Peer Review File
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Reviewer A

Comment 1:
By virtue of immunological therapies and molecular target therapy, have you seen improvements in management in general or benefits in specific surgical techniques?

Reply 1:
The study was conducted between 2018 and 2020 in Germany. 75/91 patients received palliative systemic therapy. After re-reviewing the patient files, we found that only fourteen (14/75, 19%, 14/91, 15%) patients had immunotherapy. Today, we see more and more the use of modern oncologic therapy. At the reviewer's (Reviewer A and B) request, we also conducted an additional follow-up at 54 months (range 39-69 months) concerning long-term survival. This late follow-up showed that only five patients (5/91, 5.5%) were still alive, and four received checkpoint inhibitor therapy, which shows a positive trend in modern oncology.
The impact of preoperative immuno or targeted therapy on surgical benefits or complications must be clarified and investigated today. We notified twenty-one adverse events. In this group, six patients had an infection, five of those patients had a systematic therapy, and only one had an additional checkpoint inhibitor. Although the patient population is tiny, in our opinion, modern oncologic therapy therapy does not have a negative impact on the surgical complication rate.

Changes in the text: we have modified our text and we have expanded the discussion. The new text is color-coded.

Comment 2: - In addition to the proposed treatments, mention the possibility, in special cases, of instilling other drugs into the pleural cavity or using hyperthermia. Please consult this reference: "Malignant pleural effusion in lung cancer: focus on treatment—through a review of literature" J Xiangya Med 2020;5:28 | http://dx.doi.org/10.21037/jxym-20-5 (Divisi D).

Reply 2:
According to the German guidelines, we use talc for pleurodesis. Nevertheless, there exist other substances and extracts to achieve pleurodesis. Lobaplatin or minocycline are currently being tested to improve pleura adherence, reducing LOS and costs. Other authors achieved an excellent overall response rate with the intrathoracic use of turmeric or mistletoe extract. Idopovidone has also been reported to be safe and efficient. Using the intracavitary recombinant human endostatin or combined nanoparticle albumin-bound paclitaxel plus carboplatin allowed better effusion control. (Divisi et al.) Oncologic surgery in patients with pleural carcinomatosis is controversially discussed, so pleurectomy with or without application of hyperthermic intrathoracic chemotherapy (HITOC) is not part of the German guidelines, apart from treatment of mesothelioma and thymic malignancies with pleural dissemination. (Ried et al.) However, the role of surgery and HITOC in selected cases was

discussed in the international literature so that resection associated with HITOC may be considered in patients with stage IV disease but without extrathoracic metastasis. (Divisi et al.)

Divisi D, Zaccagna G, De Vico A, et al. Malignant pleural effusion in lung cancer: focus on treatment—through a review of literature. J Xiangya Med 2020;5:28.
Ried M, Eichhorn M, Winter H, et al. Expert Recommendation for the Implementation of Hyperthermic Intrathoracic Chemotherapy (HITOC) in Germany. Zentralbl Chir 2020;145:89-98.

Changes in the text: we have modified our text and we have expanded the discussion. The new text is color-coded. We have updated our reference list after another literature search with Divisi et al.

Comment 3:
Suitable for the IPC method, but how do you explain such long post-operative days of hospitalization for the other techniques?

Reply 3:
The observation of Reviewer A is correct. The longer LOS is due to our surgical procedure because we routinely apply a level of suction of 20 cm H2O for at least 72 hours after talc pleurodesis. This method in Germany is not permitted on an outpatient basis. After removing the large chest tube, patients must stay another 24 hours for observation in the hospital.

Changes in the text: we have modified our text and we have expanded the discussion. The new text is color-coded.

Reviewer B

Comment 1:
A retrospective study comparing different therapeutic procedures for malignant pleural effusion was done. However, the criterion for choosing treatment based on the type of patient is not clear. There may be a selection bias leading to the choice of certain procedures, with a given success rate, for selected patients, thus influencing the study results.

Reply 1:
Thanks for the comment. One of the study limitations was the retrospective nature of the study. In this retrospective and observational study, there was a balanced patient distribution among the treatment modalities, and the treatment modalities were not randomized: VATS pleurodesis (N=22), VATS and IPC (N=21), a combination of VATS pleurodesis and IPC (N=22), or sole IPC placement (N=26). Each specialist/surgeon (n=4) was allowed to decide how the operation would occur. Nonetheless, in the case of an entirely trapped Lung, no pleurodesis was performed. In recent years, the use of IPC or VATS-IPC in our clinics has become dominant, and this development follows national and international trends (Markowiak et al.).

Markowiak T, Ried M, Großer C, et al. Postoperative outcome after palliative treatment of malignant pleural effusion. Thoracic Cancer. 2022;13:2158-2163.

Changes in the text: we have modified our text and we have expanded the limitation. The new text is color-coded.

Comment 1a:
The baseline characteristics (gender, age and primary malignancy) do not show statistically significant differences between the two groups. But it would be advisable to also compare other elements that could influence the efficacy of the treatment: albumin levels, comorbidities, systemic therapy and performance status. The authors are asked to add these data.

Reply: 1a:
Thank you very much for your attention. Our database was reanalyzed, and the statisticians carried out the desired tests. There were no significant differences in median survival times based on gender status (p=0.040). There were no statistically significant differences in median survival time between patients with or without multimorbidity (p=0.462). There were no statistically significant differences in median survival time between patients with or without cardiovascular disease (p=0.787). There were no statistically significant differences in median survival time between patients with or without renal disease (p=0.438). Median survival time was higher in patients without hypoalbuminemia (p=0.008). Median survival time was higher in patients with systemic therapies (p<0.001). The median survival time was 241 days (95%CI: 176.5-305.5) in the subgroup of patients with ECOG status 2. The median survival time was 98 days (95%CI: 60.8-135.2) in the subgroup of patients with ECOG status 3. The median survival time was statistically significantly higher in the subgroup of patients with ECOG status 2 (Log Rank (Mantel-Cox), Chi-Square, p=0.033).

Changes in the text: we have modified our text and we have expanded the limitation. The new text is color-coded.

Comment 1b:
The p-value for ‘age at intervention’ and ‘primary malignancy’ is missing from the baseline characteristics table. The authors are asked to add these data.
Reply 1b:
Thanks for being so attentive. Our statisticians performed the desired tests, and we reporte that the P-values were higher than 0.05. The median survival time was 226 days (95%CI: 42.0-410.0) in the subgroup of <60 year old patients. The median survival time was 179 days (95%CI: 11.8-346.2) in the subgroup of >=60 and <70 year old patients. The median survival time was 125 days (95%CI: 9.6-240.4) in the subgroup of >=70 year old patients. No statistically significant difference was observed in median survival times analysed by age-group (Log Rank (Mantel-Cox), Chi-Square, p=0.587).
The median survival time was 241.0 days (95%CI: 0.0-551.2) in the subgroup of patients with breast tumor. The median survival time was 48.0 days (95%CI: 0.0-104.0) in the subgroup of

patients with genitourinary tumor. The median survival time was 210.0 days (95%CI: 164.7-255.3) in the subgroup of patients with lung tumor. The median survival time was 125.0 days (95%CI: 0.0-278.0) in the subgroup of patients with other tumor. No statistically significant difference was observed in median survival times analysed by tumor types/primary malignancy (Log Rank (Mantel-Cox), Chi-Square, p=0.429).
The combined effect of ECOG, age and primary malignancy on survival was analysed using Cox regression. Only ECOG status showed a statistically significant association with survival time. This suggests that lower ECOG status means better survival (HR=0.481, 95%CI: 0.279-0.831; p=0.009).

Changes in the text: we have modified our text and we have expanded the results (3.3) and the baseline characteristics. The new text is color-coded.

Comment 2:
The effectiveness of the different treatments was measured on clinical, sonographic, and radiological investigations. The assessment could be expressed in terms of “success” (if there was no evidence of fluid) or “failure” (in case of recurrent or persisting symptoms related to pleural effusion or fluid on chest imaging). In daily practice the results of the treatment of a pleural effusion almost always consist in the permanence of a small amount of effusion. I was wondering if it hadn't been better to assign a more articulated score, with intermediate measures between “success” and “failure”.

Reply 2:
You are right again; in daily practice, success means the patient has a good X-ray, and we do not need to perform thoracocentesis, or we do not need to increase the oxygen supply. We could still have measured saturation or made a walk test. Unfortunately, these procedures are not part of everyday thoracic surgery in our clinics because, in our country, patients receive outpatient care after the surgery. What is crucial, in my view, is whether a second intervention took place.

Changes in the text: we have modified our text and we have expanded the methods and tables. The new text is color-coded.

Comment 3: Follow-up for survival analysis was closed in December 2020. A slightly longer follow-up might have been necessary.

Reply 3:
At the reviewer's (Reviewer A and B) request, we also conducted an additional follow-up at 54 months (range 39-69 months) concerning long-term survival. This late follow-up showed that only five patients (5/91, 5.5%) were still alive, and four received checkpoint inhibitor therapy, which shows a positive trend in modern oncology.

Changes in the text: we have modified our text and we have expanded the methods and results. The new text is color-coded.

Comment 4:
LOS is described from the day of admission and not from the day of treatment. It is a limit of the work, because it can affect its efficacy.

Reply 4:
We have not investigated it, but patients are often initially admitted with a pleural effusion of unclear origin, and the diagnosis or staging takes time. On the other hand, you can see the weakness of our healthcare system here. Although the thoracic surgeons offer a fast supply, patients are presented to us with a delay.

Changes in the text: we have modified our text and we have expanded the limitations. The new text is color-coded.

Reviewer C

Comment 1+2:
First, multiple tumors are included in the study. Different tumors have different prognosis and progression, so its survival or treatment modality could not be compared. Of course, you compared MPE but its origin could not be changed. Second, MPE in your study was a kind of metastatic disease (except one mesothelioma), so treatment of MPE is affected by primary tumor. However, you did not consider the status of primary tumor, so we could not get any valuable information by the report about MPE treatment itself. Authors had compared different diseases treated by different method with unclear indications. It would be better to consider the design of study, again.

Reply 1:
Thank you very much for asking the question. You are right, the prognosis of a tumor disease depends mainly on the stage and histology, Karnofsky index, age, and gender. For example, we see different survival curves in women with stage IV breast cancer depending on hormone receptor status and location of distant metastasis. Using the breast cancer-specific score (Graded Prognostic Assessment, assigning points for Karnofsky index, histologic subtype, age), median survival times for GPA 0-1 are 3.4 months, for GPA 1.5-2 are 7.7 months, for GPA 3 are 15 months, and for GPA 3.5-4 are 25.3 months. According to the German oncology guidelines, 5-year survival rates for stage IV tumor disease range from 2% to 20%, with the worst prognosis for esophageal cancer and the most favorable for endometrial cancer. However, survival data of patients with pleural metastasis are rare to find. In our perception, survival here is measured in months. You are right; apples and oranges could not be compared. However, patients with pleural tumor infiltration still have a uniformly poor prognosis.
Most of our patients had and-stage lung cancer, followed by end-stage breast and urogenital carcinoma. All patients were presented to the tumor board and received guideline-compliant but individualized therapy. As requested, we included the role of the *primarius* in the study and performed further statistical analyses in this regard. The median survival time was 241.0 days (95%CI: 0.0-551.2) in the subgroup of patients with breast tumor. The median survival time was 48.0 days (95%CI: 0.0-104.0) in the subgroup of patients with genitourinary tumor.

The median survival time was 210.0 days (95%CI: 164.7-255.3) in the subgroup of patients with lung tumor. The median survival time was 125.0 days (95%CI: 0.0-278.0) in the subgroup of patients with other tumor. No statistically significant difference was observed in median survival times analysed by tumor types (Log Rank (Mantel-Cox), Chi-Square, p=0.429). The combined effect of ECOG, age and tumour type on survival was analysed using Cox regression. Only ECOG status showed a statistically significant association with survival time. This suggests that lower ECOG status means better survival (HR=0.481, 95%CI: 0.279-0.831; p=0.009).

Changes in the text: we have modified our text and we have expanded the results (3.3) and the baseline characteristics. The new text is color-coded.

Comment 3:
Third, authors categorized their MPE treatment as four, but we could not get any indication for the treatments. In other words, we could not know when VATS pleurodesis was chosen and IPC was not.

Reply 3:
Thanks for the comment. In this retrospective and observational study, there was a balanced patient distribution among the treatment modalities, without any randomization: VATS pleurodesis (N=22), VATS and IPC (N=21), a combination of VATS pleurodesis and IPC (N=22), or sole IPC placement (N=26). Each specialist (n=4) was allowed to decide how the operation would occur. Nonetheless, in the case of an entirely trapped Lung, no pleurodesis was performed. In recent years, the use of IPC or VATS-IPC in our clinics has become dominant, and this development follows national and international trends. (Markowiak et al.)

Markowiak T, Ried M, Großer C, et al. Postoperative outcome after palliative treatment of malignant pleural effusion. Thoracic Cancer. 2022;13:2158-2163.

Changes in the text: we have modified our text and we have expanded the Methods. The new text is color-coded.