Editorial

The management of malignant pleural mesothelioma in the USA 2004-13—a decade of lost opportunity?

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In a detailed, recently published, retrospective analysis, Saddoughi and colleagues (1) have studied the records of patients with malignant pleural mesothelioma (MPM) held in the National Cancer Database of USA from 2004 to 2013 with their main focus being an analysis of treatment trends. From a database of over 19,000 patients one of the most disappointing statistics was the finding that around 40% of patients with MPM received no active treatment. Of the remainder, in what must be assumed to be a palliative program, chemotherapy alone was given to 31%. No details were available on individual agents or duration of regime. Analysis of the demographics of this population suggest that many patients were actually potentially suitable for radical treatment as they were relatively fit and had potentially treatable disease. Over two thirds had a reported Charlson index of 0 and many had early clinical stage disease with 35–40% T1 or T2 and an estimated 50% were node negative.

This lack of active treatment in apparently suitable patients may be explained by the concerning finding that there seemed to be little attempt at disease assessment in a large proportion. Up to 30% remained unstaged with an unknown T or N stage. Furthermore, there remained a very high level of 45% of cases with no specified cell type of mesothelioma, although this level was found to be decreasing with time. Less clinical and more pathological diagnosis did appear to be entering clinical practice.

The apparent finding that overall 1 in 4 underwent surgical resection belies the fact that there is no more detailed information about the radicality of the operation. The associated findings that only 12% underwent bimodality surgery and chemotherapy and an even smaller group of 3.3% received trimodality surgery and chemoradiotherapy suggest that most surgery was palliative and aimed at effusion control by pleurodesis. The seemingly low early (30 and 90 days) mortality again is compatible with a very low number of patients undergoing radical therapy. It is interesting to note that in nearly 1 in 7 who underwent surgery there was no cell type specified implying a lack of specialist pathological input. The anomalous finding that surgery was most frequent (38%) in those with biphasic disease is explained by the high number with no cell type (who were presumably mainly epithelioid) and the confounding factor of larger tumour sample size in those undergoing resection.

Similar to previous analyses of the SEER database (2,3), the best survival (median 20 months) was associated with trimodality treatment. It can be no coincidence that better survival in this analysis is also associated with higher income and private insurance. One can only assume that these individuals had easier access to specialized academic institutions.

It is ironic that the authors conclude that "*further research is needed to improve survival and overall patient outcomes*" after documenting the records of nearly 20,000 cases over a 10-year period. One wonders how many or indeed how

few of this enormous potential population were actually enrolled into clinical trials? Before this decade the now defunct Lung Cancer Study Group had investigated various surgical treatment regimes (4). During this period also several excellent single -institution studies had suggested potential benefits from surgical protocols including adjuvant intrapleural chemotherapy (5) and photodynamic therapy (6) and the potential benefits of lung-sparing radical surgery (7). In addition some feasibility studies were completed (8) but no full multi-centre phase III studies was ever forthcoming. The infrequent use of chemotherapy in this review is surprising since the large multi-centre, multi-national study outlining the benefit of pemetrexed was published in this time period (9).

Contrast the American experience with that of the UK and Europe. In the UK the MARS phase III feasibility study of extrapleural pneumonectomy (EPP) versus chemotherapy (10) was published, drawing heavy criticism from many in the USA (11), as was the MesoVATS complete phase III study of partial pleurectomy versus talc pleurodesis (12). In addition the EORTC (13) and the SAKK (14) in Switzerland completed phase III studies of radical trimodality therapy including EPP. The conclusions of these trials have been largely negative but they have stimulated further trials of radical surgery in the form of extended pleurectomy decortication (EPD): MARS2 (15) and EORTC 1205 (16), which are ongoing.

How much further forward in the understanding of the treatment of MPM would we be now if only a small proportion of these 19,000 patients had been enlisted into a prospective randomized trial? In terms of the incidence of MPM, the horse may have bolted well down the yard in USA now and may be heading out of the stable in Western Europe. However, in the vast potential populations India and China the effects of recent unrestricted asbestos usage on the likely epidemic of MPM are yet to be seen.

The need for prospective randomized trials to exclude selection bias in typically fit males with earlier stage disease at presentation who are suitable for radical treatment protocols is obvious (17,18). Yet one can contrast the recent transatlantic guidelines for the management of MPM to see the different approach. Whilst the British Thoracic Society (19) has adopted a typically conservative attitude when they recommend radical surgery only as part of a clinical trial and boldly declare no role for EPP (on the basis of one small feasibility study). In contrast the American Society of Clinical Oncology strongly recommended that in selected patients with early-stage disease (node negative, epithelioid) a maximal surgical cytoreduction should be performed (20). Furthermore, it is strongly recommended that patients with ipsilateral histologically confirmed mediastinal lymph node involvement should undergo maximal surgical cytoreduction in the context of multimodality therapy (neoadjuvant or adjuvant chemotherapy). Encouragingly, it is recommended that these patients should be enrolled in clinical trials.

The nihilism evident in the Saddoughi paper across USA in this time period (which was of course not unique to that side of the Atlantic) is self-fulfilling. A watch and wait policy is effectively letting the cancer take control and would be socially unacceptable in other tumour sites i.e., breast. The intention to only begin to treat cancer in an advanced stage will inevitably lead to the apparent lack of effective therapy and so the cycle is perpetuated. The increased awareness of the risk of the asbestos-exposed population should lead to earlier presentation. There is then a need for accurate initial staging and assessment, the appropriate institution of clinical trials and most importantly the reporting of stage-specific, cell-type specific long term survival. As quite cogently expressed by Valerie Rusch (21), the UK is ideally suited to conduct large, multi-centre clinical trials by virtue of the structure if its healthcare system. The difficulties in preventing voluntary cross-over in trials in USA are accepted; these are not so applicable in a state-funded, controlled healthcare system.

As the mesothelioma epidemic spreads West to East across the 21st Century and peeks in Western Europe in the next 5 years we are duty bound to recruit to treatment trials and fight back the voices of nihilism of the doomsayers. The lesson from the American experience in the last decade, nicely outlined by Saddoughi et al, must be that to do nothing is akin to doing harm and active participation must replace passive observation.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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