Pulmonary Metastasectomy: Are Observational Studies Sufficient Evidence for Effectiveness?

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A systematic review of pulmonary metastasectomy for sarcoma was published in 2012 [1]. There were no control data, only multiple surgical follow-up studies. Two further uncontrolled studies of metastasectomy for sarcoma were published in The Annals after completion of the review [2, 3]. In addition, after a search of The Annals since January 2010, 10 additional follow-up reports of pulmonary metastasectomy were found for a range of cancer types. The authors all state that they operated on carefully selected patients, but none provided the characteristics or the magnitude of the patient population from which this careful selection was made. When a practice is highly selective, the apparent benefit can be a result of choosing those naturally destined to do well rather than that the surgery benefits the patients. The argument has been well formulated previously in The Annals [4].

There are many interventions and operations in surgery that were introduced and have become established practice based on what Dr Edmunds calls “clinical impression.” The phrase is in quotation marks because the very words have come to have a pejorative ring to them, but when a treatment works dramatically and consistently, and it makes a similarly favorable impression on successive observers, there may be sufficient weight of evidence from observational studies alone.

We give two examples in which observational studies led to an accepted clinical practice. In one, uncontrolled observational evidence appears to remain sufficient. In the other, surgeons were misled for more than 80 years, and it took a randomized controlled trial to show the error. There were important differences both in the nature of the disease and in the intervention that allowed one to be regarded as proven based on uncontrolled observation, whereas the other required a controlled trial to refute it.

Thomas Splint for Femoral Fracture

Hugh Owen Thomas (1834–1891), from a family of bonesetters in Wales, invented his traction splint in 1875. Femoral fracture was a common injury in boys and men working in coalmines, on hill farms, and with horse-drawn transport. From experience in the emergency department, features of the injury are familiar, such as pain, blood loss, the limb being shortened and rotated by the pull of the thigh muscles. Application of the traction splint gently brings the leg out to length, eases pain, reduces bleeding, and allows the angle of the foot to be corrected. Before going to medical school, Robert Jones (1857–1933) worked with his uncle Hugh in Liverpool from the age of 16, and in 1915 it was Robert Jones who introduced the device to the British and French armies. There are several features that mark the Thomas splint as an intervention that can be adopted on clinical impression alone: there is a close temporal relationship between the intervention and the benefit; the traction splint makes mechanistic sense; the benefits are evident within the time frame of the clinical encounter; and the natural history of the disease is reproducibly altered for the better. By the end of the World War I in 1918, the clinical benefit was accepted and it remains so.

Halsted Mastectomy

Radical mastectomy for breast cancer, following the principles set out in 1894 by William Halsted (1852–1922), was also widely accepted. So secure was its place that a surgeon who performed a lesser resection might have been blamed for the death of any woman in whom cancer recurred. This belief was challenged in 1970 in a scholarly essay of more than 50 pages by Bernard Fisher, and the credit for clinching the argument goes to Umberto Veronesi’s randomized trial in 1981 showing no survival advantage for radical mastectomy. Unlike the Thomas splint, the time scale was far too long for effectiveness to be judged by eye. We now know that the impression of benefit was an illusion and that the natural history of breast cancer is not altered by the radicality of the surgery. Observation alone did not allow the signal to be distinguished from the noise.

Pulmonary Metastasectomy for Sarcoma

Which example is nearer to the practice of pulmonary metastasectomy for sarcoma? There can be little question that bloodborne disseminated sarcoma is a clinical situation nearer to breast cancer than femoral fracture. As a result, a randomized controlled trial may be needed to determine whether the believed survival benefit of resecting pulmonary metastases from sarcoma is “fact or fiction” [4].

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At the time of the retreat from radical surgery in the management of breast cancer in the 1970s, an advance was being made on metastatic sarcoma. Surgeons at Memorial Sloane-Kettering published the view that “Early detection of pulmonary metastases . . . and surgical excision of all metastases, by repeated thoracotomies if necessary, appear to be the treatment of choice” [5]. They followed their patients assiduously and reported on their fate more than 10 years later, and again after 20 years [6]. Sarcoma almost always returned and usually killed the patient.

In a systematic review, 20% to 50% of sarcoma patients are alive 5 years after their first pulmonary metastasectomy [1]. This survival is attributed to the effect of surgery, because the background assumption is that 5-year survival without operation is near zero. This assumption is false and misleading. In a large cancer registry, the overall 5-year survival was 25% for bone and 15% for soft tissue sarcoma metastatic at registration [1]. In addition, not all of the much smaller difference between an observed and a more realistically expected 5-year survival can be attributed to the metastasectomy [4]. Well-judged clinical selection among these patients, narrowing in on those with inherently better prognosis, means that higher 5-year survival will be observed because of the selection itself. Having a second or subsequent metastasectomy requires a patient to have survived long enough and well enough to undergo additional metastasectomies, introducing a selection bias in favor of naturally better survivors. It is not that data are scarce. In fact, data are plentiful and follow-up studies continue to appear. The problem is that data are routinely misinterpreted [2]. In the absence of a control group from which to derive the outcome without surgery, the assertion that “repeated and aggressive pulmonary resections . . . extends survival” cannot be derived from the reported observational data.

To add to our concerns, are there grounds to believe that pulmonary metastasectomy is palliative? Not in any measurable sense—breathlessness is not relieved or prevented. On the contrary, breathlessness contraindicates repeated operations [7].

Is a Trial of Pulmonary Metastasectomy for Sarcoma Ethical or Feasible?

British and European sarcoma experts who advise the European Organisation for the Research and Treatment of Cancer have responded to our suggestion that it is time for a trial [7]. They point to the small numbers of patients, the variability of the pathology, the lack of response to chemotherapy, and the perceived need to be doing something. These responses are familiar, and they indicate that a trial of pulmonary metastasectomy is impossible. Currently, whether the evidence is indeed sufficient, or that the obstacles to a randomized controlled trial are insurmountable, there is insufficient doubt among clinical experts to make a study of pulmonary metastasectomy in sarcoma workable.

Let us reexamine the sequence of events in the abandonment of radical mastectomy. Many, maybe most surgeons, were no longer performing radical mastectomy by the time Veronesi’s trial was reported. In 1978 Harold Ellis, a doyen of surgical teaching, was invited by the British Medical Journal to review treatment of breast cancer. He wrote that “A wide range of operations is available, ranging from lumpectomy at one end of the scale to super-radical metastasectomy . . . there is no evidence whatsoever that any one operation offers any increase in life expectancy over the others.” He made no further mention of radical mastectomy, and no one mentioned it in the subsequent correspondence. The operation was already in decline. With a little thought, it is evident that there has to be sufficient doubt about a practice before a trial, in which half of the patients are not given the treatment, can be run. Veronesi’s trial remains vitally important, but it is as the last word rather than the turning point. As surgeons, we should be grateful for secure evidence to add to our clinical judgment when making the most difficult of all surgical decisions: when not to do an operation.

And spare a thought for the surgeons who had tenaciously held to Halsted’s principles and had to look themselves in the mirror knowing that the world might take the view that throughout their careers they had mutilated women to no avail. We should reflect on this now as we hold the editor’s mirror to our faces. When we read in clinical reports of the repeated and aggressive surgery endured by the many patients, we must have some concern about what surgeons are willing to do and what patients are prepared to endure. Patients and their families have also wondered how much of their suffering was worth it when writing nonmedical accounts of modern cancer care. Will it perhaps be from the public that a demand for better evidence will come?

The Art of the Possible

If a trial of metastasectomy in sarcoma is impossible, why not do what is possible? Colorectal cancer is one of the three most common cancers and by far the most common reason to perform pulmonary metastasectomy. Those informing patients on management should be aware of the latest evidence from survival analyses. From one of the largest reported series to date (N = 378) authors from Duke University and Memorial Sloane-Kettering cancer centers in 2009 concluded that “medical management alone should be considered standard for patients who have both three or more pulmonary metastases and less than 1 year [disease-free interval]” [8]. Recently, in the most comprehensive systematic review to date that includes extensive metaanalysis of international data [9], the analysts found that any more than a single metastasis doubles the hazard ratio for further recurrence. The conclusion is softened with the words that “it seems currently unfair to deny surgery for those patients with two to four lesions.” The words unfair to deny convey uncertainty of the actual benefit.

Patients now can be told, and should be told, that even when metastases are few in number there is uncertainty concerning survival benefits from metastasectomy. The
situation is therefore amenable to a randomized controlled trial of pulmonary metastasectomy in colorectal cancer [10] that is currently recruiting patients in Europe.

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References