Editorial

Surgical series in mesothelioma: navigating between biases

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In the manuscript of *Translational Lung Cancer Research*, Klotz *et al.* reported their surgical multimodality treatment outcomes in a single-centre mesothelioma population treated in Heidelberg University Hospital, Germany, from 2001 to 2018 (1). From 2001 to 2012, they applied extrapleural pleuropneumonectomy (EPP) as their surgical procedure, whereby macroscopic debulking is obtained by resection of lung, pleura and adjacent tissues (pericardium, hemidiaphragm, previous incision tracks…). In 2013, they changed their modus operandi to extended pleurectomy/decortication (EPD), a less aggressive procedure in which the lung is left in place (with the exception of macroscopically invaded parts of the lung). This creates two *successive* cohorts for comparison.

EPP was popularized after the 1999 surgical series by Sugarbaker *et al.*, reporting a median overall survival (OS) of 51 months in 31 patients with epithelioid histology, negative resection margins, and negative (extrapleural) lymph nodes (2). Many surgical series were to follow. In this series, Klotz *et al.* reported a more modest median OS of 24 months (1). Because Heidelberg is not Boston? Perhaps. But not really. Sugarbaker's 31 long survivors were part of a surgical cohort of 183 patients (16.9% of EPPs), in which median OS was 15 months in the 176 patients who survived the procedure. At least part of the difference in survival is selection bias: Sugarbaker *et al.* reported on the best of the best (2). But even this series (and every surgical series with it) is reporting on the best: early-stage disease (stage I–IIIA), excellent performance score (PS) (0–1), not too old (median age reported generally <70 years, even <65 years), epithelioid histology only. In this trial, a third cohort of patients who received chemotherapy only, is reported for comparison. These significantly older patients have a significantly poorer outcome, as you would have expected, being no candidates for surgery. That this bias is not necessarily the rule is demonstrated in a fairly large series of patients (n=116) with good prognosis, i.e., epithelioid subgroup, early stages, and good PS, who had not been submitted to surgery. In the subgroup of 51 patients aged 70 years or less the 1-year survival was 88% and the 3-year survival 18%, with a median survival of 21.5 months (3).

This brings us to a second bias in surgical series: comparison bias. The ideal patient to compare your surgical patient to, is a similar patient who did not get surgery. The 2011 Mesothelioma And Radical Surgery (MARS) feasibility trial in the UK (4), tried to randomise between 'EPP' (and chemotherapy) and 'no EPP' (and chemotherapy). It did not appear this simple, as of the 24 patients in the EPP group only 16 received an EPP (and 8 adjuvant radiotherapy). Six patients randomised to 'no EPP' crossed over to some form of resectional surgery.

In the first decade of the 21st century, a number of surgical multimodality phase 2 trials (with EPP) were performed, reporting OS data of up to median 29.1 months

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in the US trimodality trial (5), at least for those who managed to tolerate all three modalities! OS was reduced to median 16.8 months in the overall population, which is not very impressive if you compare this to today's OS data in trials with systemic therapy only. The US trial emphasizes clearly the third bias in surgical series: shrinking denominator bias. Of the 77 who started neoadjuvant chemotherapy, 57 (74%) advanced to EPP; 40 (52%) eventually reached the finish line.

In order to cope with this bias, the European Organisation for the Research and Treatment of Cancer (EORTC) developed a new statistical composite endpoint, rate of success. This endpoint is defined as successful completion of all treatment modalities, being alive, with no signs of disease progression, and no residual grade 3–4 toxicity. This endpoint was first used as primary endpoint of its 08031 trial (6): 64.9% of patients successfully underwent all three modalities; but only 42.1% met the primary endpoint, due to relapse within 90 days or residual grade 3–4 toxicity. They were rewarded with a median OS of 33 months.

Today, EPP has largely been replaced by EPD as the preferred surgical intervention after the MARS feasibility trial, which concluded that 'radical surgery in the form of EPP within trimodal therapy offers no benefit and possibly harms patients', although it was not powered to draw this conclusion (4). A meta-analysis of seven surgical series by Cao *et al.* nevertheless suggested no significant difference in OS after switching to EPD (7).

In a 2004–2011 series, Lang-Lazdunski *et al.* reported on 52 British mesothelioma patients who completed the full multimodality treatment of EPD and adjuvant chemotherapy (8). With a median OS of 23 months compared to 12.8 months for a matching (but not randomly allocated) cohort with EPP (n=22), a statistically significant difference in OS was found. In epithelioid histology (as in the Heidelberg cohorts), median OS was even higher: 28.9 months [L-L]. More patients (63%) had stage III+IV compared to the Heidelberg series (23%), which may explain the median OS of 38.1 months in the latter series.

The EPP cohort received neoadjuvant chemotherapy; the optimal sequence of surgery and chemotherapy is not known, but may be relevant; this may further cloud comparison. The previously described EORTC composite endpoint has subsequently been used as primary endpoint in the EORTC 1205 trial, in which adjuvant and neoadjuvant chemotherapy are compared in patients with borderline resectable mesothelioma, applying EPD as the surgical intervention (9). Borderline resectable tumours include stage II and IIIA tumours. T3 involvement of the chest wall may be resectable on the condition that there is only limited invasion, e.g., extension along a previous thoracoport incision. Ipsilateral N1 nodes are borderline resectable when located in the mediastinum. However, bulky tumours with extracapsular involvement or invading a large vessel, e.g., the superior vena cava, are considered unresectable. Degree of involvement of the fissure till the branches of the pulmonary artery will determine whether an EPD is still possible. In case of central involvement of the pulmonary artery, an EPP is required. Results of this EORTC trial are expected shortly.

In conclusion, we recommend future retrospective series on surgery in mesothelioma to avoid the abovementioned biases by (I) including a matched cohort analysis with non-resected patients with as much as possible comparable prognostic factors; (II) reporting the results of modern systemic therapy in this cohort; and (III) reporting an intention-to treat-analysis in all patients with similar characteristics or else clearly indicate the waterfall of the shrinking denominator with its causes. Clearly, only prospective series are able to refute the perception that any surgery in mesothelioma is futile by bias.

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