Survival is higher after repeat lung metastasectomy than after a first metastasectomy: Too good to be true?

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The authors of the International Registry of Lung Metastases reported that survival was higher for a second compared with a first metastasectomy operation after 5 and 10 years (44% vs 39% and 29% vs 25%, respectively).[1] Pastorino and colleagues[1] wrote "The long-term outcome of patients who were treated by a second metastasectomy was remarkably good." The word "remarkably" provides the clue. The finding seemed to be too good to be true.

Similar observations have been made repeatedly for sarcoma, which is the most established clinical indication for lung metastasectomy. In a systematic review of 14 follow-up studies composed of 1357 patients, 579 received a repeat metastasectomy (43%; range, 21%-79%).[2] The observation that repeat metastasectomy was followed by higher survival has been made repeatedly.

- "Prognostic factors for increased survival included 3 or greater redo pulmonary operations…"[3]
- "…patients with complete resection for recurrent pulmonary metastasis show a significantly better prognosis after repeat pulmonary metastasectomy."[4]
- "…repeat metastasectomy for recurrent pulmonary metastasis also provided a favorable overall survival ($P = .041$)."[5]
- "Repeated and aggressive pulmonary resections for leiomyosarcoma metastases extend survival."[6]

The practice of repeated metastasectomy has become part of the mantra of "treating cancer as a chronic illness."[7] "…patients persistently free of the primary osteosarcoma who developed recurrent resectable metastatic disease of the lung should be considered for reoperation a second, third, or fourth time."[8]

For colorectal cancer, there is a similar acceptance of repeated lung metastasectomy that increased from a rate of 15% to more than 20% from the 1960s to 2000s in an analysis of 51 studies including 3504 patients.[9] Repeated metastasectomy was noted as practice in the review of lung metastasectomy in 1539 patients[10] that formed part of the European Society of Thoracic Surgeons Lung Metastasectomy Project.[11] It was also recorded in a later comprehensive analysis of colorectal cancer lung metastasectomy in 2925 patients.[12]

In this statistical analysis, we take a closer look at how survival data are presented and suggest that a more skeptical view of this conclusion is warranted.

GRAPHIC DISPLAYS OF SURVIVAL: WE SHOULD NOT ASSUME THAT THE LINES CAN BE COMPARED

The Roman surgeons Tommaso Mineo and Vincenzo Ambrogi had for 25 years followed a policy of repeat metastasectomy. A Kaplan–Meier analysis undertaken for them showed that of patients who underwent multiple metastasectomy operations, 65% were alive at 5 years compared with 42% who underwent only 1 metastasectomy operation (Figure 1). In common with the authors of the landmark International Registry of Lung Metastases, they found this somewhat counterintuitive and invited the co-authors (Francesca Fiorentino and Tom Treasure) to review the analysis.

Figure 1 shows a familiar generic approach to displaying survival data that would be entirely appropriate if there were 2 treatment strategies randomly assigned. To permit comparison, a specified starting point is taken as time zero on the horizontal axis and the vertical axis shows the loss of patients due to death, accounting for censoring. The explicit purpose is to allow visual comparison. If the patients had been randomly assigned to *either* a policy of once only metastasectomy *or* a policy of repeated metastasectomy, then the inference might be drawn that a difference in survival was due to the different treatment plans. The method fails as a means of fair comparison if the patients themselves differ in ways that influence survival. Then the difference may be due to the patients' characteristics rather than the treatment they received. We will call the summary of these patient characteristics "survivability." Clinicians are aware of these patient characteristics, but they cannot all be retrieved from even a comprehensive research database and certainly not from a registry.[13]

THE IMPORTANCE OF THE DENOMINATOR

Estimates from various sources indicate that of all patients who are found to have metastases, less than 1 in 20 will

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Received for publication Nov 25, 2014; revisions received Jan 17, 2015; accepted for publication Jan 29, 2015; available ahead of print March 20, 2015.

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J Thorac Cardiovasc Surg 2015;149:1249-52
0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2015.01.067

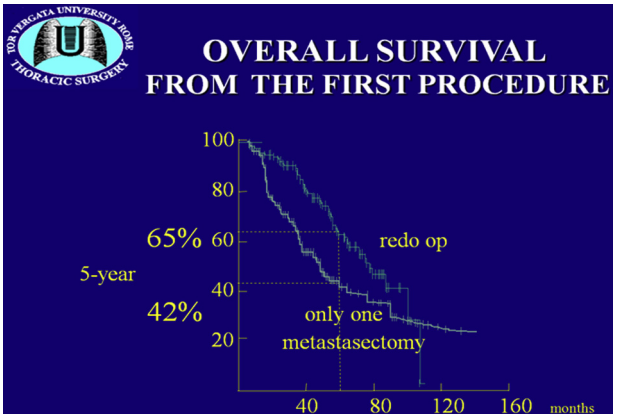

FIGURE 1. Kaplan–Meier analysis of 113 patients who underwent repeat metastasectomy operations alongside that for patients who underwent only 1 metastasectomy. Used with permission from Mineo TC, Ambrogi V, Tacconi F, Mineo D. Multi-reoperations for lung metastases. *Future Oncol*. 2015;11:37-41.

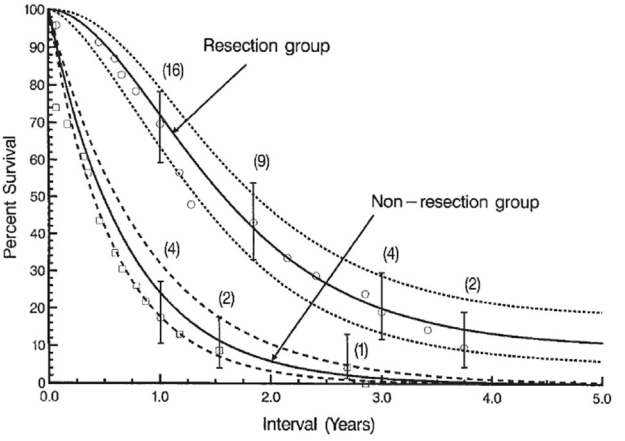

FIGURE 2. Survival after the last appearance or resection of metastases in the resection and nonresection groups. Each *symbol* represents a death, positioned according to Kaplan–Meier nonparametric estimates with *vertical bars* equivalent to 1 standard error. The *solid lines* are parametric survival estimates enclosed within confidence intervals (*dashed lines*) equivalent to 1 standard error. The numbers of patients living and being followed up are shown in parentheses.

have a lung metastasectomy.[14-18] With each successive metastasectomy, the degree of selection from the original denominator is greater; the apparent denominator diminishes as seen in the Roman surgeons' data (Table 1). We can deduce that approximately 1 in 100 of the original denominator received a second metastasectomy and 1 in 1000 received a fifth metastasectomy. These were not randomly selected from the original denominator; at the very least, they had to still be alive. Difference in survival cannot be ascribed to the number of metastasectomy operations they had undergone.

In a study of liver and lung metastasectomy from the Cleveland Clinic, denominators are provided.[16] The upper line on the graph in Figure 2 relates to 25 patients who underwent both a liver and a lung metastasectomy. Seventeen patients who underwent a first liver metastasectomy had a subsequent lung metastasectomy, and 6 patients underwent a lung metastasectomy first. The lower line relates to 23 patients who had both liver and lung metastases but did not undergo any liver or lung metastasectomy. During the same time frame, 5787 patients had resections of primary colorectal carcinomas, 466 patients had resections of isolated colorectal hepatic metastases, and 72 patients had resections of isolated lung metastases. The selection of patients for metastasectomy was by individual clinical evaluation, and proceeding with the second metastasectomy operation was contingent on further individual clinical evaluation of the patient. The outcome was not reported on intention to treat but on completed treatment.

However sophisticated the analysis, it is impossible to know how much of the survival difference shown was due to inadvertent selection of patients inherently most likely to live longer (survivability) rather than an effect of sequential metastasectomy operations. Although the analysis is carefully justified in the text, it might be argued that it was misleading to put the lines next to each other in the depiction, implicitly inviting a comparison between 25 and 23 patients with lung and liver metastases who in the event (but not by intention to treat) had both or neither resected.

READING THE SHAPE OF THE CURVE

If a picture is worth a thousand words, it is worth studying the survival graph to see what the picture tells us. We are familiar with cancer survival curves that generally follow the shape of the lower lines in Figures 1-3. The upper line in each has an early more horizontal component *not* seen in natural cancer survival graphs. Lung metastases are

TABLE 1. Intraoperative intervals

Metastasectomy operations	Patients	Interval before	Median months	Minimum	Maximum	25%	75%
		First	14	0	70	5	24
≥2	113	Second	22	6	96	14	34
≥3	54	Third	23	10	64	17	39
≥4	31	Fourth	22	6	44	12	27
≥5	8	Fifth	13	4	96	11	13
6	4	Sixth	8	7	70	7	9

Unpublished data (T. Mineo, V. Ambrogi, June 2014). The available data can be obtained by request to the authors.