Obtaining an upper estimate of the survival benefit associated with surgery for mesothelioma∗,∗∗

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Abstract

Objective: This study aimed to obtain an upper estimate of any survival benefit conferred by resection in patients with a diagnosis of malignant pleural mesothelioma. Methods: We analysed published data concerning survival from diagnosis among four groups of patients with mesothelioma, identified by ascending level of intervention: (A) no surgery; (B) thoracotomy but no resection; (C) resection but no adjuvant treatment; and (D) resection as part of multimodality treatment. Mean survival was estimated for each of these four groups. Mean survival was also estimated for all those having resection (groups C and D) and for all those not having a resection (groups A and B). Results: Mean survival was 16.8, 17.8 and 17 months for those having no surgery, thoracotomy alone and resection with no adjuvant treatment respectively (groups A, B and C) and 32.9 months for those having multimodality treatment (group D). Mean survival was 25.6 months in those who had resection and 17.1 months in those that did not. The survival advantage of any management that included surgical resection was estimated as being no more than 9 months. This is the most optimistic estimate and requires all observed differences in survival to be attributed to the effect of treatment and none to selection for treatment. Furthermore, within this upper estimate is included any benefit from other components of multimodality treatment. Conclusions: Given the burden of morbidity of resection in the management of pleural mesothelioma, this most optimistic estimate of the magnitude of any survival benefit should be taken into account in any policy decision, in clinical trial proposals and in strategies adopted by clinical teams.

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1. Introduction

The European epidemic of malignant pleural mesothelioma (MPM) is yet to peak [1—3]. Britain and Australia [4] are amongst the countries where death rates are highest and a considerable burden of disease is anticipated in the developing world [5]. The evidence for surgery relies largely on follow-up of surgical case-series. When presenting outcome data concerning patients that had a surgical intervention, there is a tendency to attribute survival that is longer than expected to the surgical intervention, commonly without reference to a comparator group of patients that did not have surgery [6].

An exception in this regard is a report of survival amongst 945 patients from Memorial Sloan-Kettering Cancer Centre (MSKCC), which constitutes the largest single-institution study of patients with a diagnosis of MPM [7]. It provides information on the composition of the patient group with respect to age, sex, smoking history, asbestos exposure, the side of the chest involved with MPM, histology, stage and the type of surgery. Kaplan—Meier survival analysis was performed for patient subgroups defined by these features.

Amongst those who had a thoracotomy, the decision to perform extra-pleural pneumonectomy (EPP, N = 208), pleurectomy/decortication (P/D, N = 176) or no resection (N = 174) was made intra-operatively [7]. Of the 384 patients who had either form of resection, 42 had both adjuvant chemotherapy and radiotherapy, 130 had radiotherapy, 35 had chemotherapy and 177 had neither.

The MSKCC authors also provided data on survival in 387 patients in the same MSK database who did not have surgical exploration. In 76, it was because of stage IV disease and in seven because of sarcomatoid disease; however, in the majority, 304 patients, it was because they ‘refused surgery or were deemed medically inoperable’ [7]. These survival data allow an opportunity to gauge the potential survival benefit conferred by surgery.

Outside of randomised controlled trials, the evaluation of surgical interventions is susceptible to selection bias. Based on a multivariate analysis intended to adjust for other recorded data items, the MSKCC authors concluded that

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resection is 'associated' with longer survival. A limitation in this dataset is the level of missing data; for instance, histology was unclassified in 51% and stage was unknown in 49% of patients. Since this information is more likely to be missing amongst the 40% un-operated patients, the adjustment may be unreliable [8]. Another consideration is that, for burdensome treatments, it is important to consider the 'scale' of any benefit rather than focus on a statistical assessment of whether there is some benefit, however small.

A direct approach at gauging the potential survival benefit is to obtain an upper estimate on the quantity of interest, in this case the greatest survival benefit that might be conferred by resection. This is known as a bounding study [9].

2. Methods

2.1. Data

The data required to obtain an upper estimate for any benefit conferred by management of MPM incorporating resection were available in the form of survival curves presented in different figures contained within the article of Flores et al. [7] pertaining to:

(A) survival following diagnosis for patients that had no thoracotomy;
(B) survival following diagnosis for patients that had a thoracotomy but no resection;
(C) survival following diagnosis for patients that had surgical resection only;
(D) survival following diagnosis for patients that had surgical resection as part of multimodality treatment (chemotherapy and/or radiotherapy).

The lead author of the MSKCC paper was contacted for access to the dataset used in constructing these survival curves but without success. We, therefore, used the software tool 'UN-SCAN-IT' (Silk Scientific, Inc, Orem, UT, USA) to read the data directly from images of the survival curves taken from the publication. We conducted a number of experiments to estimate the scale of any error introduced by using this software.

2.2. Analysis

Given that in MPM the published survival curves fall close to zero, it is possible to estimate the mean survival in different patient groups. We did this for each of the four groups A–D listed above by estimating the area under the relevant survival curve (see Fig. 1). We then calculated the mean survival for all those that had resection (C and D) and then for all those that did not (A and B). We obtained an upper estimate for any survival benefit associated with management incorporating resection by taking the difference between these last two estimates.

3. Results

The accuracy of the UN-SCAN-IT software was measured as ±0.3%, with repeated scanning of the exploratory thoracotomy survival curve yielding estimates of the mean survival that varied by no more than 7 h. We considered this performance of the software sufficient for the purpose.

Fig. 2 shows the number of patients in each group of interest as a flow chart, based on the breakdown of the 945 patients in the MSKCC report diagnosed with malignant pleural mesothelioma, along with the calculated mean survival for several groupings.

Mean survival was estimated as 16.8, 17.8 and 17.0 months for those having no surgery (A), thoracotomy alone (B) and resection with no adjuvant treatment respectively (C) and 32.9 months for those having multimodality treatment (D) (Fig. 2). The mean survival for those having resection (groups C + D) was estimated as 25.6 months and the mean survival for patients having no resection (groups A + B) was estimated as 17.1 months. We, therefore, estimate that the survival benefit attributable to management including resection is at most 9 months, noting that this is consistent with there being no benefit whatsoever [9].

This estimate of 9 months is the most optimistic estimate and requires all observed differences in survival to be attributed to the effect of treatment and none to selection for treatment. Furthermore, within this upper estimate is included any benefit from other components of multimodality treatment.

4. Discussion

First, the use of mean rather than median survival in this analysis must be explained; different statistical measures have different uses. The median is a summary statistic familiar to, and appropriately used by, surgeons because it is less sensitive to the inevitably skewed nature of the data we often work with, such as the length of stay in hospital or postoperative blood loss. We know that for these variables there are patients in whom the data are extreme. An occasional patient who lingers for 6 months in hospital or one
who receives 30 l of transfusion, for example, does not reflect what a typical patient might expect. However, an analysis of resource consumption would, appropriately, be based on the arithmetic mean.

In cancer surgery, median survival is used to quantify treatment effects for a different reason. The median provides a stable summary statistic once the survival curve falls <50% [10]. However, it has its limitations. Suppose that a life-saving treatment is possible for an otherwise 100% lethal constellation of injuries in young men involved in motorcycling. There is an early mortality of 51% but the 49% surviving live a normal life span, of say, 45 more years after operation. The median survival would remain zero the addition to the mean life expectancy would be >20 years. Benefits in mesothelioma do not come close to these figures but the operation is performed in the hope that some patients, probably a minority, will go on to be long-term survivors. The median will not capture those gains.

The critical piece of information a patient might want to know is how much time the treatment might add. Multivariate analysis can be used to generate a plethora of P-values [7,11] such that in a very large dataset a very small difference (which in drug trials may be a few weeks) may generate P < 0.001, but a well-informed patient might not consider the expected gain in time sufficient to undergo trimodality therapy.

Analysis of survival based on observational data has limitations. First, any differences in survival between groups having different interventions may be entirely due to careful and well-informed clinical selection either prior to or at thoracotomy. Second, there may be a self-selecting survivor effect: a patient undergoing the second component of multimodality treatment, in whatever order treatments are administered, has to be alive, and well enough, to enter the second component. However, it is in the nature of surgical reports that survival analysis relies heavily on observational data and we have to do the best we can with what we have.

By assuming that there was no selection bias in favour of un-operated patients and then attributing all observed survival differences to resection, we obtained an upper bound of ~9 months for any survival benefit associated with management incorporating resection (Fig. 2).

The MSKCC report does not allow any more information to be extracted about the relative merits of EPP versus P/D [7]. Other reports suggest that there is no disadvantage in terms of survival for patients having lung-sparing surgery [11,12] and that the more radical operation of EPP rarely if ever results in disease-free (R0) resection margins [4].

MPM is not a disease in which we are making progress with surgery. Recently, Tillman et al. reported 13-month survival in patients having EPP with hyperthermic intra-operative chemotherapy, but 10 years ago the same group reported a rather longer 19-month survival [13,14]. It has now been shown by the Mesothelioma and Radical Surgery (MARS) trialists that a randomised trial is possible [15] but in planning future studies we need data on which to design and power a clinical trial. Multivariate analysis may indicate prognostic difference between groups of patients with various factors, such as histological type, but what we require is an estimate of the effect attributable to surgery, that is, the added time of survival in months or years. Based on our analysis the most it can be is ~9 months. The authors of the MSKCC report conclude that their study ‘provides a modern benchmark against which future studies can be compared’ and we have re-analysed their data with that objective in mind.

References


