Aspirin and non-small cell lung cancer resections: effect on long-term survival

Eustace Fontaine, James McShane, Richard Page, Michael Shackcloth, Neeraj Mediratta, Martyn Carr, Ajab Soorae, Michael Poullis* 

Liverpool Heart and Chest Hospital, Thomas Drive, Liverpool, L14 3PE England, United Kingdom

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Abstract

Objective: Survival after resections for non-small cell lung cancer remains poor. Recurrent lung cancer remains common. Due to the common risk factor of smoking, cardiovascular deaths occur in the absence of recurrent lung cancer in up to 15% of patients. Aspirin has been proven to reduce cardiovascular mortality as a secondary prophylactic agent, but not as a primary agent. Aspirin being a COX-2 inhibitor has been shown to reduce the chance of metastasis in adenocarcinoma but not squamous carcinoma. We sought to investigate the effect of long-term aspirin therapy on survival post potentially curative surgery.

Methods: We analysed a prospective thoracic surgical database, from time period 2003 to date. Patients who were on aspirin pre-operatively, \( N = 412 \) were compared to non users, \( N = 1353 \). Patient long-term outcome was assessed utilising the national strategic tracking service that operates in the United Kingdom. Cox proportional hazards analysis was used to determine significant factors affecting survival.

Results: 100% survival follow up was achieved. Regular users of aspirin had >5% increased survival, which was significant, \( p = 0.05 \), despite having a higher cardiovascular risk profile. Mode of death data was not available.

Conclusions: Adjuvant aspirin post resection for potentially curative non-small cell lung cancer significantly increases survival. The mechanism of increased survival needs further investigation and is the basis for the trial: Adjuvant Aspirin for Non-Small cell Lung Cancer — The Big A Trial. www.TheBigATrial.co.uk.

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Keywords: Aspirin; Lung cancer; Resection; Survival; Adjuvant

1. Introduction

Carcinoma of the lung remains a common cancer with a poor prognosis [1]. Of new cases only 10—15% undergo potentially curative surgical resections. Of these survival is still only about 50% at five years. The peak age incidence of lung cancer is 70—85, with the common risk factor being a history of cigarette smoking (http://info.cancerresearchuk.org/cancerstats).

Cardiovascular deaths peak between the ages of 70 and 85, and have a common risk factor with lung cancer, cigarette smoking [2]. Of patients with lung cancer a significant number die from cardiovascular disease and not from their lung cancer [3—5]. This forms the basis of actual versus actuarial survival [6]. An agent that reduces the risk of cardiovascular deaths from smoking related cardiovascular disease and reduces the incidence of lung cancer simultaneously would potentially have enormous clinical benefit.

As aspirin is known for its secondary preventive role with regard to cardiovascular disease [7,8] and is associated with an increased survival benefit in patients with adenocarcinoma [9,10].

We hypothesised that aspirin would reduce cardiovascular deaths in all patients post resection for lung cancer and would have an additional beneficial effect with regard to developing recurrent disease in patients who have an adenocarcinoma.

We retrospectively analysed a prospective thoracic surgery database to investigate whether the use of aspirin would be associated with an increased survival post potentially curative lung resection.

2. Materials and methods

A prospective thoracic surgery database was analysed. Between October 2001 and March 2009, 1816 patients underwent a lung resection for proven or suspected non-small cell lung cancer (NSCLC). 51 patients were later found to have stage IV disease or small cell cancer. These were excluded from the analysis. Of the remaining 1765 patients, 412 (23.3%) were recorded as regularly taking aspirin...
survival analysis was undertaken to compare survival in those taking aspirin versus those not taking the drug.

2.1. Benchmarking

We benchmarked out long-term outcomes following resection for non-small cell lung cancer, Fig. 1, against the IASLC Lung Cancer Staging Project 7th edition outcome figures [11,12].

2.2. Crude analysis

Kaplan–Meier survival curve in Fig. 2a demonstrates the crude survival curve for the aspirin, N = 412, and non-aspirin, N = 1765, groups, for all stages.

2.3. Study group characteristics

Possible confounding differences in case-mix between the groups are shown in Table 1, pre-operative characteristics, and Table 2, histology and operative characteristics. Differences in categorical variables were evaluated using chi-squared tests, while the Wilcoxon test was used for continuous variables. The influence on survival, of these potentially confounding factors, was investigated further.

2.4. Univariate analyses

Univariate analysis of all variables in Table 1 was performed first, with the objective of identifying significant factors for inclusion in a multivariate Cox regression model.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demonstrates the pre-operative characteristics of the two groups in the study.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No aspirin (n = 1353)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>649 (48.0)</td>
</tr>
<tr>
<td>Age at operation</td>
<td>68 (60—74)</td>
</tr>
<tr>
<td>% FEV1</td>
<td>80 (65—93)</td>
</tr>
<tr>
<td>BMI &gt;30 (%)</td>
<td>228 (16.9)</td>
</tr>
<tr>
<td>NYHA (%)</td>
<td>0 365 (27.1)</td>
</tr>
<tr>
<td></td>
<td>1 446 (33.1)</td>
</tr>
<tr>
<td></td>
<td>2 458 (34.0)</td>
</tr>
<tr>
<td></td>
<td>3 76 (5.6)</td>
</tr>
<tr>
<td></td>
<td>4 2 (0.2)</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>318 (23.5)</td>
</tr>
<tr>
<td>Emphysema (%)</td>
<td>59 (4.4)</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td>440 (32.6)</td>
</tr>
<tr>
<td></td>
<td>825 (61.2)</td>
</tr>
<tr>
<td></td>
<td>83 (6.2)</td>
</tr>
<tr>
<td>Excess alcohol (%)</td>
<td>172 (12.7)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>105 (7.8)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>437 (32.3)</td>
</tr>
<tr>
<td>History of IHD (%)</td>
<td>262 (19.4)</td>
</tr>
<tr>
<td>PVD (%)</td>
<td>137 (10.1)</td>
</tr>
<tr>
<td>TIA/CVA (%)</td>
<td>79 (5.8)</td>
</tr>
<tr>
<td>Previous DVT (%)</td>
<td>50 (3.7)</td>
</tr>
<tr>
<td>Renal disease (%)</td>
<td>23 (1.7)</td>
</tr>
</tbody>
</table>

Categorical variables quoted as number of patients (%), with continuous variables quoted as median (inter-quartile range).
Categorical variables were assessed using the Log-Rank Test. For each of the continuous variables, a univariate Cox regression was performed. Tables 3 and 4 show the results of the univariate analysis.

2.5. Histological subtype analysis

Kaplan–Meier sub analysis by adenocarcinoma and squamous carcinoma is shown in Fig. 2b and c, respectively.

Table 2
Demonstrates the histology and procedural breakdown of the two study groups.

<table>
<thead>
<tr>
<th></th>
<th>No aspirin (n = 1353)</th>
<th>Aspirin (n = 412)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op chemo (%)</td>
<td>91 (6.7)</td>
<td>19 (4.6)</td>
<td>0.12</td>
</tr>
<tr>
<td>Procedure (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wedge</td>
<td>125 (10.0)</td>
<td>56 (13.6)</td>
<td></td>
</tr>
<tr>
<td>Lobectomy</td>
<td>1010 (74.7)</td>
<td>311 (75.5)</td>
<td></td>
</tr>
<tr>
<td>Pneumo</td>
<td>208 (15.4)</td>
<td>45 (10.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Histology (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoca</td>
<td>644 (47.6)</td>
<td>196 (47.6)</td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>564 (41.7)</td>
<td>180 (43.7)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>145 (10.7)</td>
<td>36 (8.7)</td>
<td>0.47</td>
</tr>
<tr>
<td>Cancer stage (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I(a)</td>
<td>383 (28.3)</td>
<td>144 (35.0)</td>
<td></td>
</tr>
<tr>
<td>I(b)</td>
<td>500 (37.0)</td>
<td>162 (39.3)</td>
<td></td>
</tr>
<tr>
<td>II(a)</td>
<td>55 (4.1)</td>
<td>14 (3.4)</td>
<td></td>
</tr>
<tr>
<td>II(b)</td>
<td>237 (17.5)</td>
<td>46 (11.2)</td>
<td></td>
</tr>
<tr>
<td>III(a)</td>
<td>134 (9.9)</td>
<td>36 (8.7)</td>
<td></td>
</tr>
<tr>
<td>III(b)</td>
<td>44 (3.3)</td>
<td>10 (2.4)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Categorical variables quoted as number of patients (%), with continuous variables quoted as median (inter-quartile range).

Table 3
Univariate survival analysis – pre-op patient characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>0.91 (0.77—1.07)</td>
<td>0.26</td>
</tr>
<tr>
<td>Female</td>
<td>0.76 (0.66—0.88)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Age at operation</td>
<td>1.02 (1.02—1.03)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% FEV1</td>
<td>0.54 (0.38—0.78)</td>
<td>0.0008</td>
</tr>
<tr>
<td>BMI &gt; 30</td>
<td>0.74 (0.61—0.89)</td>
<td>0.004</td>
</tr>
<tr>
<td>NYHA 0</td>
<td>0.75 (0.64—0.88)</td>
<td>0.001</td>
</tr>
<tr>
<td>NYHA 1</td>
<td>1.01 (0.87—1.18)</td>
<td>0.91</td>
</tr>
<tr>
<td>NYHA 2</td>
<td>1.17 (1.01—1.36)</td>
<td>0.03</td>
</tr>
<tr>
<td>NYHA 3 or 4</td>
<td>1.19 (0.90—1.58)</td>
<td>0.19</td>
</tr>
<tr>
<td>COPD</td>
<td>1.20 (1.02—1.42)</td>
<td>0.02</td>
</tr>
<tr>
<td>Emphysema</td>
<td>1.08 (0.76—1.52)</td>
<td>0.66</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>1.11 (0.95—1.29)</td>
<td>0.17</td>
</tr>
<tr>
<td>Ex</td>
<td>1.03 (0.89—1.19)</td>
<td>0.70</td>
</tr>
<tr>
<td>Non</td>
<td>0.45 (0.33—0.61)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Excess alcohol</td>
<td>1.40 (1.11—1.76)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.10 (0.85—1.42)</td>
<td>0.44</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.02 (0.88—1.18)</td>
<td>0.80</td>
</tr>
<tr>
<td>History of IHD</td>
<td>1.06 (0.90—1.24)</td>
<td>0.49</td>
</tr>
<tr>
<td>PVD</td>
<td>1.31 (1.05—1.63)</td>
<td>0.007</td>
</tr>
<tr>
<td>TIA/CVA</td>
<td>0.98 (0.75—1.27)</td>
<td>0.86</td>
</tr>
<tr>
<td>Previous DVT</td>
<td>1.24 (0.84—1.83)</td>
<td>0.24</td>
</tr>
<tr>
<td>Renal disease</td>
<td>1.29 (0.73—2.31)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Categorical variables evaluated using Log-Rank Test. Continuous variables using univariate Cox regression.

Table 4
Univariate survival analysis of the histology and procedural breakdown of the two study groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op chemo (%)</td>
<td>1.14 (0.84—1.53)</td>
<td>0.36</td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wedge</td>
<td>0.98 (0.77—1.24)</td>
<td>0.84</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>0.71 (0.60—0.84)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pneumo</td>
<td>1.67 (1.34—2.07)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoca</td>
<td>1.15 (0.99—1.32)</td>
<td>0.06</td>
</tr>
<tr>
<td>Squamous</td>
<td>1.01 (0.88—1.17)</td>
<td>0.87</td>
</tr>
<tr>
<td>Others</td>
<td>0.68 (0.54—0.85)</td>
<td>0.004</td>
</tr>
<tr>
<td>Cancer stage (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0.45 (0.38—0.52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>II</td>
<td>1.46 (1.21—1.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>III</td>
<td>2.73 (2.12—3.51)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Categorical variables evaluated using Log-Rank Test. Continuous variables using univariate Cox regression.

Table 5
The Cox multivariate regression model in its final form.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter estimate</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>0.17582</td>
<td>0.84</td>
<td>0.05</td>
</tr>
<tr>
<td>Female</td>
<td>0.15986</td>
<td>0.85</td>
<td>0.04</td>
</tr>
<tr>
<td>Age at operation</td>
<td>0.03071</td>
<td>1.03</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI &gt; 30</td>
<td>0.23447</td>
<td>0.72</td>
<td>0.002</td>
</tr>
<tr>
<td>FEV1%</td>
<td>0.51930</td>
<td>0.60</td>
<td>0.009</td>
</tr>
<tr>
<td>NYHA 1</td>
<td>0.19895</td>
<td>1.22</td>
<td>0.05</td>
</tr>
<tr>
<td>NYHA 2</td>
<td>0.23611</td>
<td>1.27</td>
<td>0.02</td>
</tr>
<tr>
<td>NYHA 3 or 4</td>
<td>0.43550</td>
<td>1.55</td>
<td>0.007</td>
</tr>
<tr>
<td>Never smoked</td>
<td>0.60497</td>
<td>0.55</td>
<td>0.007</td>
</tr>
<tr>
<td>Excess alcohol</td>
<td>0.40283</td>
<td>1.50</td>
<td>0.002</td>
</tr>
<tr>
<td>PVD</td>
<td>0.22855</td>
<td>1.26</td>
<td>0.03</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>0.22199</td>
<td>1.25</td>
<td>0.03</td>
</tr>
<tr>
<td>Stage 2 cancer</td>
<td>0.53042</td>
<td>1.70</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stage 3 cancer</td>
<td>1.23734</td>
<td>3.45</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

2.6. Multivariate Cox regression

As confounding variables can cause significant predictors to fail to achieve a p-value <0.05 at the univariate level, univariate predictors were considered potentially important and included in the multivariate model if they were found to have a p-value of less than 0.25. Aspirin use fell just short at 0.26 but, being the variable of interest was also offered to the model.

Following entry into the multivariate Cox regression, a significance level of p <0.05 was considered necessary for variables to remain in the model. Table 5 shows the Cox regression model in its final form.

Using the final Cox regression model shown in Table 5, the aspirin versus non-aspirin survival curves were risk-adjusted and re-plotted. Therefore, any differences between the curves in Fig. 3 are solely due to the aspirin effect.

3. Results

100% survival follow up of all patients in our study population was achieved.
3.1. Benchmarking

Benchmarking revealed no significant differences in our long-term outcomes compared to the IASLC Lung Cancer Staging Project 7th edition outcomes.

3.2. Crude analysis

The Kaplan—Meier survival curve in Fig. 2a demonstrates the crude survival curve for the aspirin, \( N = 412 \), and non-aspirin, \( N = 1765 \) groups, for all stages. There is no significant difference.

3.3. Study group characteristics

It can be seen from Table 1 that the aspirin group having significantly older patients, who were more short of breath, and had a higher incidence of diabetes, hypertension, history of ischaemic heart disease, and peripheral vascular disease.

Data in Table 2 demonstrates that the aspirin group were significantly more likely to undergo a wedge, less likely to undergo a pneumonectomy, and had an earlier stage. There was no significant difference between the incidence of adenocarcinoma or squamous carcinoma.

3.4. Univariate analyses

Univariate analysis, Tables 3 and 4 that revealed, female sex, age at operation, lung function, body mass index above 30, New York Heart Association status, history of chronic obstructive airway disease, having never smoked, excess alcohol consumption, peripheral vascular disease, lobectomy and pneumonectomy, and cancer stage were all significantly associated with survival.

3.5. Histological subtype analysis

Kaplan—Meier sub analysis by adenocarcinoma and squamous carcinoma is shown in Fig. 2b and c, respectively demonstrates no significant difference in the outcomes for either subtype of non-small cell lung cancer.

3.6. Multivariate Cox regression

Table 5 shows the Cox regression model. In Fig. 3 the Cox adjusted survival estimate of the aspirin effect for all patients, demonstrates that aspirin has a significant survival benefit \((p = 0.05)\). The mean value of categorical covariates was utilised.

3.7. Long-term follow up

Our follow up data is up to eight years. Most lung cancer studies only go up to five years. It can be seen that at eight years the aspirin and non-aspirin curves converge. This is due to the natural lifespan of patients, average age 69 in our study and the average life expectancy in the United Kingdom of 77, i.e. eight years.

4. Discussion

Aspirin may improve survival in patients undergoing potentially curative resections for carcinoma of the lung. This was despite the aspirin group having significantly more cardiovascular risk factors for death than the non uses group. Aspirin thus reduced the mortality in a cohort of patients that would have statistically been expected to have a worse five-year outcome.

Whether the data was analysed by stage, histology type or resection type, aspirin resulted in little/no benefit in the first three years postoperatively on outcome. We speculate that death in this period is mainly due to recurrence and aspirin has minimal effect on this. However after three years aspirin seemed to have a significant effect on survival. This beneficial effect seemed to be unaffected by histological type, making our initial hypothesis of adenocarcinomas having a better outcome seem incorrect, implying a beneficial cardiovascular effect for the aspirin.

Basic science research has shown that COX-2 inhibition is associated with a decreased incidence of metastatic disease in adenocarcinoma \([13–15]\). Unfortunately sole use of a selective COX-2 inhibitor is associated with an excess of cardiovascular deaths \([16]\). One of the putative mechanisms of aspirin improving patient survival as a secondary prophylactic agent is via its COX-1 effects on platelet function \([7]\). Aspirin has unique pharmacological properties due to its irreversible non selective effects of inhibition of COX-1 and COX-2 \([17]\). Aspirin should be anti metastatic in adenocarcinoma but have little effect with regard to metastasis in squamous carcinoma. The anti platelet effects of aspirin with regard to anti metastatic properties is unknown.

We thus hypothesised that aspirin should reduce recurrent disease in patients with adenocarcinoma and reduce cardiovascular events in all patients. The cardiovascular event rate and mortality can be predicted by utilising the Framingham or POCKEN risk calculator \([18]\). These calculators estimate that the average 75-year-old smoker who undergoes resection for a potentially curative smoker of the lung has between 4 and 8% chance of dying in the next five years from a cardiovascular event.
Secondary prevention of cardiovascular events is proven to occur with the use of non-selective COX inhibition with aspirin. In addition selective COX-2 inhibition is known to increase the cardiovascular mortality rate of patients [16]. Primary prevention of cardiovascular disease with aspirin in unproven, though widely advocated in high risk patients [7]. We were unable to demonstrate any beneficial effects of aspirin dependent on histology subtype. This has previously been described in prostate cancer [19], also an adenocarcinoma [9,10].

Adjuvant therapy post potentially curative lung resections is still in a state of flux. Treatment of humans with the selective COX-2 inhibitor celecoxib augments the antitumor effects of chemotherapy in patients with non-small cell lung cancer [15,20].

In conclusion aspirin use is significantly associated with increased survival post resection for potentially curative carcinoma of the lung.

5. Limitations

The United Kingdom strategic tracking service does not provide information on mode of death, making elucidation of the mechanism of beneficial effects of aspirin difficult to evaluate. The dose of aspirin was not recorded, although the majority would be on 75 mg/day. About 30% of the population is resistant to the effects of aspirin. The definition of aspirin resistance is difficult to define as no gold standard test exists. We did not test our patients with bed side or formal aggreometry to assess if their platelets were inhibited. In addition we did not analyse platelet count as this data was unavailable.

6. Future work

A prospective randomised trial of prophylactic aspirin in patients undergoing potentially curative resection for carcinoma of the lung is warranted. (Adjuvant Aspirin for Non-Small cell Lung Cancer — The Big A Trial. www.TheBigATrial.co.uk).

Accepting the suggested hazard ratio of 0.84 and a difference in five-year survival of approximately 6%, various power calculations were performed to derive an estimate of the sample size required for such a trial. Depending on the aspirin:non-aspirin ratio and based on standard assumptions, a combined total of between 2000 and 3000 patients would need to be recruited to detect a significant difference in survival.

References


Appendix A. Conference discussion

Dr E. Lim (London, United Kingdom): I would like a few points of clarification before I ask my question. In the multivariable model, you have included values with a p-value of 0.25 or less, and that seems somewhat unusual, because normally when people do a backward or a forward stepwise regression model, we use 0.05 or 0.1, and given that the aspirin p-value was 0.26 and the fact that you have chosen the inclusion p-value of 0.25, can you explain that to us, why it’s so coincidental?

Dr Fontaine: Well, most people, when they do a regression model, they will use a p-value of much less.
Dr Lim: Yes. I mean the two normal figures are 0.05 and 0.1.
Dr Fontaine: Yes.
Dr Lim: Just sheer luck, good luck?
Dr Fontaine: Yes.
Dr Lim: Secondly, in your modelling, your categorical variables in a Cox model, the first variable is always a reference variable, it does not have a hazard ratio or a p-value, but yet on your tables, on your first variable you have put in the hazard ratio and the p-values, and that seems to be counter-intuitive to Cox modelling. How did you get the p-values for the first reference values?
Dr Fontaine: If you do a univariate Cox regression where you’re just using the individual variable, then it gives you the hazard ratio.
Dr Lim: So despite it being a categorical variable, you have taken it apart and used it as an independent variable, each producing one hazard ratio?
Dr Fontaine: Yes, that’s right. I’ve seen that in a lot of the papers.
Dr Lim: I think my question for you is probably asked on behalf of the entire audience. Do you think that this is an aspirin effect on lung cancer or do you think it’s an aspirin effect on ischemic heart disease? There are several features in your analysis which, to me, suggest that this might be the latter. The first is that there is no independent effect of aspirin on overall survival. Secondly, cancer deaths, as you’ll notice from your survival plot, happen in the first year. If there is a genuine aspirin effect, it will be strongest when all the cancer deaths are happening in the first year, but yet the aspirin effects tend to happen in the years out towards 4, 5, and onwards to 8, and this may reflect the attrition of the patients with ischemic heart disease with time, and therefore I would propose to you that there is a significant proportion of patients in the non-aspirin group with undiagnosed ischemic heart disease who do not derive the benefit from the aspirin, accounting for the difference in survival.
Dr Fontaine: You’re probably right, the effect of the aspirin is probably more on the cardiovascular events than the actual effect on tumorigenesis, because at three years there is no difference in the aspirin and the non-aspirin group, but at five years, then you’re seeing a difference.
Dr Lim: I don’t think it necessarily detracts from the value of your study, because it could be that lung cancer patients, a lot of them have undiagnosed ischemic heart disease, and if you give them aspirin, then it might prolong their survival.
Dr McShane: I have one more point about the first point you made about taking a p of 0.25 for entry into the model. A lot of evidence that I’ve seen in the past, there may be confounding factors at the univariate level which could cause potentially significant variables to not achieve the 0.05 level of significance at univariate. In the forward stepwise model, in order to stay in the model, you would then have to achieve 0.05 in the multivariate. But you can miss important variables by keeping it at 0.05 for entry.
Dr T. Dosios (Athens, Greece): It is well known that 90% of the patients who die after resection of lung cancer have as a cause of death the lung cancer itself. This is the main cause. It’s hard to believe that aspirin has an effect on the cause of death in those patients. So it remains that aspirin may prevent cardiovascular events in the remaining 10%. Do you think that this reduction in the death rate is the cause of this difference you found?
Dr Fontaine: Probably a reduction in the cardiovascular event rate, yes.
Dr Dosios: Yes, in 10% of the patients.
Dr Fontaine: The improved survival is about more than 5% coming from the two groups. Well, we do know that the overall survival for all patients coming in for lung cancer surgery is about 50% five-year survival.
Dr Dosios: Yes, and of the 50 patients who died during the first five years, 40 of them died because of lung cancer.
Dr Fontaine: Of recurrent disease, yes.
Dr Dosios: Recurrent disease, local or distant. So the remaining 10 patients, maybe aspirin has some effect on cardiovascular events. This is my understanding.
Dr Fontaine: But if you look at all the patients coming in for surgery, there will be 50% that won’t be alive in, say, five years’ time for all stages. So the effect we are seeing at five years is about a 5% difference in survival for the aspirin and the non-aspirin group.
Dr P. Sardari Nia (Edegem, Belgium): The smoking status that you depicted in your slides is probably smoking status at the time of diagnosis or operation, so you don’t have any data over the years of follow up of the smoking status. That would be a very important confounder in your analysis, because smoking is associated with poor prognosis, especially in lung cancer patients, but also for cardiovascular disease. So if you don’t have any information about that, you never know if it is the effect of aspirin or the effect of continued smoking among some subgroups.
Dr Fontaine: But even if you do give up smoking, your risk doesn’t fall back to the general population.