

Clinical value of pulmonary metastasectomy for thyroid malignancies: a systematic review and meta-analysis

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ABSTRACT

Background: There is currently no consensus on the role of pulmonary metastasectomy (PM) for thyroid malignancies. The main objective of this study is to determine if there is any survival benefit to PM and determine good candidates for metastasectomy.

Methods: A systematic review of relevant studies was performed, evaluating articles identified using the PubMed, Cochrane, and MEDLINE databases according to PRISMA-guidelines.

Results: The initial literature search yielded 18 articles of which 7 met inclusion criteria. Only data on thyroid cancers were included in the systematic review. A total of 174 patients who underwent PM were analyzed. The mean age was 54.8 (range: 10–90), and 52.5% of patients were female. The overall absolute 5-year survival rate was 67.7% (range: 32.5–84.0%) for patients undergoing PM. The reported post-surgical complication rate overall was 14.4% and two peri-operative deaths were reported. Three papers reported the following as good prognostic factors: Papillary histology, younger age (<45 years), disease free interval >3 years, R0 (microscopic margin free) resection, systematic lymphadenectomy, thyroglobulin <10 ng/mL, and thyroglobulin reduction >80% after metastasectomy.

Conclusion: This study is the first systematic review evaluating the clinical role of PM for thyroid cancer in the literature to date. PM may offer prolonged survival over traditional therapy for selected patients.

Keywords: Thyroid malignancy, pulmonary metastasis, metastasectomy, survival outcomes

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy worldwide, and the reported prevalence of thyroid cancer is increasing.^{1,2} While select early stage thyroid cancers may be observed or treated with thyroid lobectomy alone, the standard treatment of thyroid cancer consists of surgical resection with total thyroidectomy sometimes followed by radioactive iodine (RAI), which ablates residual primary tumor and metastases.^{3,4} This approach is generally

effective, resulting in a no evidence of disease status in most patients and achieving an overall estimated 85%–93% 10-year survival rate in patients with differentiated thyroid malignancies.^{4,5} Thyroid cancer tends to invade locoregional lymph nodes and uncommonly invades distant nodes, with estimated rates ranging from 4% to 30%.^{2,4,6,7} However, distant metastasis is strongly associated with poor treatment outcomes and reduced long term survival. The majority of distant metastases occur in the chest, with the most common site being the lung.^{3,4,5} Radioactive iodine is the first line treatment protocol in patients with pulmonary metastasis; unfortunately, RAI is not always curative, and more than half of patients experience disease progression despite repeated ablations, resulting in a reported 10-year survival rate of 10–18% for RAI

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treatment in patients with pulmonary metastasis.^{8,9,10} Molecular targeted therapy for locally advanced or metastatic iodine-refractory differentiated thyroid cancer (DTC) have been approved; however, while these approaches prolong survival, outcomes are unsatisfactory.^{11,12,13}

Surgical resection of head and neck and upper mediastinal metastases can prove effective for patients with RAI-resistant disease, but resection of pulmonary metastases is more controversial, despite its having a standard role in the treatment of other malignancies, including sarcomas, germ cell tumors, and other carcinomas.^{4,7} Several studies suggest that pulmonary metastasectomy (PA) may be an effective treatment option in RAI refractory pulmonary metastasis. However, there is currently no consensus among practitioners regarding its use, indications, and associated morbidity and mortality in thyroid cancer patients. We therefore aim to systematically analyze the literature examining the role of PM in thyroid cancer to better delineate its clinical value.

METHODS

SEARCH STRATEGY

Articles reporting pulmonary metastasectomy in patients with thyroid malignancies were systematically identified using the electronic PubMed, Cochrane, and MEDLINE databases. Keywords used included “pulmonary metastasectomy” (PM), “lung metastasectomy” AND “thyroid cancer” or “thyroid malignancy” or “papillary thyroid cancer” or “follicular thyroid cancer.” Only articles published in English were considered for review. One hundred and seventy-four abstracts were reviewed, and 155 of these articles were excluded from further consideration (Figure 1). All remaining articles (n = 18) were analyzed using selection criteria based on PRISMA guidelines.

SELECTION CRITERIA

Our inclusion criteria required that the study: 1) describe patients who underwent pulmonary metastasectomy for thyroid cancers, and 2) provide treatment outcomes of pulmonary metastasectomy. We

excluded papers if they: 1) only detailed pulmonary metastasectomy for patients who didn't have thyroid malignancy, 2) provided information for fewer than five patients, and 3) did not describe treatment outcomes. All articles remaining after applying exclusion criteria (n = 7) were included in the systematic review and meta-analysis.

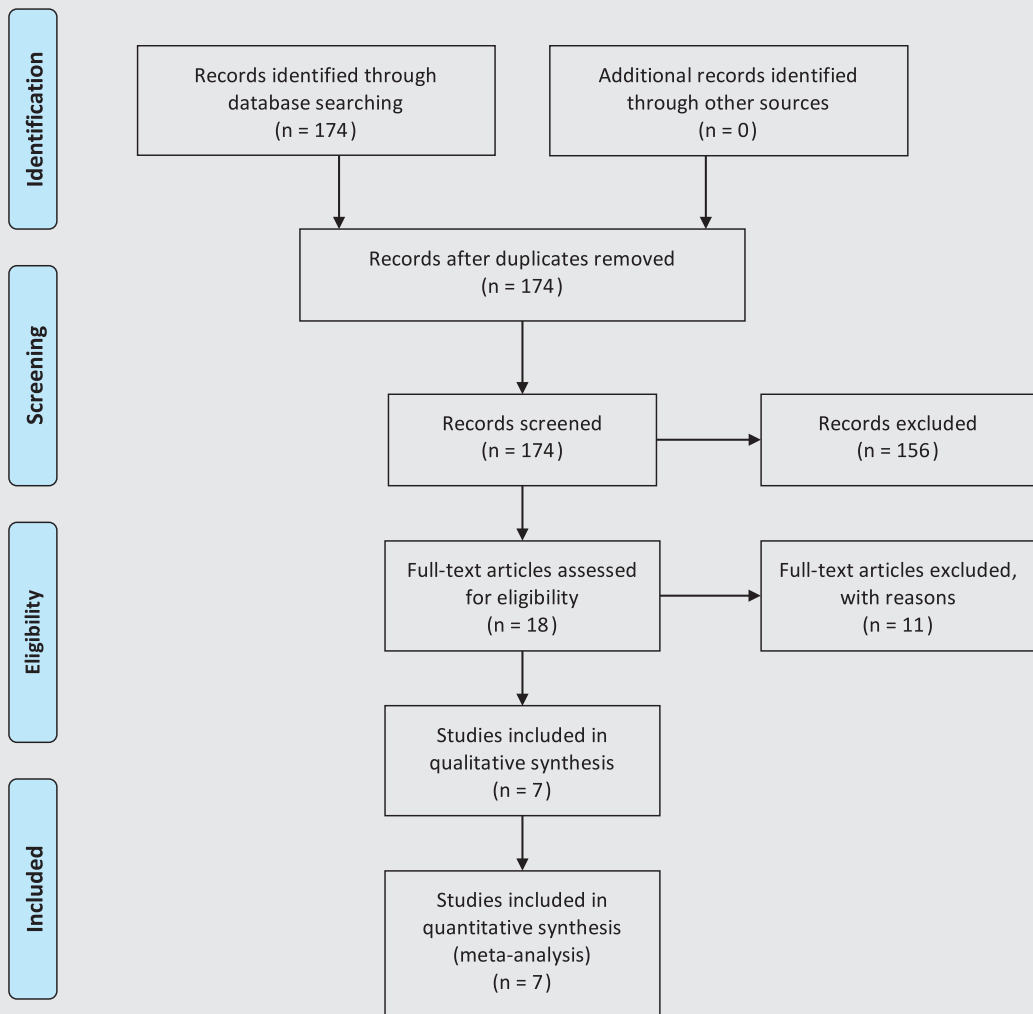
DATA EXTRACTION

From seven retrospective chart reviews, we extracted the following information to include in our database: total number of thyroid cancer patients who underwent PM, mean age at thyroid cancer diagnosis, age range for all patients, type of surgical approach used for PM, number and type of surgical complication, five-year survival rate, sex, average age, laterality of pulmonary metastases, perceived favorable prognostic factors, and primary tumor pathology. Data were then tabulated in Excel and statistical analysis was performed for cumulated data. Demographic variables, treatment outcomes, and complication rates were calculated by using descriptive statistics. Heterogeneity was examined by using Cochrane's Q test and I² statistic.

RESULTS

Seven studies published between 1998 and 2017 were reviewed. The total number of patients with a thyroid cancer diagnosis who underwent PM was 174. Of the patients whose sex was provided (n = 107), 52.3% were male, 47.7% were female, and the average patient age was 54.8 with a pooled age range of 10–90. Characteristics of the seven studies, including patient age and sex, are reported in Table 1. The most common primary thyroid tumor pathology was papillary (48.0%; n = 73), followed by follicular (37.5%; n = 57), medullary (7.9%; n = 12), Hurthle (5.9%; n = 9), and anaplastic (0.7%, n = 1). The distribution of thyroid cancer histology is summarized in Figure 2. Pulmonary metastases were more frequently reported to be bilateral (n = 57) than unilateral (n = 37), and thoracotomy (n = 68) was more frequently used as the surgical approach to PM than sternotomy (n = 28) or thoracoscopy (n = 14).

Figure 1. Flow chart describing identification of studies to be included in the systematic review. Adopted from PRISMA guidelines.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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The overall absolute 5-year survival rate post-PM was 67.7% (average survival rate based on pooled data) with a pooled range of 32.5%–84.0%; one paper did not report the 5-year survival rate. Sampson et al reported a 3-year survival rate of 77%, and Porterfield et al and Moneke et al reported 37.5% and 56% survival rates, respectively, at 10 years post-surgery (Table 2). Three papers described favorable prognostic factors for patients who underwent PM, with two papers reporting young age (45 years old) at initial

cancer diagnosis and papillary histology of the primary tumor (Figure 3a, Figure 3b) as predictors of a favorable outcome. Others included a disease free interval of greater than three years, iodine avidity of the thyroid cancer, thyroglobulin levels of less than 10 ng/mL (Figure 3c), thyroglobulin level reduction of 80% post-metastasectomy, age less than 45 at time of thyroid cancer diagnosis, R0 (negative microscopic margins) metastasectomy, and systematic mediastinal lymphadenectomy.

Table 1. Study and Patient Characteristics

Author	Year	Study country	No. patients	Males (%)	Females (%)	Mean age	Age range
Khan ²¹	1998	USA	8	ND	ND	ND	ND
Liu ¹¹	1999	USA	8	ND	ND	ND	ND
Protopapas ²²	2001	England	16	12 (75.0)	4 (25.0)	47	19–77
Pak ⁴	2003	USA	29	12 (41.3)	17 (58.6)	48	12–72
Sampson ²³	2007	Canada	22	7 (31.8)	15 (68.1)	68	19–70
Porterfield ²	2009	USA	48	25 (52.0)	23 (47.9)	53	20–79
Moneke ⁷	2017	Germany	43	19 (44.1)	24 (55.8)	57	10–77
TOTAL			174	75 (47.4)	83 (52.5)		

“ND” signifies that the data was not provided by the study.

The most common complications from PM reported in the seven papers were transient atrial fibrillation (total number of patients = 3) and surgical wound infection (total number of patients = 3). However, only 25 out of 174 patients (14.4%) were reported to have complications post-surgery, and only two patients died due to surgical complications. All observed complications are described in Table 3.

DISCUSSION

The first-line treatment for thyroid cancer metastasis to the lung is radioactive iodine (RAI), which offers only a 50% survival rate at six months and less than a 20% 10-year survival rate.^{5,14} Having RAI refractory PM is considered a poor prognostic factor. In contrast, pulmonary metastases secondary to renal

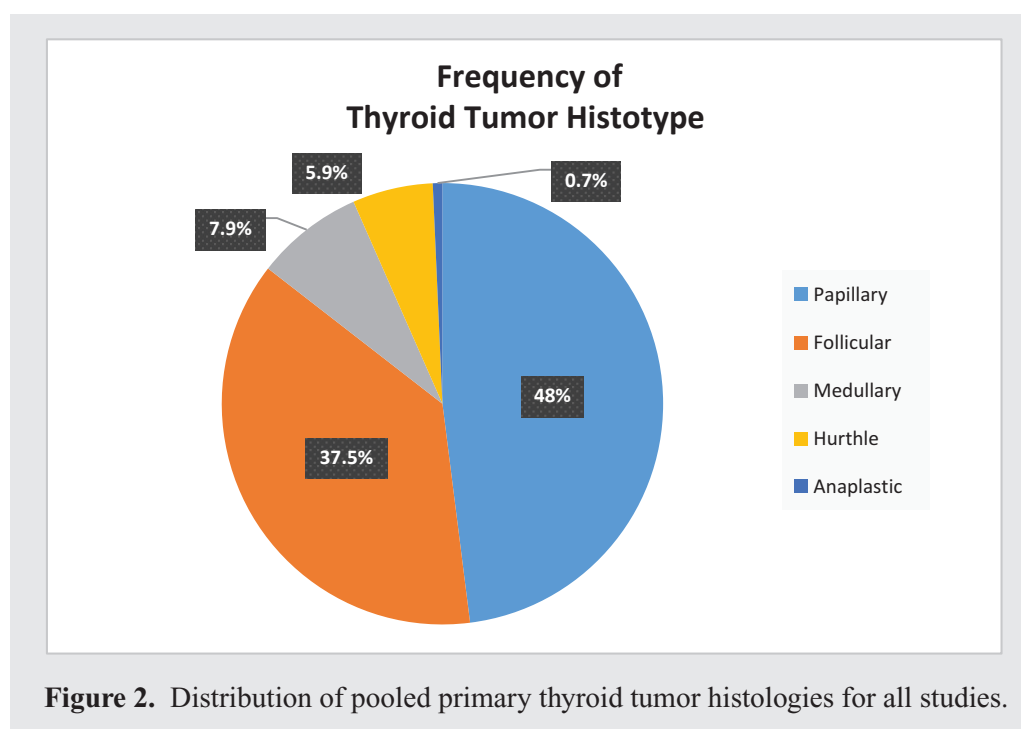


Table 2. Survival Outcomes

Author	3-Year	5-Year	10-Year
Khan ²¹		58.0	
Liu ¹¹		75.0	
Protopapas ²²		32.5	
Pak ⁴		78.5	
Sampson ²³	77.0		
Porterfield ²		60.0	37.5
Moneke ⁷		84.0	56.0

cell carcinoma, colorectal carcinoma, testicular cancers, and sarcomas are routinely treated surgically.¹⁴ Similarly, Finley et al found that those undergoing PM for squamous cell carcinomas of the head and neck (selected patients with limited pulmonary metastasis) had significantly higher survival rates than those who did not.¹⁵ Considering the success of PM in improving survival in patients with other cancers, it is likely that surgical resection of metastases could improve outcomes for thyroid cancer patients with pulmonary metastases. The data collected from these

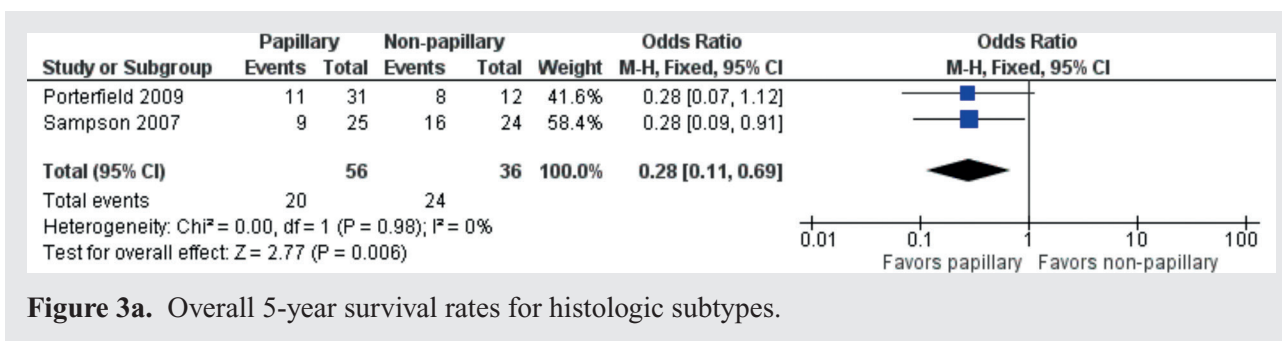


Figure 3a. Overall 5-year survival rates for histologic subtypes.

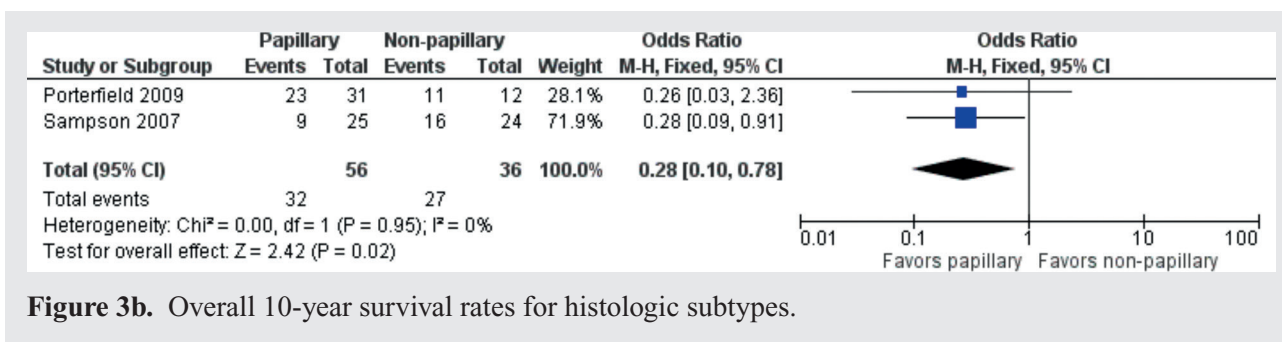


Figure 3b. Overall 10-year survival rates for histologic subtypes.

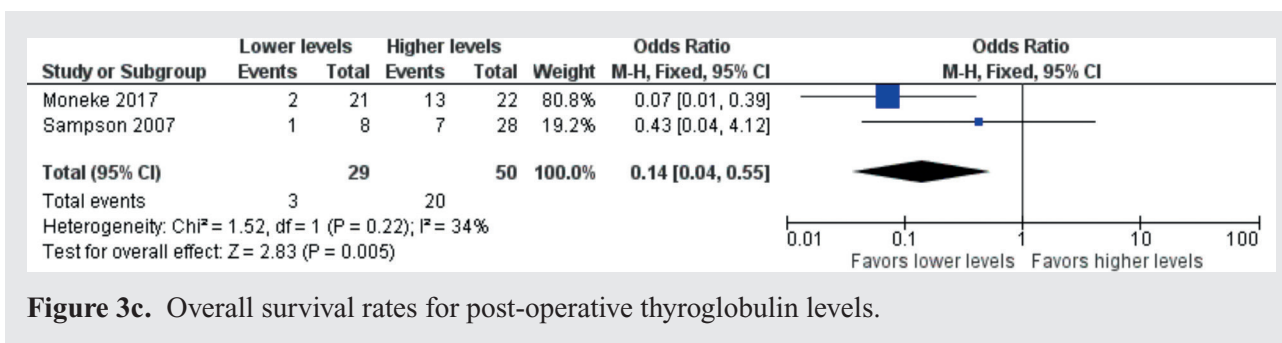


Figure 3c. Overall survival rates for post-operative thyroglobulin levels.

Table 3. Adverse outcomes following pulmonary metastasectomy

Outcome	Number
Atrial Fibrillation	3
Surgical Wound Infection	3
Respiratory Distress	2
Hemorrhage	2
Chylothorax	2
Death	2
All others	11
TOTAL	25

“All others” includes hypotension, brachial plexus injury, nerve paresis, Horner syndrome, pneumonia, ileus, and sternal dehiscence.

retrospective chart reviews do, in fact, suggest that pulmonary metastasectomy in thyroid cancer patients can greatly decrease mortality with an absolute overall 5-year survival rate of 67.7% reported. Given that this rate greatly exceeds those of RAI reported in the literature, this would suggest that PM is potentially a highly effective treatment for RAI-refractory metastases. More important, PM appears to carry a low risk of morbidity and mortality. Only 14.4% of all patients experienced a surgical complication, and only two out of 174 patients died as a result of surgery. Considering the significant decreases in mortality reported by all seven papers, it therefore seems likely that the benefits to PM outweigh the risks.

The advent of effective multitargeted kinase inhibitors for recurrent/metastatic DTC creates another option for patients with PM from iodine refractory thyroid cancer. In particular, the multitargeted kinase inhibitor lenvatinib was approved for iodine-refractory recurrent/metastatic disease on the basis of progression free survival improvements in the phase III SELECT trial greater than had been achieved in other placebo-controlled trials in DTC.^{11,12,13} The 65% response rate and improvement in progression free survival from 3.6 months to 18.3 months creates an attractive potential alternative option. None of the studies that we identified compared results with PM versus targeted therapy. Future studies could compare

outcomes of either multitargeted kinase inhibitors or combination therapy. Since many patients with metastatic DTC will have prolonged survival, they may benefit from such an aggressive approach.

In 1947 Alexander and Haight suggested the first known selection criteria for PM, which were later revised by Thompson in 1965. These are: 1) the primary tumor must be controlled, 2) no extrathoracic metastases exist, with the exception of hepatic metastases, 3) the metastases are resectable, and 4) the risks of surgery are acceptable.^{16,17} Additionally, the International Registry of Lung Metastases lists disease free index, complete resection, and number of nodules as favorable prognostic factors.¹⁸ Although these criteria are used today by surgeons to guide selection of patients for PM, there is no current consensus on favorable prognostic factors for patients with thyroid cancer metastases to the lung specifically. The reviewed literature suggests that younger patients have a lower mortality rate. However, whether older age should be considered a relative contraindication for PM or simply increases disease-specific mortality regardless of treatment modality is unclear.¹⁹ Additionally, although it appears that papillary thyroid carcinoma carries a better prognosis over other thyroid cancer histotypes post-metastasectomy, it is possible that this trend is due to the lower mortality of papillary thyroid carcinoma in general.²⁰ Thyroglobulin levels of lower than 10 ng/mL and relative decreases of at least 80% have been suggested by Moneke et al to positively correlate with improved survival.⁷ Furthermore, they reported that R0 (microscopic negative margins) resection of pulmonary metastases is associated with a significantly increased survival rate versus incomplete resection, and that systematic mediastinal lymphadenectomy also significantly decreases mortality, possibly through improved cancer staging in addition to removal of the metastases.⁷ These findings suggest that outcomes can be improved with more complete surgical resection, supporting the role of aggressive treatment in these patients.

Admittedly, this study has several limitations, mainly owing to the small number of papers that met our inclusion criteria. There are few studies that specifically examine the role of pulmonary metastasectomy

in thyroid cancer treatment, and to our knowledge there are no prospective studies that compare morbidity and mortality rates between medical and surgical treatment in these patients. It is therefore difficult to determine precisely the degree to which PM improves survival rate over RAI and other treatment modalities. Additionally, even among the seven papers that met our inclusion criteria there is heterogeneity in the outcomes and patient characteristics measured. Therefore, we can only draw limited conclusions regarding survival rates, surgical complications, and prognostic factors. Future randomized studies should compare PM to other treatment modalities, including RAI alone, to conclusively determine that it provides a statistically and clinically significant benefit and to more completely determine whether it is safe both peri-operatively and long-term. Additional research should seek to define prognostic factors for morbidity and mortality and to identify characteristics of good surgical candidates.

CONCLUSION

This is the first study to systematically review the role of pulmonary metastasectomy in patients with

thyroid cancer; the study design was adapted from PRISMA checklist (Table 4). The data collected in our study demonstrate that PM is associated with superior survival rates to those reported for radioactive iodine treatment alone, with approximately two-thirds of patients surviving at five years' follow-up. Moreover, PM appears to be associated with low morbidity and a very low mortality rate suggesting that it is both a safe and effective option for patients when indicated. Factors that seem to indicate a favorable prognosis after metastasectomy include papillary histology of the primary tumor and young age of the patient at the time of thyroid cancer diagnosis; lower thyroglobulin levels and more aggressive surgical treatment possibly improve outcomes. It is possible that these characteristics may be used to select good surgical candidates. In patients with pulmonary metastases secondary to thyroid cancer, surgical intervention should be considered after radioactive iodine ablation fails in patients without contraindications. We recommend prospective randomized studies be conducted to confirm that a survival benefit for PM over RAI alone exists. Future studies should also try to better characterize indications for surgery and to assess long-term morbidity of PM.

Table 4. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2

Table 4. PRISMA checklist (Continued)

Section/topic	#	Checklist item	Reported on page #
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2,3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2,3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2,3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2,3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2,3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2,3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	n/a
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	14,15,16
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3,12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	3,9,10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	3,4

Table 4. PRISMA checklist (Continued)

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	3,4
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	4,5
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	5
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title Page

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