Surgical Oncology 44 (2022) 101824

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

Review

Adjuvant chemotherapy could improve the survival of pulmonary sarcomatoid carcinoma: A systematic review and meta-analysis

Noémi Zombori-Tóth [a], Szabolcs Kiss [b,c], Eduard Oštarijaš [d], Hussain Alizadeh [b,e], Tamás Zombori [f,*]

[a] Csongrád-Csanád County Hospital of Chest Diseases, Deszk, Hungary
[b] Doctoral School of Clinical Medicine, University of Szeged, Szeged, Hungary
[c] Heim Pál National Pediatric Institute, Budapest, Hungary
[d] Institute for Translational Medicine, University of Pécs Medical School, Pécs, Hungary
[e] Division of Haematology, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary
[f] Department of Pathology, Albert Szent-Györgyi Clinical Centre, University of Szeged, Szeged, Hungary

ARTICLE INFO

Keywords:
Meta-analysis
Pulmonary sarcomatoid carcinoma
Therapy
Survival

ABSTRACT

Background: Complete surgical removal is currently considered to be the best treatment option for pulmonary sarcomatoid carcinoma (PSC) especially in early stage operable disease; however, the reported recurrence-free survival is low. Benefits of adjuvant chemotherapy in PSC patients are still controversial, and there is no obvious agreement on the optimal treatment modalities of this disease. Therefore, we aimed to investigate the prognosis in terms of overall survival (OS) in patients with PSC who received adjuvant chemotherapy.
Methods: The review protocol was registered in PROSPERO (CRD42022306084). Patients with PSC who underwent surgical therapy with or without adjuvant chemotherapy were included into the meta-analysis. Hazard ratios (HR) with 95% confidence intervals (CIs) for OS were pooled and ROBINS-I tool was used to assess risk of bias of the included studies.
Results: We identified four retrospective cohort studies with 6768 records from MEDLINE, Embase, and CENTRAL databases up to 9th September 2021, and altogether 1835 patients were included to the analysis. The present meta-analysis shows that patients receiving adjuvant chemotherapy had a significantly longer OS than patients who underwent surgical treatment alone (HR = 0.5657, 95%CI: 0.4391–0.7290, $p < 0.0001$).
Conclusions: Despite the limited information on the chemotherapy regimens in the included studies, patients with PSC may benefit from adjuvant chemotherapy. More publications are required to evaluate and compare efficient adjuvant chemotherapy protocols in PSC cases.

1. Introduction

Pulmonary sarcomatoid carcinoma (PSC) was initially reported as 'carcinoma with pleomorphic, sarcomatoid or sarcomatous elements' in the World Health Organization's (WHO) classification of lung tumours in 1999 [1]. In the 2021 WHO classification, it is defined as an overarching term, that is divided into 5 subgroups, namely pleomorphic carcinoma (PPC), spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma [2]. The incidence of PSC is very low, it accounts for less than 1% of lung cancers [3] and 0.1–0.4% among non-small cell lung cancers (NSCLC) [4]. PSC is mainly found in males and in heavy smokers. At the time of diagnosis, PSC usually has large diameter, aggressive clinical behaviour and high local invasion tendency. The latter features contribute to its poor survival outcome even in patient with early-stage disease [5–7]. Its 5-year overall survival (OS) rate ranges from 12.6 to 34.6% [8,9]. However, Ung et al. have demonstrated low recurrence-free survival with a median survival of 6.8 months [10]. Complete surgical removal is currently considered to be the best treatment option. Currently, there is no standard treatment for advanced PSC. However, targeted therapies for patients with specific mutations may be effective. The benefits of postoperative chemotherapy for OS in patients diagnosed with PSC are still controversial. Therefore, larger prospective studies are needed to further define the efficacy and role of systemic chemotherapy and immunotherapy in patients with

* Corresponding author. Department of Pathology, Albert Szent-Györgyi Clinical Centre, University of Szeged, Állomás u. 1, Szeged, 6725, Hungary.
E-mail address: zombori.tamas@med.u-szeged.hu (T. Zombori).

https://doi.org/10.1016/j.suronc.2022.101824
Received 28 March 2022; Received in revised form 1 July 2022; Accepted 24 July 2022
Available online 31 July 2022

PSC.

Specific therapeutic guidelines are not available for PSC, therefore the NSCLC treatment protocols are generally applied. In 2017, the European Society for Medical Oncology (ESMO) reported a clinical practice guideline about the management of NSCLC. In early stages (stages I–II) and non-metastatic cases, surgical resection is recommended (III, A) and anatomical resection is preferred to wedge resection (I, A). This also suggested a complete surgical resection for patients with multifocal lung cancer with discussion of the cases at the multidisciplinary tumour board (III, B) [11]. In 2021, ESMO updated its clinical practice guideline, and recommended adjuvant chemotherapy with two-drug combination for resected stage IIB–III NSCLC and for stage IB with primary tumours larger than 4 cm (II, B) [12]. In advanced, metastatic cases without actionable driver mutations, benefits of chemotherapy versus best supportive care were observed and the former was associated with 1.5-month absolute survival increase and an improved quality of life [13–15]. Survival benefit of two-drug combinations versus one-drug chemotherapy has also been reported [16].

There is still no consensus on the management of PSC. Several studies reported its resistance to chemotherapy, while others emphasized the benefits of adjuvant chemotherapy. Raveglia et al. reported only 5 months median disease-free survival (DFS) and 8 months OS in PPC patients who underwent surgical resection and received adjuvant chemotherapy. They concluded that prognosis was poor regardless of surgery and adjuvant chemotherapy due to early relapse of the disease [17]. Steuer et al. investigated patients who received chemotherapy (38.6% of all) and found that the median OS for early stages (stages I–II) PSC was only 16.9 months and concluded that surgery was the best treatment method for PSC and the role of chemotherapy and radiation was controversial [18].

On the contrary, Chaft et al. pointed out that the median disease-free probability of patients who received perioperative chemotherapy was 34 months compared to patients without chemotherapy, in whom it was 12 months only [19]. Furthermore, Huang et al. revealed that adjuvant chemotherapy had significant impact on OS [20]. In addition, Hou et al. found in univariate analysis that patients receiving complete resection and chemotherapy had significantly better OS [21]. Li et al. reviewed the clinicopathological features and management of PSC, and based on several publications, they established a flow diagram for the management of PSC. They suggested that the primary treatment of PSC should be surgical resection. Patients can be treated with radiotherapy or targeted therapy preoperatively. In case of progression, (combined platinum-based) chemotherapy with or without targeted therapy is recommended after surgery. Finally, early use of antivascular therapy combined with immunotherapy could maximize patient's treatment responses [22].

Based on the aforementioned publications, one can realize that there is still no consensus on administration of adjuvant chemotherapy in PSC. Therefore, the aim of this study was to (1) investigate the benefit of adjuvant chemotherapy for OS of patients with a diagnosis of PSC, (2) investigate the discrepancies of the management of PSC in published studies and (3) make recommendations for future research.

2. Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement [23]. The study protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42022306084), and we did not deviate from this protocol.

2.1. Search strategy

The systematic literature search was completed by two independent review authors in three scientific databases, namely MEDLINE (via PubMed), Embase, Cochrane Central Register of Controlled Trials (CENTRAL) up to 9th September 2021. The following search key was used in all databases: ("sarcomatoid carcinoma" OR "pleomorphic carcinoma" OR "spindle cell carcinoma" OR "giant cell carcinoma" OR "carcinosarcoma" OR "blastoma") AND (lung OR pulmonary). No filter was applied. Reference lists of the eligible studies and the citing articles (via Google Scholar search engine) were also screened to identify relevant publications.

2.2. Selection and eligibility criteria

Randomized controlled trials (RCTs) and non-randomized controlled studies might be eligible for inclusion based on the search strategy; however, only latter study design was found and included in our meta-analysis. Retrospective cohort studies that compared the outcomes of surgical therapy alone (Intervention) with surgery and adjuvant chemotherapy (Control) in patients with PSC (Population) were eligible for inclusion. Studies that did not report both abovementioned therapeutic modalities and did not contain hazard ratio (HR) measurement of OS were excluded. OS was defined as the time from the date of resection to death from any cause. Duplicates were reviewed by two independent review authors based on 'title', 'publication year' and 'author' labels using a reference management software (EndNote X9, Clarivate Analytics). A third investigator resolved the possible disagreements. After removal of duplicates, titles, abstracts then full texts were screened and selected independently by two researchers based on predefined criteria, and a third investigator resolved all disagreements.

2.3. Data extraction

Two independent review authors extracted data from the eligible studies into a standardized data collection form. All discrepancies were resolved by an independent third author. From the selected studies, the following data were extracted: title, first author, publication year, Digital Object Identifier (DOI), total number of patients in each study, number of patients in surgery alone arm (Intervention), number of patients in surgery and adjuvant chemotherapy arm (Control), sex distribution, age and type of adjuvant chemotherapy regimen. Furthermore, HRs with the corresponding 95% confidence intervals (CIs) for OS of both univariate and multivariate analysis were also extracted.

2.4. Risk of bias assessment

Based on the recommendations of Cochrane Collaborations [24], two independent review authors investigated the quality of the included studies using the ROBINS-I risk of bias assessment tool [25] which consist of seven domains, namely bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result. Finally, low, moderate and serious overall risk of bias were defined as described by Sterne et al. [25]. Any discrepancies were resolved by an independent third investigator.

2.5. Certainty of the evidence

Certainty of the evidence was evaluated by two independent investigators with GRADE profiler software (GRADEpro GDT: GRADEpro Guideline Development Tool) [26] based on the approach proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group [27]. Any discrepancy was resolved by a third researcher.

2.6. Statistical analysis

We provided summaries of intervention effects for each study by calculating pooled ratios (HRs) for OS using R statistical software

(v4.1.2) with meta (v5.1-0) package. HRs were pooled using the random-effects model and inverse variance method with the restricted maximum-likelihood (REML) estimation and displayed on forest plots. Summary HR estimation and 95% CIs were calculated. Statistical heterogeneity was also analysed using the I^2 statistic and the χ^2 test to acquire probability values; $p < 0.1$ was defined to indicate significant heterogeneity. The minimum number of studies for performing the meta-analysis was three. As the number of eligible studies for the outcome was below 10, we were not able to test the presence of publication bias.

3. Results

3.1. Results of systematic search and selection

The PRISMA flow diagram (Fig. 1.) displays the details of selection process. 6768 records were identified in the three major scientific databases. After removal of duplicates, screening and evaluation for eligibility, four retrospective studies were included in our meta-analysis [28–31]. Each study investigated both surgery alone and surgery and adjuvant chemotherapy arms in patients having PSC. In one study, two cohorts were reported separately; therefore, we handled and analysed them separately [30].

3.2. Characteristics of the studies included

Table 1 contains the characteristics of the studies included. From the four articles, altogether 1852 patients treated with either surgery alone or surgery and adjuvant chemotherapy were included. Diagnosis of PSC was based on resection specimens. Of all participants, only 682 patients' therapeutic regimen was supplemented with adjuvant chemotherapy. From the four articles, only two studies reported precisely the type of adjuvant chemotherapy. In study of Iijima et al., in three cases, tegafur and uracil were administered and in four cases, platinum-based chemotherapy was utilized [29]. In other study, combined platinum-based adjuvant chemotherapy (pemetrexed + cisplatin) was administered [31].

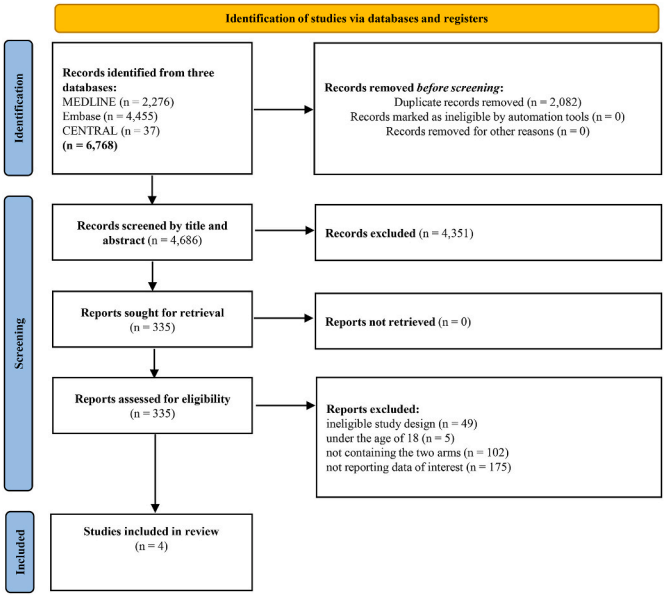

Fig. 1. PRISMA flow diagram (2020) showing details our systematic search and selection process (PRISMA: Preferred Reporting Items for Systematic Reviews, CENTRAL: Cochrane Central Register of Controlled Trials).

3.3. Quantitative synthesis of OS

From the 4 articles altogether 5 cohorts (n = 1852) were included for univariate analysis: 1170 patients underwent surgical treatment only; whereas 682 patients received adjuvant chemotherapy. As Fig. 2 displays, no statistically significant differences in HR were found between surgery alone and administration of adjuvant chemotherapy treatment modalities in univariate analysis (HR = 0.7138, 95%CI: 0.4989–1.0213, $p = 0.0651$).

Altogether three articles [28,30,31] reporting on four PSC cohorts were included for multivariate analysis. Of all participants, 1835 patients were included. As Fig. 2 demonstrates, there was a statistically significant difference between the HR of surgery alone and administration of adjuvant chemotherapy treatment modalities in multivariate analysis (HR = 0.5657, 95%CI: 0.4391–0.7290, $p < 0.0001$).

Based on the recommendations of the Cochrane Collaboration, statistical heterogeneities in both univariate and multivariate analyses were substantial ($I^2 = 77.7\%$, $p < 0.01$ and $I^2 = 66.0\%$, $p = 0.03$) [24].

3.4. Risk of bias assessment

In both univariate and multivariate analyses, the overall risk of bias for OS was evaluated as moderate. In both analyses, the most common reason for this moderate risk classification was the insufficient description of any analysis for avoiding systematic errors in measurements. Only in one study [28], was propensity score match utilized in order to minimize confounding factors. Based on the 'bias in selection of the reported result' domain, studies included were sound for a non-randomized study but cannot be considered comparable to a well-performed randomized trial. Detailed results of the quality assessment are found in Supplementary Fig. 1. (univariate analysis for OS) and Supplementary Fig. 2. (multivariate analysis for OS).

3.5. Certainty of the evidence

In both univariate and multivariate analysis for OS, certainty of evidence was 'very low'. The most common reasons of downgrading were the study design and the indirectness (different chemotherapy protocols). Detailed assessment is presented in Supplementary Fig. 3.

4. Discussion

The rarity of PSC and the difficulty of pathological diagnosis make it a difficult malignancy to study. According to our findings, based on the multivariate analysis, significantly better HRs for OS were found for patients who received adjuvant chemotherapy following surgical therapy; however, in univariate analysis, there was no significant difference between the HRs for OS of patients with PSC who underwent surgical therapy alone and those who received adjuvant chemotherapy. The difference between the findings of multivariate and univariate analyses could stem from the covariates used in the multivariate analysis, namely age, gender, race, body mass index (BMI), surgery type (lobectomy and sublobectomy), receiving chemotherapy, grade (grade I–II versus III–IV), histological subtype, tumour size, pathological and clinical stage and nodal metastasis.

In the literature, there are several publications evaluating the different managements of PSC and their impact on OS. Systemic chemotherapy alone did not improve survival in patients with PSC. Surgery provides the greatest overall survival benefit and adjuvant chemotherapy may also improve survival.

Lin et al. investigated the prognostic factors of PSC. The presence of distant metastasis (RR [relative risk] for OS with 95%CI: 10.752 (3.201–36.117), $p < 0.001$), pleomorphic subtype (RR for OS with 95% CI: 0.596 (0.394–0.900), $p = 0.014$) and incomplete surgical resection (RR for OS with 95%CI: 2.590 (1.083–6.193), $p = 0.032$) were found to be adverse prognostic factors on OS. For all patients who received

Table 1
Characteristics of the included studies ([a] first author and publication year,[b] mean or median, N: number, S: surgery, CT: chemotherapy, N.R.: not reported).

Study name[a]	Study design	N of patients (S alone)	N of patients (adjuvant CT)	Age[b]	Females (%)	CT regimen
Cen et al., 2020	cohort	611	254	69	43.9	N.R.
Sun et al., 2020 (A cohort)	cohort	464	313	71.5	41.59	N.R.
Sun et al., 2020 (B cohort)	cohort	54	78	65.67	14.29	N.R.
Wang et al., 2020	cohort	31	30	63.49	24.18	platinum-based
Iijima et al., 2020	cohort	10	7	N.R.	0	tegafur-uracil, platinum-based

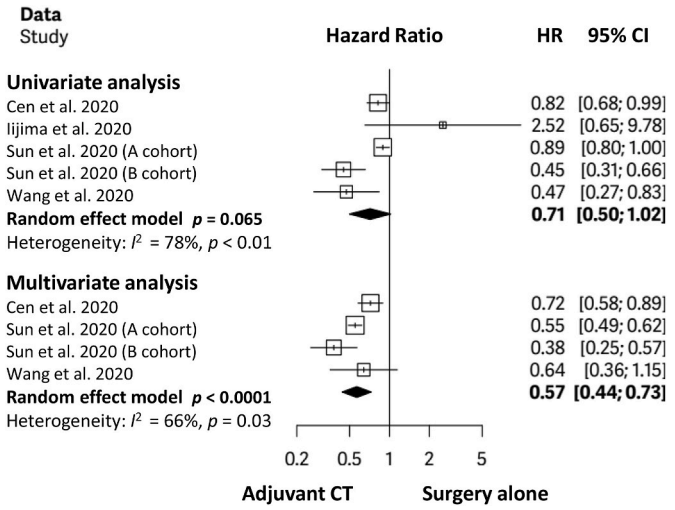

Fig. 2. Forest plots of univariate and multivariate analyses of the studies included (CI: confidence interval, HR: Hazard ratio, CT: chemotherapy).

complete resection, regardless of whether they received adjuvant chemotherapy or radiotherapy, the adjuvant treatments did not affect OS ($p > 0.05$) [32]. Iijima and associates investigated 17 patients diagnosed with PPC. Of all 17 participants, 7 patients were administered adjuvant chemotherapy (tegafur-uracil and platinum-based) but only a single patient survived 96 months the median OS was only 25.3 months. They proposed that immunological mechanisms played a role in relatively long survival of their unique patient. They found no significant prognostic impact of adjuvant chemotherapy on OS or DFS among PPC patients. They identified complete surgical resection as the most effective treatment option and PPC was described as a neoplasm resistant to both chemotherapy and radiotherapy [29].

Hendricksen et al. investigated 310 patients with PPC. Patients with stage I disease, who were treated with surgery alone versus surgery with chemotherapy had 5-year overall survival rates of 55.2% and 53.7%, respectively ($p = 0.2868$) [33]. Karim et al. evaluated 25 patients with PSC and they compared different therapeutic modalities. Chemotherapy was most often used in stage III and IV and treatment with systemic chemotherapy did not show a significant improvement in outcome (HR: 0.638, $p = 0.451$). Those patients who underwent surgery and systemic chemotherapy showed a trend toward improvement in outcome (HR: 0.04, $p = 0.08$). Their median OS was 457.6 days. Finally, patients who underwent surgical resection alone had the best median OS of 713.5 days. They concluded that surgery had the greatest OS benefit in early stage disease and chemotherapy did not appear to significantly improve OS and may not even be useful in advanced cases [34]. Lococo et al. investigated 142 patients with PSC who underwent surgical resection and 67% of patients also received adjuvant chemotherapy. They found no significant survival advantage between surgery with versus without chemotherapy (5-year long-term survival (LTS) 6.6% and 23.2%, respectively, $p = 0.293$). Moreover, they found that distant recurrences frequently occurred after surgical treatment (81%), even in pathological stage I tumours that underwent R0 resection (62%). They concluded that patients receiving adjuvant chemotherapy did not show a LTS advantage compared with patients who did not. However, they reported that several confounding selection biases should be considered with regard to this finding [35].

Concerning the early stages of PSC, Hendricksen et al. [33] and Karim et al. [34] both favoured surgery alone which is similar to the general management of NSCLC. However, Lococo et al. [35] reported a high recurrence rate after this treatment modality. In addition, Karim et al. reported that chemotherapy is not suggested for advanced stage PSC. The findings of the three aforementioned publications are opposite to ours, namely that surgery followed by adjuvant chemotherapy has significant benefit for patients with PSC regardless of stage. Possible explanation for the discrepancies may be the different cohort sizes and the different stages, therefore further detailed investigations are required to evaluate prognosis of surgery with chemotherapy in different stages.

Several studies reported that PSC has more than 70% recurrence rate after surgical therapy, and distant metastases are found more frequently than local metastases [10,35,36]. Because of the high recurrence rate and distant metastases, perioperative chemotherapy would have a better efficacy than radiotherapy [28]. On the contrary to the abovementioned studies [33–35], other publications reported beneficial effect of adjuvant chemotherapy on prognosis. Sun et al. reported that patients receiving adjuvant chemotherapy have a significantly better prognosis, particularly in younger patients with higher BMI and advanced stage [30]. According to the results of Cen et al., lobectomy and additional chemotherapy should be considered for PSC patients in stages II and III, especially in younger age, female gender, poor differentiation or undifferentiated histology and large tumour size [28]. Huang et al. investigated 51 PSC patients and found significantly higher OS estimates in patients receiving adjuvant chemotherapy versus those who did not (5-year OS rates of 38.4% and 8.5%, respectively, $p = 0.029$) [20]. Hou et al. investigated 114 patients with PSC and found that patients receiving complete resection and chemotherapy had significantly better OS estimates [21].

These latter results are in keeping with ours. In our meta-analysis, OS was more favourable in patients who underwent surgical resection and received adjuvant chemotherapy. Further investigations are required to evaluate outcomes based on different stages and chemotherapy protocols.

Because PSC is often diagnosed at an advanced stage and frequently leads to relapse, not only systemic chemotherapy but also targeted therapies are crucial to investigate. Schrock et al. evaluated the genomic alterations in PSCs. They detected more frequent TP53 gene and KRAS genomic alterations in these neoplasms. In addition, other potentially targetable genomic alterations, namely those affecting MET, EGFR, BRAF, HER2 and RET were also identified in PSCs. MET exon 14 alterations were significantly more frequent ($p < 0.0001$), and tumour mutational burden was higher ($p = 0.05$) in PSCs compared to other NSCLCs. They conclude that the use of comprehensive genomic profiling in clinical practice may provide important treatment options for this rare, but aggressive neoplasm [37]. Sun et al. investigated the efficacy of target therapy in patients diagnosed with unresectable, locally advanced PSCs. They found similar results of disease control rate after chemotherapy (58.62%) and after targeted therapy (57.14%) [30]. In contrast, Wang et al. reported that in selected patients who received adjuvant chemotherapy combined with targeted therapy, the outcome was more

favourable than for surgical treatment alone (HR 0.148; 95%CI 0.030–0.726, $p = 0.019$) [31]. Therapies targeting the programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) pathway are an emerging treatment for lung cancer. Vieira et al. investigated 75 patients with PSC who underwent lung resection. Although PD-L1 expression was higher in PSCs (53%) than in other NSCLC cases (20%) ($p < 0.0001$), PD-L1 expression did not influence the OS in survival analysis [38]. Velcheti et al. evaluated the expression of PD-L1 in 13 PSC and 445 other type of NSCLC patients. A positive PD-L1 status was found in 69.3% of PSC cases. Furthermore, the extent of PD-L1 expression was higher in PSC patients than in other types of NSCLC ($p = 0.01$) [39]. Evaluation of the efficacy of chemotherapy and immune/target therapy requires further investigation.

Up to February 13, 2022, some ongoing clinical trials (interventional study type), which investigate the different treatment modalities in PSC, have been found registered on the website 'clinicaltrial.gov'. One of them with a 'not yet recruiting' status aims to evaluate the efficacy and safety of the combination therapy of camrelizumab and famitinib in patients with advanced or metastatic PSC [40]. There are two interventional studies with 'recruiting' status. One of them is investigating the efficacy and safety of first-line toripalimab combined with bevacizumab, nab-paclitaxel and carboplatin in the treatment of patients with advanced PSC [41]. The other study evaluates the efficacy and safety of durvalumab in combination with doxorubicin and ifosfamide in patients with PSC [42]. Finally, there is one clinical trial with an 'active, not recruiting' status which aimed to assess the objective response rate, progression-free survival and OS for savolitinib administered orally in patients diagnosed with locally advanced/metastatic PSC and other NSCLC with MET Exon 14 mutation and failure or intolerance of first-line chemotherapy [43]. Some further ongoing clinical trials can be identified, but these interventional studies do not investigate PSC patients after surgical resection. Clinical trials, mainly RCTs, are required to evaluate the beneficial effect of adjuvant chemotherapy in PSC patients, particularly with different chemotherapy regimens.

In the literature, there are several case reports and retrospective studies which evaluate the prognosis of PSC based on different treatment modalities; however, to our knowledge, this is the first meta-analysis which compared the two therapeutic modalities of surgery alone and surgery with adjuvant chemotherapy in PSC patients. In addition, included studies are not outdated and were published recently, not before 2020. Along with these strengths, there are also limitations. Firstly, our results are not from RCTs, as there are no such studies fulfilling the inclusion criteria. Secondly, there is substantial clinical heterogeneity among the studies included regarding different chemotherapies, histological subtypes and pathological stages.

4.1. Implications for future practice and research

Based on our findings, after surgical resection, which is needed to establish an adequate histological diagnosis, administering chemotherapy is beneficial and recommended. Our analysis suggests that patients with PSC have a better survival with adjuvant chemotherapy. However, based on the limited information on the chemotherapy regimens in the studies included, more RCTs are required to evaluate the adequate chemotherapy protocols after surgical resection. Further studies should be conducted to evaluate the efficacy of various chemotherapy regimens as well as, treatment modalities including immunotherapy and target therapy among patients diagnosed with PSC. In addition, subgroup analyses are required to evaluate the prognosis for OS in PSC patients with the following factors: different pathological stages, tumour size, nodal status, type of surgery (sublobectomy, lobectomy) and histological subtype.

5. Conclusion

In summary, our meta-analysis suggests that patients diagnosed with PSC who underwent surgical treatment and were administered adjuvant chemotherapy have a significantly better OS compared to those who did not receive adjuvant chemotherapy.

Author contributions

NZT: Conceptualization, Methodology, Investigation, Data curation, Writing- Reviewing and Editing.

SK: Conceptualization, Methodology, Investigation, Writing-Reviewing and Editing.

EO: Formal analysis, Writing- Reviewing and Editing.

HA: Writing- Reviewing and Editing.

TZ: Conceptualization, Data curation, Investigation, Writing-Reviewing and Editing.

Funding

Open access fee was provided by University of Szeged, Hungary. Grant number: 5753.

Declaration of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2022.101824.

References

[1] E. Brambilla, W.D. Travis, T.V. Colby, B. Corrin, Y. Shimosato, The new World Health Organization classification of lung tumours, Eur. Respir. J. 18 (2001) 1059–1068. http://doi: 10.1183/09031936.01.00275301.

[2] WHO Classification of Tumours Editorial Board, Thoracic Tumours, in: WHO Classification of Tumours Series, fifth ed., vol. 5, International Agency for Research on Cancer, Lyon (France), 2021. Available from: https://tumourclassification.iarc.who.int/chapters/35.

[3] W.D. Travis, E. Brambilla, A.G. Nicholson, Y. Yatabe, J.H.M. Austin, M.B. Beasley, L.R. Chirieac, S. Dacic, E. Duhig, D.B. Flieder, K. Geisinger, F.R. Hirsch, Y. Ishikawa, K.M. Kerr, M. Noguchi, G. Pelosi, C.A. Powell, M.S. Tsao, I. Wistuba, WHO Panel, The 2015 World Health Organization Classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 Classification, J. Thorac. Oncol. 10 (2015) 1243–1260. http://doi: 10.1097/JTO.0000000000000630.

[4] S. Yendamuri, L. Caty, M. Pine, S. Adem, P. Bogner, A. Miller, T.L. Demmy, A. Groman, M. Reid, Outcomes of Sarcomatoid Carcinoma of the Lung: a Surveillance, Epidemiology, and End Results Database Analysis, 152 Surgery, 2012, pp. 397–402. http://doi: 10.1016/j.surg.2012.05.007.

[5] K. Ito, S. Oizumi, S. Fukumoto, M. Harada, T. Ishida, Y. Fujita, T. Harada, T. Kojima, H. Yokouchi, M. Nishimura, Lung cancer clinical study Group, clinical characteristics of pleomorphic carcinoma of the lung, Lung Cancer 68 (2010) 204–210. http://doi: 10.1016/j.lungcan.2009.06.002.

[6] F. Chen, M. Sonobe, T. Sato, H. Sakai, C.L. Huang, T. Bando, H. Date, Clinicopathological characteristics of surgically resected pulmonary pleomorphic carcinoma, Eur. J. Cardio. Thorac. Surg. 41 (2012) 1037–1042. http://doi: 10.1093/ejcts/ezr136.

[7] G. Pelosi, P. Gasparini, A. Cavazza, G. Rossi, P. Graziano, M. Barbareschi, F. Perrone, M. Barberis, M. Takagi, T. Kunimura, T. Yamada, Y. Nakatani, U. Pastorino, P. Scanagatta, G. Sozzi, M. Garassino, F. De Braud, M. Papotti, Multiparametric molecular characterization of pulmonary sarcomatoid carcinoma reveals a nonrandom amplification of anaplastic lymphoma kinase (ALK) gene, Lung Cancer 77 (2012) 507–514. http://doi: 10.1016/j.lungcan.2012.05.093.

[8] J. Yin, Y. Yang, K. Ma, X. Yang, T. Lu, S. Wang, Y. Shi, C. Zhan, Y. Zhu, Q. Wang, Clinicopathological characteristics and prognosis of pulmonary pleomorphic carcinoma: a population-based retrospective study using SEER data, J. Thorac. Dis. 10 (2018) 4262–4273. http://doi: 10.21037/jtd.2018.06.71.

[9] A. Weissferdt, N. Kalhor, A.M. Correa, C.A. Moran, Sarcomatoid" carcinomas of the lung: a clinicopathological study of 86 cases with a new perspective on tumor classification, Hum. Pathol. 63 (2017) 14–26. http://doi: 10.1016/j.humpath.2016.12.010.

[10] M. Ung, I. Rouquette, T. Filleron, K. Taillandy, L. Brouchet, J. Bennouna, J. P. Delord, J. Milia, J. Mazières, Characteristics and clinical outcomes of sarcomatoid carcinoma of the lung, Clin. Lung Cancer 17 (2016) 391–397. http://doi: 10.1016/j.cllc.2016.03.001.

[11] P.E. Postmus, K.M. Kerr, M. Oudkerk, S. Senan, D.A. Waller, J. Vansteenkiste, C. Escriu, S. Peters, ESMO Guidelines Committee, Early and locally advanced non-

small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 28 (2017) iv1-iv21, http://doi: 10.1093/annonc/mdx222.
[12] J. Remon, J.C. Soria, S. Peters, ESMO Guidelines Committee, Early and locally advanced non-small-cell lung cancer: an update of the ESMO clinical practice guidelines focusing on diagnosis, staging, systemic and local therapy, Ann. Oncol. 32 (2021) 1637–1642. http://doi: 10.1016/j.annonc.2021.08.1994.
[13] Non-small Cell Lung Cancer Collaborative Group, Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials, BMJ 311 (1995) 899–909.
[14] NSCLC Meta-Analyses Collaborative Group, Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials, J. Clin. Oncol. 26 (2008) 4617–4625. http://doi: 10.1200/JCO.2008.17.7162.
[15] Non-Small Cell Lung Cancer Collaborative Group, Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer, Cochrane Database Syst. Rev. 12 (2010). CD007309, http://doi: 10.1002/14651858.CD007309.pub2.
[16] C. Delbaldo, S. Michiels, N. Syz, J.C. Soria, T. Le Chevalier, J.P. Pignon, Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen in advanced non-small-cell lung cancer: a meta-analysis, JAMA 292 (2004) 470–484. http://doi: 10.1001/jama.292.4.470.
[17] F. Raveglia, M. Mezzetti, T. Panigalli, S. Furia, L. Giuliani, S. Conforti, S. Meda, Personal experience in surgical management of pulmonary pleomorphic carcinoma, Ann. Thorac. Surg. 78 (2004) 1742–1747. http://doi: 10.1016/j.athoracsur.2004.04.084.
[18] C.E. Steuer, M. Behera, Y. Liu, C. Fu, T.W. Gillespie, N.F. Saba, D.M. Shin, R. N. Pillai, S. Pakkala, T.K. Owonikoko, F.R. Khuri, S.S. Ramalingam, Pulmonary sarcomatoid carcinoma: an analysis of the national cancer data base, Clin. Lung Cancer 18 (2017) 286–292. http://doi: 10.1016/j.cllc.2016.11.016.
[19] J.E. Chaft, C.S. Sima, M.S. Ginsberg, J. Huang, M.G. Kris, W.D. Travis, C.G. Azzoli, Clinical outcomes with perioperative chemotherapy in sarcomatoid carcinomas of the lung, J. Thorac. Oncol. 7 (2012) 1400–1405. http://doi: 10.1097/JTO.0b013e3182614856.
[20] S.Y. Huang, S.J. Shen, X.Y. Li, Pulmonary sarcomatoid carcinoma: a clinicopathologic study and prognostic analysis of 51 cases, World J. Surg. Oncol. 11 (2013) 252. http://doi: 10.1186/1477-7819-11-252.
[21] J. Hou, L. Xing, Y. Yuan, A clinical analysis of 114 cases of sarcomatoid carcinoma of the lung, Clin. Exp. Med. 18 (2018) 555–562. http://doi: 10.1007/s10238-018-0517-2.
[22] X. Li, D. Wu, H. Liu, J. Chen, Pulmonary sarcomatoid carcinoma: progress, treatment and expectations, Ther Adv Med Oncol 12 (2020), 1758835920950207. http://doi: 10.1177/1758835920950207.
[23] MjJ. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, R. Chou, J. Glanville, J. M. Grimshaw, A. Hróbjartsson, M.M. Lalu, T. Li, E.W. Loder, E. Mayo-Wilson, S. McDonald, L.A. McGuinness, L.A. Stewart, J. Thomas, A.C. Tricco, V.A. Welch, P. Whiting, D. Moher, The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, BMJ 372 (2021) n71. http://doi: 10.1136/bmj.n71.
[24] (updated February 2021). CochraneJ.P.T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M.J. Page, V.A. Welch (Eds.), Cochrane Handbook for Systematic Reviews of Interventions, 2021. Available from:, version 6.2. www.training.cochrane.org/handbook.
[25] J.A.C. Sterne, M.A. Hernán, B.C. Reeves, J. Savović, N.D. Berkman, M. Viswanathan, D. Henry, D.G. Altman, M.T. Ansari, I. Boutron, J.R. Carpenter, A. W. Chan, R. Churchill, J.J. Deeks, A. Hróbjartsson, J. Kirkham, P. Jüni, Y.K. Loke, T.D. Pigott, C.R. Ramsay, D. Regidor, H.R. Rothstein, L. Sandhu, P.L. Santaguida, H.J. Schünemann, B. Shea, I. Shrier, P. Tugwell, L. Turner, J.C. Valentine, H. Waddington, E. Waters, G.A. Wells, P.F. Whiting, J.P.T. Higgins, ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions, BMJ 355 (2016) i4919, http://doi: 10.1136/bmj.i4919.
[26] G.D.T. GRADEpro, GRADEpro Guideline Development Tool [Software], McMaster University and Evidence Prime, 2021 (Available from: gradepro.org).
[27] H. Schünemann, J. Brożek, G. Guyatt, A. Oxman (Eds.), GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations, The GRADE Working Group, 2013. Updated October 2013, (Available from: guidelinedevelopment.org/handbook).
[28] Y. Cen, C. Yang, J. Ren, Y. Gong, C. Xie, Additional chemotherapy improves survival in stage II-III pulmonary sarcomatoid carcinoma patients undergoing surgery: a propensity scoring matching analysis, Ann. Transl. Med. 9 (2021) 24. http://doi: 10.21037/atm-20-3226.
[29] Y. Iijima, Y. Nakajima, H. Kinoshita, Y. Nishimura, T. Iizuka, H. Akiyama, T. Hirata, Clinicopathological Analysis of 17 Surgically Resected Pulmonary Pleomorphic Carcinoma Cases, vol. 27, Ann Thorac Cardiovasc Surg, 2021, pp. 1–9. http://doi: 10.5761/atcs.oa.20-00018.
[30] L. Sun, J. Dai, Y. Chen, L. Duan, W. He, Q. Chen, H. Wang, Y. Zhu, H. Zhang, G. Jiang, P. Zhang, Pulmonary sarcomatoid carcinoma: experience from SEER database and shanghai pulmonary hospital, Ann. Thorac. Surg. 110 (2020) 406–413. http://doi: 10.1016/j.athoracsur.2020.02.071.
[31] Y. Wang, Y. Cao, J. Liu, The role of prognostic nutritional index in the management of pulmonary sarcomatoid carcinoma, Clin. Sarcoma Res. 10 (2020) 26, hhtp://doi: 10.1186/s13569-020-00148-2.
[32] Y. Lin, H. Yang, Q. Cai, D. Wang, H. Rao, S. Lin, H. Long, J. Fu, L. Zhang, P. Lin, G. Xu, T. Rong, X. Xiong, G. Ma, Y. Liang, Characteristics and prognostic analysis of 69 patients with pulmonary sarcomatoid carcinoma, Am. J. Clin. Oncol. 39 (2016) 215–222. http://doi: 10.1097/COC.0000000000000101.
[33] B.S. Hendriksen, C.S. Hollenbeak, M.F. Reed, M.D. Taylor, Perioperative chemotherapy is not associated with improved survival in stage I pleomorphic lung cancer, J. Thorac. Cardiovasc. Surg. 158 (2019) 581–591. http://doi: 10.1016/j.jtcvs.2019.04.005.
[34] N.A. Karim, J. Schuster, I. Eldessouki, O. Gaber, T. Namad, J. Wang, C. Xie, J. C. Morris, Pulmonary sarcomatoid carcinoma: University of Cincinnati experience, Oncotarget 9 (2017) 4102–4108. http://doi: 10.18632/oncotarget.23468.
[35] F. Lococo, C. Rapicetta, G. Cardillo, A. Stefani, S. Margaritora, G. Leuzzi, G. Rossi, Petracca Ciavarella, U. Morandi, F. Facciolo, T. Ricchetti, A. Cesario, M. Paci, Pathologic findings and long-term results after surgical treatment for pulmonary sarcomatoid tumors: a multicenter analysis, Ann. Thorac. Surg. 103 (2017) 1142–1150. http://doi: 10.1016/j.athoracsur.2016.08.114.
[36] J.S. Park, Y. Lee, J. Han, H.K. Kim, Y.S. Choi, J. Kim, Y.M. Shim, K. Kim, Clinicopathologic outcomes of curative resection for sarcomatoid carcinoma of the lung, Oncology 81 (2011) 206–213. http://doi: 10.1159/000333095.
[37] A.B. Schrock, S.D. Li, G.M. Frampton, J. Suh, E. Braun, R. Mehra, S.C. Buck, J. A. Bufill, N. Peled, N.A. Karim, K.C. Hsieh, M. Doria, J. Knost, R. Chen, S.I. Ou, J. S. Ross, P.J. Stephens, P. Fishkin, V.A. Miller, S.M. Ali, B. Halmos, J.J. Liu, Pulmonary sarcomatoid carcinomas commonly harbor either potentially targetable genomic alterations or high tumor mutational burden as observed by comprehensive genomic profiling, J. Thorac. Oncol. 12 (2017) 932–942. http://doi: 10.1016/j.jtho.2017.03.005.
[38] T. Vieira, M. Antoine, C. Hamard, V. Fallet, M. Duruisseaux, N. Rabbe, A. Rodenas, J. Cadranel, M. Wislez, Sarcomatoid lung carcinomas show high levels of programmed death ligand-1 (PD-L1) and strong immune-cell infiltration by TCD3 cells and macrophages, Lung Cancer 98 (2016) 51–58. http://doi: 10.1016/j.lungcan.2016.05.013.
[39] V. Velcheti, D.L. Rimm, K.A. Schalper, Sarcomatoid lung carcinomas show high levels of programmed death ligand-1 (PD-L1), J. Thorac. Oncol. 8 (2013) 803–805. http://doi: 10.1097/JTO.0b013e318292be18.
[40] https://clinicaltrials.gov/ct2/show/record/NCT04888429?cond=pulmonary+sarcomatoid+carcinoma&draw=2&rank=3. (Accessed 13 February 2022).
[41] https://clinicaltrials.gov/ct2/show/record/NCT04725448?cond=pulmonary+sarcomatoid+carcinoma&draw=2&rank=2&view=record. (Accessed 13 February 2022).
[42] https://clinicaltrials.gov/ct2/show/record/NCT04224337?cond=pulmonary+sarcomatoid+carcinoma&draw=2&rank=5. (Accessed 13 February 2022).
[43] https://clinicaltrials.gov/ct2/show/record/NCT02897479?cond=pulmonary+sarcomatoid+carcinoma&draw=2&rank=6. (Accessed 13 February 2022).