr>
<tr>
<td>897 [733-1169]</td>
</tr>
<tr>
<td><strong>Time in SB [%]</strong></td>
</tr>
<tr>
<td>74 [67-79]</td>
</tr>
<tr>
<td><strong>LIPA [%]</strong></td>
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<tr>
<td><strong>MVPA [%]</strong></td>
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<tr>
<td>8 [6-11]</td>
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<tr>
<td><strong>Time in prolonged bouts of SB [%]</strong></td>
</tr>
<tr>
<td><strong>LIPA [%]</strong></td>
</tr>
<tr>
<td>1 [0-2]</td>
</tr>
<tr>
<td><strong>MVPA [%]</strong></td>
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<tr>
<td>1 [0-2]</td>
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<tr>
<td><strong>PA [%]</strong></td>
</tr>
<tr>
<td>9 [5-14]</td>
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</table>

<sup>a</sup>p-value based on transformed variables. <sup>b</sup>p-value of the mixed models analysis with time of measurement as within group factor (restricted maximum likelihood and a heterogeneous first-order autoregressive structure). <sup>c</sup>p-value from Friedman’s ANOVA. Significant post-hoc comparisons (SIDAK corrected): <sup>d</sup>t1-t0: p = .004; <sup>e</sup>t0-t1: p = .022; <sup>f</sup>t0-t1: p = .040.

Abbreviations: cpm, counts per minute; MVPA, moderate-to-vigorous physical activity; PAL, physical activity level; SB, sedentary behavior.

Fig. 3. Physical behavior patterns of NSCLC patients from preoperative to 6 months postoperative.

The same color represents the same patient in each graph.

Dotted black line is the median for that time point.

Abbreviations: mth, month; MVPA, moderate-to-vigorous physical activity; pMVPA, prolonged MVPA bouts; pPA, prolonged physical activity bouts; pSB, prolonged SB bouts; post, postoperative; SB, sedentary behavior.
Table 3

<table>
<thead>
<tr>
<th>Health outcomes</th>
<th>Preoperative (t0)</th>
<th>1 month post (t1)</th>
<th>3 months post (t2)</th>
<th>6 months post (t3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWD (metres)</td>
<td>521 ± 78</td>
<td>444 ± 118</td>
<td>515 ± 87</td>
<td>537 ± 84</td>
</tr>
<tr>
<td>Physical function</td>
<td>71 ± 19</td>
<td>60 ± 25</td>
<td>69 ± 21</td>
<td>77 ± 16</td>
</tr>
<tr>
<td>Global QOL</td>
<td>8 [0-33]</td>
<td>33 [17-54]</td>
<td>17 [0-50]</td>
<td>17 [0-33]</td>
</tr>
<tr>
<td>Pain</td>
<td>11 ± 5</td>
<td>14 ± 5</td>
<td>12 ± 4</td>
<td>10 ± 5</td>
</tr>
<tr>
<td>MFI General</td>
<td>10 ± 4</td>
<td>13 ± 5</td>
<td>12 ± 4</td>
<td>10 ± 5</td>
</tr>
<tr>
<td>Fatigue Physical</td>
<td>11 ± 5</td>
<td>14 ± 4</td>
<td>11 ± 5</td>
<td>10 ± 5</td>
</tr>
<tr>
<td>Fatigue Reduced</td>
<td>8 [3-13]</td>
<td>7 [4-12]</td>
<td>7 [4-17]</td>
<td>6 [3-8]</td>
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<tr>
<td>Distress (HADS)</td>
<td></td>
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Abbreviations: 6MWD, six minute walk distance; EORTC-C30, European Organization for the Research and Treatment of Cancer questionnaire; HADS, Hospital Anxiety and Depression Scale; MFI, Multidimensional Fatigue Inventory; QOL, quality of life.

adjuvant treatment [2,12,13,34–37].

Therefore, future longitudinal studies should confirm the existence of physical behavior profiles through objective monitoring of physical behavior, classify “problematic” physical behavior profiles, and identify predictors for these profiles. Second, experimental studies are needed that evaluate the acceptability and effect of tailored physical behavior interventions on both health outcomes and physical behavior on the short and long term, and how possible confounders may alter this effect in operable NSCLC patients.

5. Conclusion

Our study shows that, on average, curative lung resection has a negative impact on physical behavior. Patients who were more active in the first month following surgery reported better health outcomes six months postoperative. Due to the considerable variability in activity patterns observed between operable NSCLC patients, we would emphasize the need for so-called physical behavior ‘profiling’ through detailed monitoring of physical behavior to facilitate tailored goal setting in interventions that target change in physical behavior.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.lungcan.2018.03.006.

References


