

Prognostic Factors for Pulmonary Metastasectomy in Soft Tissue Sarcoma: An Integrative Review

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ABSTRACT

The lung is one of the most common sites of metastasis from soft tissue sarcoma (STS). In the absence of a randomized control trial, pulmonary metastasectomy is commonly performed in an effort to improve survival. However, data from retrospective analysis and case series remain subject to selection bias. The aim of this study was to review the published data, especially to identify prognostic factors, to inform future clinical practice in the field of pulmonary metastasectomy for metastatic soft tissue sarcoma. We searched the SCOPUS database using the terms “pulmonary metastasectomy” or “lung resection” or “lung metastasectomy” or lung metastasectomies” and sarcoma and survival in the title, abstract, and keywords of all documents. Over the study period (1976-June 2021), a total of 438 documents of published articles were retrieved and 192 were identified for bibliometric analysis, and of those, 128 articles were included in the content analysis. No randomized trial was identified. ‘Bradford’s law’ was applied to classify journals into ‘zones’ and 6 journals appeared to publish 70/192 (36.4%) of all articles, receiving 52% of the citations. The vast majority of articles 64% were retrospective cohort analyses. A total of 49 articles reported on prognostic factors. Pulmonary metastasectomy is frequently performed for lung metastases originating from STS. The literature continues to evolve in the form of retrospective cohort studies. It is important to review and utilize the prognostic factors to identify patients for pulmonary metastasectomy to enhance the survival outcome.

Keywords: Pulmonary, metastases, soft tissue sarcoma, curriculum, prognostic factors, integrative review, Oman.

INTRODUCTION

The lung is one of the most common sites of metastatic disease [1]. Sarcomas are a heterogeneous group of malignancies with a marked propensity to metastasize to the lungs [2]. The lung is the most frequent site of metastasis from soft tissue sarcomas (STS), and 20 to 40% of patients with sarcoma develop metastasis to the lung without involving any other organ [3]. Systemic chemotherapy or targeted therapy remains of unproven benefit for the vast majority of patients with pulmonary metastasis from sarcoma [4]. Pulmonary metastasectomy is commonly performed as part of a concept of personalized treatment for advanced cancer and in an effort to improve survival. 5-year survival rates of 30 to 50% have been reported following the wedge resection of metastases from the lung [5].

In the absence of randomized controlled trials, most of the data on the effectiveness of pulmonary metastasectomy comes from retrospective cohort analyses, or case series and case reports. Data from retrospective analysis and case series remain subject to selection bias especially because investigators use different criteria for the selection of patients. Over the last few years, excellent systematic reviews have described the outcomes of patients who undergo pulmonary metastasectomy for

STS [6-9]. Also, The role of video-assisted thoracoscopic surgery compared to the traditional open thoracotomy has been reviewed [10]. Furthermore, the role of repeat surgical resection has also been reviewed [11]. However, there is no integrated bibliometric review of the subject.

We reviewed the published literature with several objectives. Firstly, to report the trend and pattern of publications over the last several years; secondly, to review the source dynamics, thirdly, to identify gaps in the published literature, and finally, to identify prognostic factors for survival considered by investigators before metastasectomy.

METHODS

We conducted a systematic integrative review of the literature to inform future clinical practice in the field of pulmonary metastasectomy for metastatic STS. Relevant articles were searched using the SCOPUS database. SCOPUS is commonly used to carry out citation-based systematic literature reviews [12-16]. There are several advantages of using SCOPUS compared to other databases, such as Web of Science, ProQuest, as SCOPUS includes the widest range of articles with complete reference sets in a consistent and reliable form [17] (Corbet *et al.* 2019).

The initial search was done on June 4, 2021, using the terms “pulmonary metastasectomy” or “lung resection” or “lung metastasectomy” or lung metastasectomies” and sarcoma and survival in the title, abstract, and keywords of all documents.

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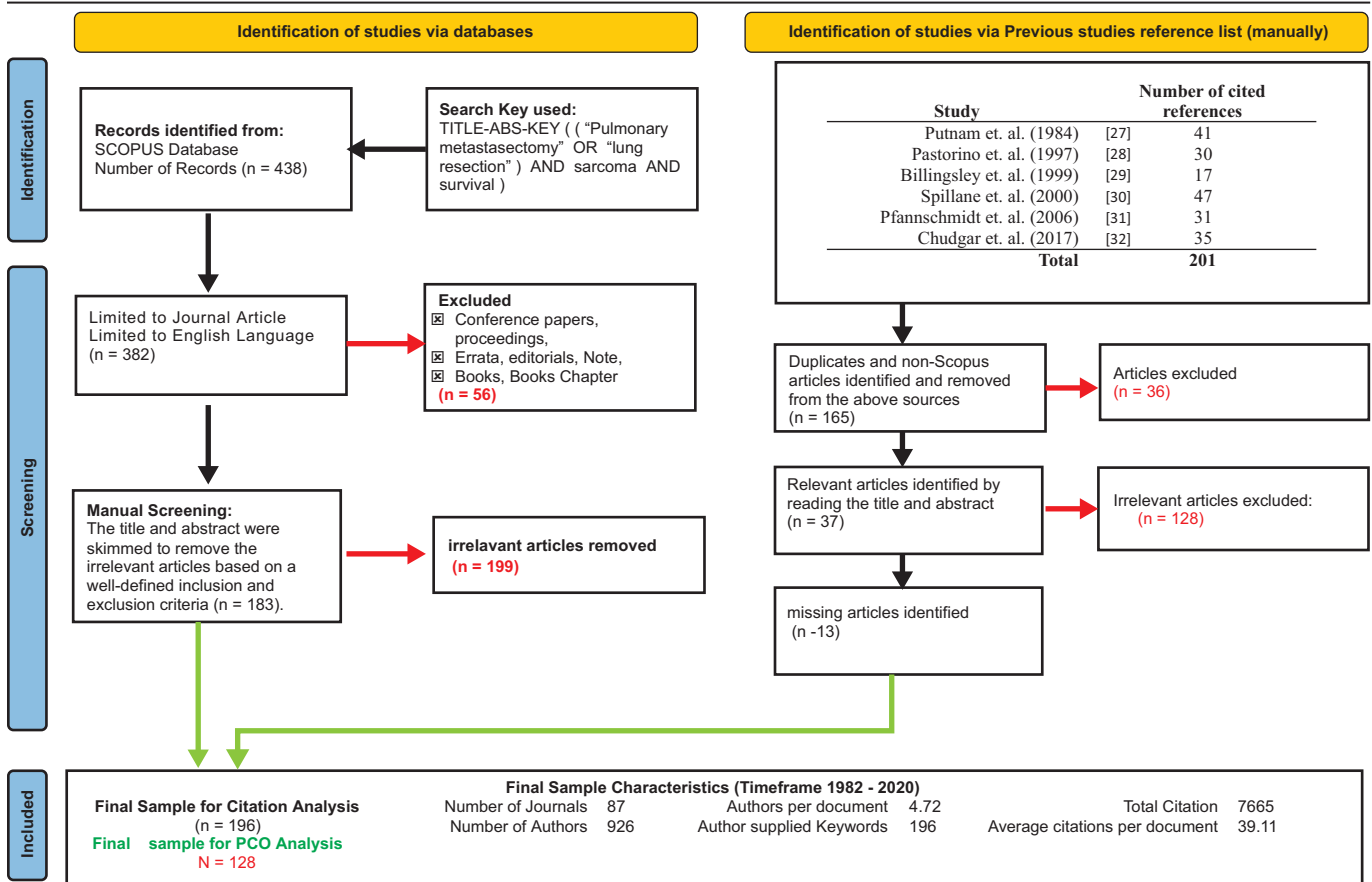


Fig. (1): Article Selection Flow Chart (PRISMA).

A total of 438 documents were retrieved. Fifty-six articles written in languages other than English, and not written in scientific journals were excluded. For the remaining 382 articles published in peer-reviewed journals, abstracts or the whole text were reviewed manually to remove irrelevant articles. ‘Relevant’ articles were defined as articles describing the survival of patients with sarcoma, who underwent pulmonary metastasectomy. Articles describing pulmonary metastasectomy for other indications were excluded. Also, articles related to pulmonary metastasectomy, but not describing survival outcomes were excluded. Some studies have been identified using the reference list of previous studies. The whole process of article selection process using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) has been explained in Fig. (1). A total of 196 articles were included in the final citation analysis. Almost 82% of 196 articles were published in journals indexed in PubMed. These articles had been published in 87 different journals and by 926 authors. Moreover, these articles received 7665 total citations with an average of 39.11 citations per document. Finally, review articles, commentaries, editorials, and case reports were excluded for the purposes of content analysis. Content analysis was performed on a total of 128 articles.

The data were then plotted over time (number of publications), or analyzed using Bradford’s law [18].

RESULTS

Over the study period (1976-June 2021), a total of 196 published articles were identified for bibliometric analysis, and of those 128 articles were included in the content analysis. The trends of publication and citations over the study period are shown in Fig. (2). An increase in the number of articles was observed after 2009. Since then, between 5 and 15 articles are published every year.

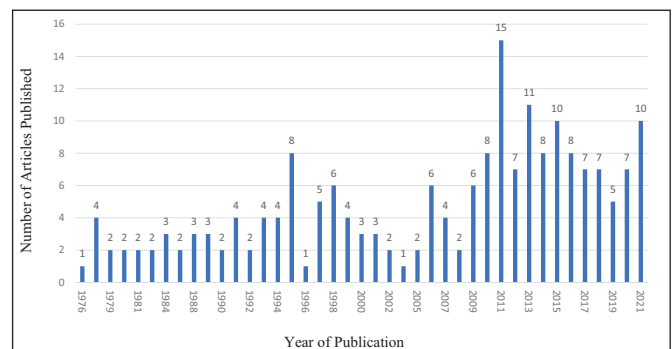


Fig. (2): Time trends of publications.

We applied ‘Bradford’s law’ to classify journals into ‘zones’ based on the total number of articles published. Bradford’s law states that “If journals were arranged in order of decreasing productivity of articles on a given subject, they may be divided into a nucleus particularly

devoted to the subject, and several zones containing the same number of articles as the nucleus”.

In the current study, the journals were divided into three zones with an almost equal number of publications. A total of 6 core journals published 70 articles. These articles were cited 3993 times. Another 21 and 60 journals appeared in the 2nd and the 3rd zones, publishing 62 and 64 articles, and receiving 1998 and 1674 citations respectively.

We then looked at the source dynamics. **Fig. (3)** shows the six ‘core’ journals publishing almost 1/3rd of all articles and the time trends of the number of publications in the core journals.

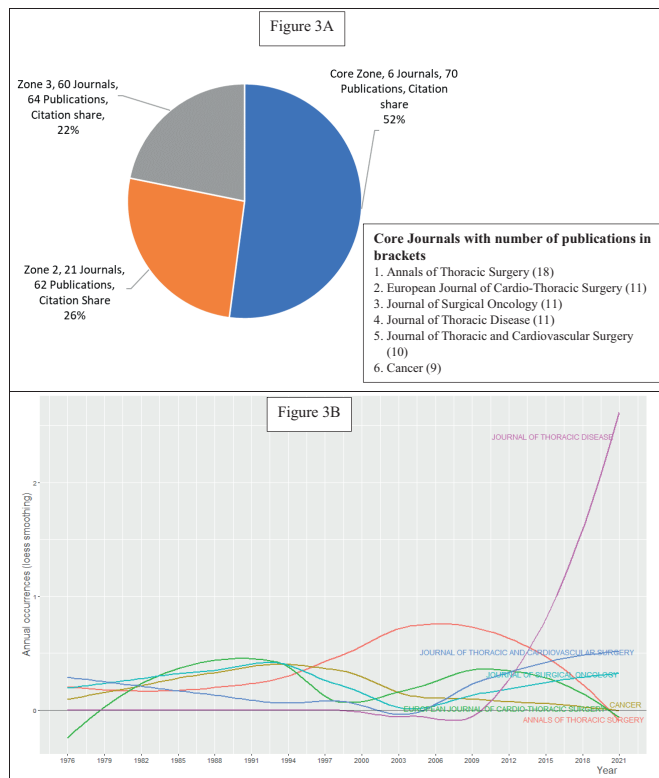


Fig. (3A and 3B): Bradford law and journals’ publication trends.

CONTENT ANALYSIS

Of the 196 articles, 128 were selected for content analysis (retrospective and prospective cohort studies and one meta-analysis). The details of the categories of the articles are shown in **Fig. (4)**.

Histological subtypes of sarcoma are shown in **Table 1A** and the type of surgical intervention is shown in **Table 1B**. A total of 34/122 (28%) of studies reported on STS, 20% of studies reported on a mix of different types of sarcomas, and another 18% of the studies included other types of cancer, in addition to sarcoma. Almost 2/3rd of the studies explored the role of pulmonary metastasectomy, whereas, other studies also explored the role of the addition of chemotherapy, or more extensive type of surgery, such as segmentectomy or pneumonectomy

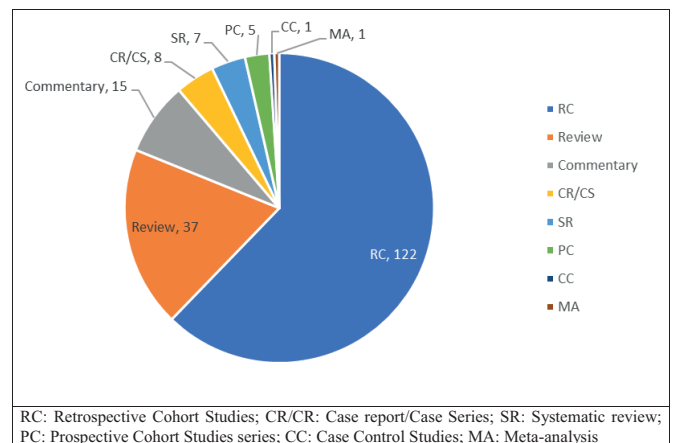


Fig. (4): Type of study.

Table 1A: Sarcoma sub-type.

Type of Sarcoma	Retrospective Cohort	Prospective Cohort	Meta-analysis	Total
Soft-tissue sarcoma	34	4	1	39
Different types of sarcoma	25	1	-	26
Sarcoma and other cancer types	23	-	-	23
Osteosarcoma	8	-	-	8
STS and Osteosarcoma	6	-	-	6
STS and Bone sarcoma	5	-	-	5
Synovial sarcoma	4	-	-	4
Miscellaneous	17	-	-	17

Table 1B: Type of intervention.

Type of intervention	Retrospective Cohort	Prospective Cohort	Meta-analysis	Total
Metastasectomy	81	-	-	81
Metastasectomy with or without chemotherapy	8	-	-	8
Repeat pulmonary metastasectomy	4	1	1	6
Video-assisted thoracoscopic surgery	5	1	-	6
Wedge resection and lobectomy	5	-	-	5
Pneumonectomy	3	-	-	3
Miscellaneous	16	2	-	17

Out of the 128 articles, a total of 49 publications reported on prognostic factors to help select patients for a favorable outcome. The most often reported prognostic factors from the 49 publications are shown in **Table 2**. The most often reported prognostic factors included disease-free interval (31/49 = 63%), followed by the number of metastases (28/49 = 57%), and the surgeon’s assessment of resectability (20/49 = 40%).

DISCUSSION

To the best of our knowledge, this is the first integrative review on the subject of pulmonary metastasectomy in recurrent STS. The vast majority of studies were

Table 2: Prognostic factors.

Prognostic Factor	Number of Studies Reporting the Prognostic Factor
Disease-free interval	31
Number of pulmonary metastases	28
Surgeon's assessment of resectability	20
Primary tumor sub-type, grade	15
Repeat resection	11
Size of metastases	10
Miscellaneous (Laterality, age, gender, use of chemotherapy, metastases doubling time, absence of symptoms, growth pattern)	27

retrospective cohort studies. A small number of studies also reported on repeat pulmonary metastasectomy. We reviewed prognostic factors employed by different investigators and observed disease-free intervals, the number of pulmonary metastases, the surgeon's assessment of resectability, and consideration of the biology of the disease to be most often considered prognostic factors. Since the vast majority of studies are retrospective, reported on small sample size, and were reported over almost 50 years, it is difficult to suggest which prognostic factors are more important. However, based on the information provided in the study, a prognostic model can be built and tested prospectively.

Patients with pulmonary metastases secondary to STS appear to benefit most from resection because of the unique biology of sarcomas, with their predilection for the lung as the only metastatic site. However, the median overall survival for pulmonary metastatic disease with multidisciplinary treatment is approximately 12 to 14 months [19]. The majority of patients who develop pulmonary metastases are asymptomatic and are diagnosed during routine follow-up visits. Pulmonary metastasectomy is associated with improved overall survival only in patients with complete surgical resection. The majority of resectable patients have peripheral lesions [20]. Although pulmonary metastasectomy has been practiced for several years, the procedure is not supported by a randomized trial. It is even argued, that the procedure may be potentially harmful [21], as the concept of oligometastases is not very well defined, and there may be a selection or publication bias in the often-reported literature. Hence it is important to identify prognostic factors for patients who may undergo resection.

Several prognostic factors have been reported and include disease-free interval, the number of pulmonary nodules, the ability to achieve R0 resection, the number of nodules, progression after chemotherapy, favorable tumor histology, low histological grade, age less than 50 years, *etc.* [22-24]. We identified disease-free interval, a number of pulmonary metastases, surgeons' assessment of resectability and the primary tumor

histological sub-type as the most frequently identified prognostic factors. Our results are consistent with the earlier observations. Of note, whereas, objective parameters, such as, younger, age, longer disease-free interval, a fewer number of pulmonary metastases, the favorable tumor histology continue to be important and relevant prognostic markers, assessment of resectability by an experienced surgeon is equally important. This observation underscores the need for an experienced, high-volume surgeon to make the decision, preferably, in the setting of a multidisciplinary tumor board.

There are limitations of an integrative review. An integrative review is a method that summarizes past empirical and theoretical literature to provide a more comprehensive understanding of a particular phenomenon or healthcare problem [25]. On the one hand, an integrative review allows for the inclusion of diverse methodologies, and review evidence and gaps in the literature, on the other, the combination and complexity of the subject can contribute to a lack of rigor [26]. Furthermore, because of the complexity of the method of analysis, firm conclusions cannot be drawn. However, given the nature of the question in this study, *i.e.* prognostic factors determining a favorable outcome after pulmonary metastasectomy in recurrent STS, this review provides an insight into the absence of randomized trials.

CONCLUSION

In conclusion, although sarcomas are a group of rare neoplasms, the various and varied histological sub-types make the feasibility of running a randomized trial difficult. At the same time, lung metastases arising from sarcomas remain all too common. Pulmonary metastasectomy is frequently performed for lung metastases. The literature continues to evolve in the form of retrospective cohort studies. VATS and even repeated resections are being contemplated. The content analysis in this integrative review identifies the most frequently employed prognostic factors employed by various investigators and may help busy clinicians quickly review their cases for potential metastasectomy in light of these results.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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