The Need for Randomized Trials in Mesothelioma: Let's Walk the Talk

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In reviewing the use of radiotherapy for malignant pleural mesothelioma (MPM) in this issue, Price is unable to find evidence for benefit for any of the three clinical applications he considers: modifying the progression of disease, its local control, or palliation of pain [1]. Since the comprehensive and systematic review from McMaster University [2], now 5 years old, Price finds that nothing has happened and suggests that more randomized trials are needed.

The plea for more randomized controlled trials (RCTs) of radiotherapy by Price and others [3] has a certain irony. The only RCTs of radiotherapy in MPM concern port site prophylaxis, for which he finds that radiotherapy continues to be performed despite the lack of convincing supporting evidence. In the meantime, the big questions such as “can radiotherapy prolong life?” and “does radiotherapy achieve useful palliation?” have not even been properly addressed let alone answered. This is a sorry state of affairs. It appears that as far as MPM is concerned, radiation oncologists may be open to the same criticism as was leveled at surgeons in the now notorious *Lancet* editorial comparing surgical research with “comic opera” [4]. The Mesothelioma and Radical Surgery (MARS) trial, an RCT of extrapleural

pneumonectomy (EPP) followed by radiotherapy, proved that such trials are feasible, but accrual was slow and the difficulty in conducting such trials should not be underestimated [5]. But when random allocation appears difficult to the point of impossibility, rather than simply give up, we should consider alternative means of achieving fair but critical evaluation of our interventions.

It is worth deconstructing the RCT paradigm to consider the individual merits of its several features; there are a number of elements to an RCT other than randomization. Detailing the inclusion and exclusion criteria in the study protocol allows the scientific community to know how well the sample studied reflects the intended population. In an RCT, the outcomes of interest are prespecified and are recorded for all patients entering the study. Patient characteristics and outcomes are recorded for all patients entering the planned treatment, not just for those completing it, and the outcomes reported should be those planned [6]. This level of rigor need not be limited to RCTs and provides valuable information not captured with retrospective chart review. We know from the nonrandomized European Organization for Research and Treatment of Cancer 08031 study, for ex-

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ample, exactly how many patients completed the planned treatment within the planned time frame [7]. In contrast, the paper that “heralded” a resurgence of interest in EPP for MPM illustrates the consequences of omitting these elements. “The treatment plan” was EPP, chemotherapy, and radiotherapy, but only 120 patients who completed all three components were reported [8]. Patients who completed radiotherapy, the third modality, are inevitably selected both by their survival and by clinical judgment as they progressed through such an arduous course. In a subsequent report, perioperative deaths were also omitted [9]. Clinicians justify extreme treatments, among which trimodality therapy for mesothelioma must surely qualify as “at least giving hope,” but the hopeful patient is entitled to know what happened to other patients who embarked on the journey.

With regard to “intention to treat” analysis, more recent publications show better reporting. The MD Anderson results of intensity-modulated radiotherapy (IMRT) were not presented as 63 patients receiving radiotherapy, but as 100 patients intended for the treatment, of whom 37 did not get as far as receiving radiotherapy [10]. As Price correctly points out, radiation oncologists should be more critical in evaluating combined modality treatments for MPM. IMRT is a technique that allows for better sparing of critical organs in close proximity to the target volume. In the setting of MPM after EPP, radiation oncologists are confronted with patients who have survived major surgery, and the hope is that mopping up the remaining cells with radiotherapy will improve survival. The challenge posed by close proximity of critical organs, such as the heart, liver, and contralateral lung, has led to an undue focus on techniques using recent advances in thoracic radiotherapy to minimize collateral damage. We need to know the outcomes for all patients for whom such treatment was intended.

In an RCT, as much attention is paid before randomization to characterizing patients who, as yet unidentified, will ultimately constitute the control group; after randomization, their outcomes are as assiduously collected. In uncontrolled studies, surely some reasonable effort should go into estimating the contemporary survival for patients like those who have been treated. For mesothelioma, such data exist. Consider survival among eight groups numbering 136–381 patients, to a total of 1,821. Some data come from RCTs of chemotherapy [11, 12], in which an 8-month median survival time for untreated patients and a 9- to 12-month median survival time for patients treated with various chemotherapy regimens have been reported. A large institutional database [13] showed a 10-month median survival duration for patients selected for nonoperative management

and a 13-month median survival duration for patients having only exploratory thoracotomy. Prior to embarking on the MARS trial, median survival of patients (untreated as far as is known) were found to be 7 months ($n = 175$) and 13 months ($n = 234$) in different London hospitals, one inner city and one suburban [14]. So we have survival data in the range of 7–13 months. The problem is that, depending on whether you chose 7 or 13 months, a 10-month median survival time [10] might appear to be a 3-month loss or 3-month gain and authors have felt free to choose. An RCT is ultimately the only way to ensure that a fair comparison is made.

An RCT also protects against unwarranted optimism in recall of the data. Hope is a gentler word than bias, but nonetheless it can stand between us and objectivity in assessing the real effects of our treatments. Presumption of efficacy is one of the inevitable biases when practitioners review their own practice [15]. “We tried so hard—surely there must have been some benefit”: these are thoughts shared by doctor and patient. In the repeated use of the phrase “a role for” radiotherapy, Price is reasonably seeking effectiveness for the treatment radiation oncologists are there to deliver [1], but to an outsider it might sound like Mark Twain’s apocryphal man with a hammer. Practitioners would be well advised to seek formal and impartial evaluation of treatments in collaboration with independent health service researchers [2, 16].

But there is a fundamental flaw in the cry for more RCTs. It is in the nature of randomized studies that there must already be uncertainty before we can randomly allocate patients to forgo a particular treatment. Berwick [17] used radical mastectomy as a classical example wherein an RCT [18] changed practice and yet a contextualized reading of the historical evidence shows that the practice had already moved away some years earlier [19]. The RCT was preceded by considerable doubt about the merits of radical mastectomy rather than prompting that doubt: practice was already changing. It is to be hoped that such changes are based on something more than “prevailing . . . fashion” (*pace* Price) [1].

There are areas of MPM practice in which RCTs may be unnecessary. Pre-emptive radiotherapy to port site drain tracts may be illustrative. If port site recurrence is not regarded by patients as a significant problem, as Price reveals [1], then radiotherapy could be held in reserve for the instances when it is a problem. An RCT is a cumbersome way of discovering such fundamental information more easily found in a well-planned observational study. Establishing whether trimodality therapy as a package improved survival has not been resolved by observational studies, however [15, 20]. Results of the MARS randomized trial, if

accepted, would make trimodality therapy including EPP no longer justified [21], and post-EPP radiotherapy may come under scrutiny after results of the ongoing Swiss SAKK trial become available (ClinicalTrials.gov Identifier, NCT00334594). Without prior EPP surgery, high-dose hemithoracic radiotherapy is not feasible with the involved lung in situ. Radiation oncologists would do well to focus on the big picture and run appropriate studies to resolve big questions, rather than immerse themselves in details of de-

livery approaches for MPM, such as volumetric modulated arc therapy [22] and proton therapy [23]. So let's walk the talk and plan studies appropriate to the question and where necessary, they should be randomized.

AUTHOR CONTRIBUTIONS

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