Early versus Delayed Post-Therapy Whole Body Scintigraphy for Well-Differentiated Thyroid Carcinoma: a Meta-Analysis

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ABSTRACT

Introduction:

No clear consensus exists as to the optimal timing for conducting whole body scintigraphy (WBS) after radioactive iodine (RAI) therapy for differentiated thyroid carcinoma.

Objective:

This study aimed to compare the utility of early versus delayed post-therapy WBS in identifying residual lesions and metastases .

Methods:

A systematic review of existing literature was done, yielding 6 observational studies relevant to the subject. Meta-analyses were done comparing lesion detecting rates of early (3-4 days post-RAI) and delayed (7-11 days post-RAI) post-therapy WBS for thyroid remnants and metastases in the lymph nodes, lungs, and bone using a random-effects model with odds ratios (OR) and 95% confidence intervals (CIs). A subgroup analysis was also done relating to the type of collimator used in imaging.

Results:

There was no evidence to support that conducting WBS at either an early or delayed time after RAI therapy is superior to the other in detecting thyroid remnants (OR 1.11; 95% CI 0.86 – 1.42; p = 0.42), nodal (OR 1.01; 95% CI 0.74 – 1.38; p = 0.97), lung (OR 0.79; 95% CI 0.55 – 1.13; p = 0.20), and bone (OR 0.89; 95% CI 0.56 – 1.43; p = 0.64) metastases.

Conclusion:

There is no significant difference between early and delayed post-therapy whole body scintigraphy in terms of detecting thyroid remnants and nodal, lung, and bone metastases in patients with well-differentiated thyroid carcinoma.

Keywords*: post-therapy whole body scintigraphy (WBS), Iodine-131 (I-131), radioactive iodine (RAI) therapy, thyroid cancer*

INTRODUCTION

Thyroid cancer remains one of the most common malignancies worldwide, with a global incidence that is expected to continually rise throughout the coming years [1]. Differentiated thyroid carcinoma accounts for majority of thyroid malignancies [2], and among the mainstays of treatment for such cancers is total thyroidectomy with subsequent radioactive iodine (RAI) therapy. Therapy with iodine-131 (I-131) is given to achieve three main goals, namely 1) remnant ablation; 2) adjuvant treatment; and/or 3) treatment of known disease [3].

Whole body scintigraphy (WBS) after administration of therapeutic doses of I-131 for thyroid cancer is now often routinely performed as a means of demonstrating thyroid remnant uptake as well as presence and extent of metastatic disease. Indeed, compared to pre-therapy diagnostic scans that are commonly done after surgery, post-therapy WBS demonstrates increased sensitivity for for tumor localization and characterization, even showing improved detection of occult metastasis [4, 5].

However, debate remains as to the optimal time for conducting the post-therapy WBS. Though current clinical practice guidelines recommend doing WBS after RAI therapy and suggest conduction of such as early as 2 days to as late as 14 days after the date of therapy [6, 7, 8], a clear consensus has yet to be reached regarding the optimal timing of the scan. Previous observational studies aimed at determining when best to do the post-therapy WBS have had mixed conclusions, with some in favor of early imaging (i.e. 3-4 days after RAI) [9, 10] and others more for delayed imaging (i.e. 7-10 days after RAI) [11, 12], depending on which scanning time was able to reveal more detectable thyroid remnants and/or metastatic lesions.

Therefore, this meta-analysis aims to compare utility of the early and delayed post-therapy WBS in identifying residual lesion, locoregional, and distant metastases.

METHODS

This study was conducted in compliance with the guidelines set by the Meta-analyses of Observational Studies in Epidemiology (MOOSE) group (Appendix 1).

A. Search and selection process

Electronic databases (PubMed/MEDLINE, Google Scholar, and the Cochrane Library) were systematically searched for relevant articles from the date of publication up to December 2022.

A combination of the following terms was used in the search: “thyroid cancer” OR “thyroid carcinoma”, “post-therapy whole body scintigraphy” OR “post-therapy whole body scan” OR “WBS”, “iodine-131” OR “I-131”, AND “time” OR “early” AND “delayed”. Related articles were also manually searched, as were any gray literature and the reference lists of the preliminary yields.

Article titles and abstracts were then subjected to initial screening, and relevant articles subsequently underwent review of full texts. Any articles of which desired information was found to be ambiguous during the screening phase were automatically reviewed in full.

Inclusion criteria for studies were as follows: 1) study population of patients with well-differentiated thyroid cancer who underwent RAI therapy; 2) study population must have undergone both early and delayed post-therapy imaging; and 3) number of thyroid remnants and metastatic lesions reported and detected by experienced physician readers. Excluded from this analysis were case reports, reviews, editorials, and studies not written using the English language.

B. Data extraction and quality assessment

Data relevant to the study were extracted from the included articles by means of a thorough review. Information derived and thus reported include number of thyroid remnant lesions detected; number of metastatic lesions detected (nodal, lung, and/or bone, whichever were available); the study’s primary investigator; the year of publication; the country of origin; the total population of subjects; the mean age; the sex distribution; the diagnosis of the patients; the imaging hardware and type of collimator used for imaging; the mean administered dose for RAI; and the temporal definitions for early and delayed imaging.

The quality of the included studies was evaluated using the adapted Newcastle-Ottawa Quality Assessment Scale [13, 14]. Articles were evaluated based on selection, comparability of subjects, and outcome. The highest total score that could be achieved was 10. A score of at least 5 was considered satisfactory.

C. Data synthesis and statistical analysis

Statistical analyses were conducted using the Cochrane Review Manager program (Rev. Man. 5.4.1) [15]. Comparison of lesion detection rates for early and delayed imaging was done using odds ratios (OR) and 95% confidence intervals (CI). The Mantel-Haenzel method through a random-effects model was used in pooling the ORs across all the included studies for each outcome being measured. Two-tailed p values of < 0.05 were considered statistically significant for all analyses done. Heterogeneity among studies was evaluated using Cochran’s Q Chi-square test and I^2 statistics.

D. Sensitivity analysis and publication bias

Sensitivity analysis using the leave-one-out method was done to examine the effect of each included study on the overall results. Publication bias was assessed using the

Begg and Mazumdar rank correlation test and Egger's regression test via the jamovi software (version 1.6 MAJOR) [16].

RESULTS

A. Literature search

There were initially 55 studies identified from databases and manual searching. After duplication removal, 51 studies were kept for title and abstract screening as to the relevancy to the topic of interest. Subsequently, 38 studies were excluded, while 13 articles were sought for retrieval. Full text articles of 2 studies could not be found. The remaining 11 studies were assessed in full for eligibility. Of these, 2 studies were excluded because of different outcome measures presented; while 3 other studies were only available as conference abstracts that did not provide enough data for comprehensive analysis. Finally, a total of 6 studies were included in the meta-analysis. Figure 1 shows a schematic diagram of the study selection flow.

The included studies that encompassed post-therapy scans done from 2009 to 2022 report on a variety of detected lesions, namely number of thyroid remnants and metastatic lesions in the lymph nodes, lungs, and bones, with individual studies accounting for all or a select combination of the aforementioned. The 6 studies, a majority of which were conducted in Asian countries, involved a total of 691 patients with well-differentiated thyroid cancer who underwent RAI therapy with administered doses ranging from 1110 – 9250 megabecquerels (MBq). For these studies, early imaging was done 3-4 days after RAI, while delayed imaging was done 7-11 days after RAI. Five studies made use of dual-head gamma cameras. A summary of the characteristics of the included studies is shown in Table 1.

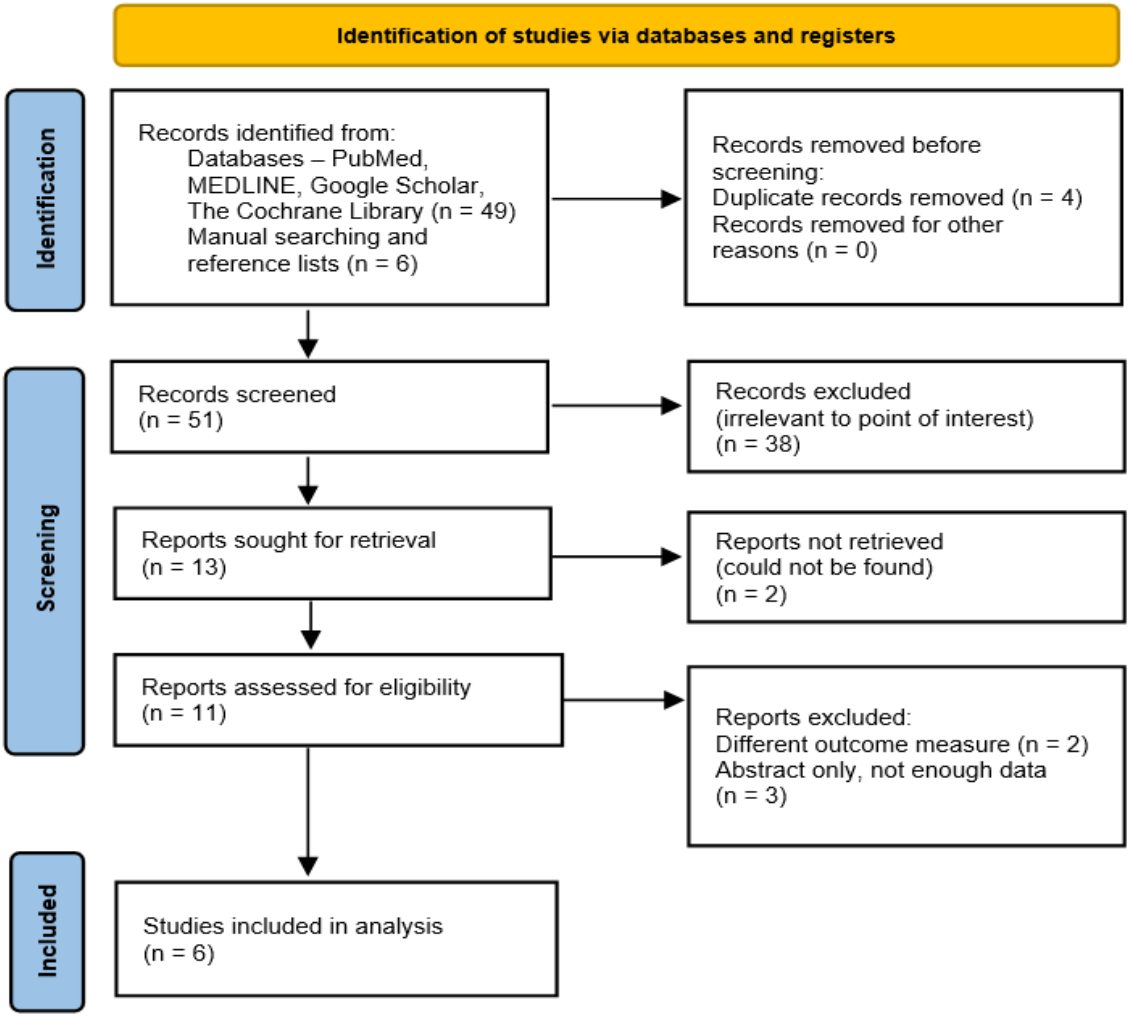

FIGURE 1. Schematic diagram of the study selection process

TABLE 1. Study characteristics of the included studies

Author (Year)	Country	Design	N (M/F)	Thyroid CA PTC/FTC	Mean RAI Activity	Mean Age	Early Imaging	Delayed Imaging	Hardware (Collimator)	Lesions Reported
Liu et al. (2022) [17]	China	Retrospective	161 (68/93)	152/9	3700 – 7400 MBq (100 – 200 mCi)	44.75 ± 14.43	3 days	7 days 10 days	SPECT/CT – Siemens Symbia T2 (HEPH)	Remnants, Nodal, Lung
Salvatori et al. (2013) [18]	Italy	Retrospective	134 (31/103)	123/11	3700 – 7400 MBq (100 – 200 mCi)	51 ± 16	3 days	7 days	Dual head – [unspecified] (HEPH)	Remnants, Nodal, Lung, Bone
Kodani et al. (2012) [19]	Japan	Retrospective	24 (10/14)	21/3	1850 – 3700 MBq (50 – 100 mCi)	61	3 days	7-9 days	Dual head – Philips PRISM 2000XP (HEPH)	Remnant, Lung, Bone
Lee et al. (2011) [10]	South Korea	Retrospective	81 (14/67)	79/2	3700 – 7400 MBq (100 – 200 mCi)	52 ±13	3 days	10 days	Dual head – ADAC Vertex V60 (MEPH)	Remnants *Unspecified Metastases
Chong et al. (2010) [11]	South Korea	Retrospective	52 (16/36)	45/7	5550 – 9250 MBq (150 – 250 mCi)	54 ±16	3 days	7 days	Dual head - GE Millennium VG (MEPH)	Lung, Bone
Hung et al. (2009) [9]	Taiwan	Retrospective	239 (67/172)	205/34	1110 – 7400 MBq (30 – 200 mCi)	45.8 ± 15	3-4 days	10-11 days	Dual head - GE VariCAM (MEPH)	Remnants, Nodal, Lung, Bone

Legend: *PTC - papillary thyroid carcinoma; FTC - follicular thyroid carcinoma; HEPH – high-energy parallel hole collimator; MEPH – medium-energy parallel hole collimator*

TABLE 2. Study quality assessment of the included studies based on the Newcastle-Ottawa criteria

	SELECTION				COMPARABILITY of subjects in different groups on basis of design or analysis with confounding factors	OUTCOME		Total Scores
	Representativeness of cases	Sample size	Non-respondents	Exposure ascertainment / Risk factor		Ascertainment of outcome	Statistical Test	
Liu et al. (2022) [17]	*		*	*	**	**	*	8
Salvatori et al. (2013) [18]	*		*	*	**	**	*	8
Kodani et al. (2012) [19]	*		*	*	**	**	*	8
Lee et al. (2011) [10]	*		*	*	**	**	*	8
Chong et al. (2010) [11]	*		*	**	**	**	*	9
Hung et al. (2009) [9]	*		*	*	**	**	*	8

B. Quality assessment

Quality assessment of the studies using the Newcastle-Ottawa scale resulted in scores ranging from 8-9, indicating adequate and overall good quality of study methodology. (Table 2)

C. Meta-analysis of included studies

Thyroid Remnants

Five of the 6 included studies reported detected thyroid remnant lesions using post-therapy WBS at both early and delayed imaging times for a total of 639 patients with well-differentiated thyroid cancer. Among the 639 patients, early imaging detected 465 thyroid remnant lesions (73%) while 452 lesions (71%) were detected using delayed imaging. Figure 2 demonstrates that there is no evidence to support that conducting post-therapy WBS at either an early or delayed time is superior to the other in detecting thyroid remnant lesions (OR 1.11; 95% CI 0.86 – 1.42; p = 0.42). Low heterogeneity was noted in the analysis of thyroid remnant detection (I^2= 0%; Tau^2 = 0.00; p = 0.83).

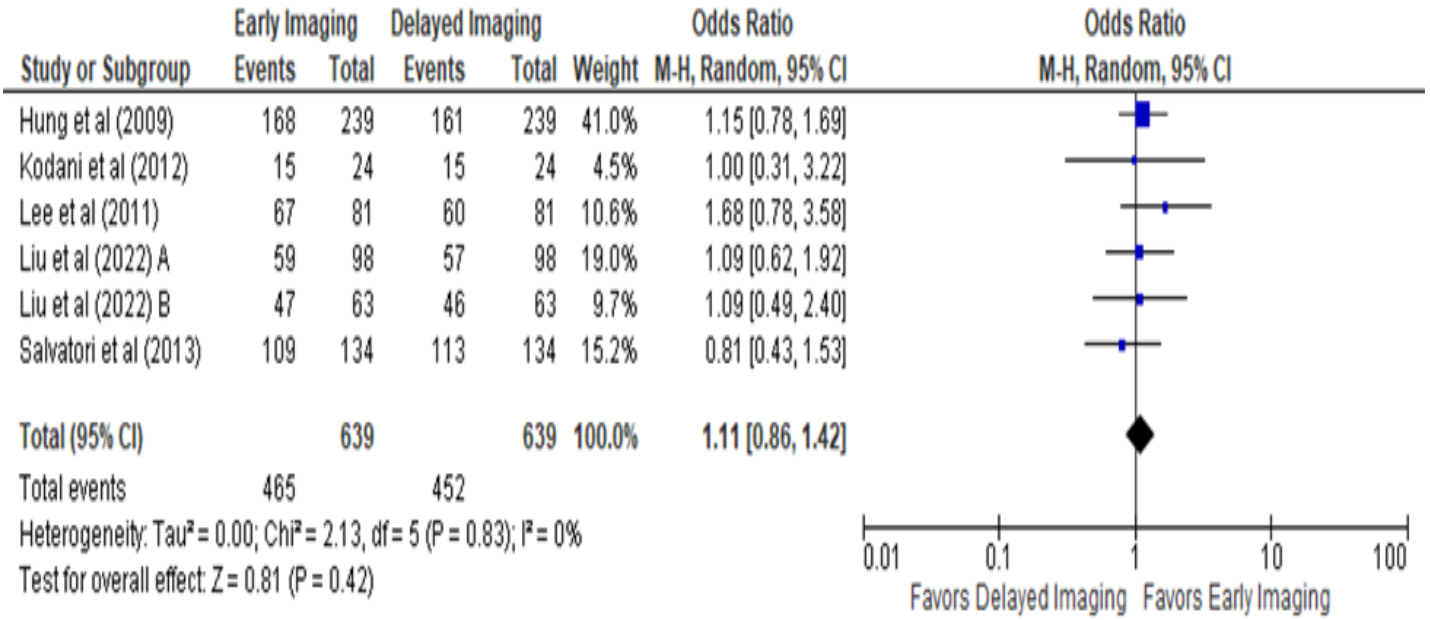

FIGURE 2. Thyroid remnants meta-analysis of early and delayed post-therapy WBS

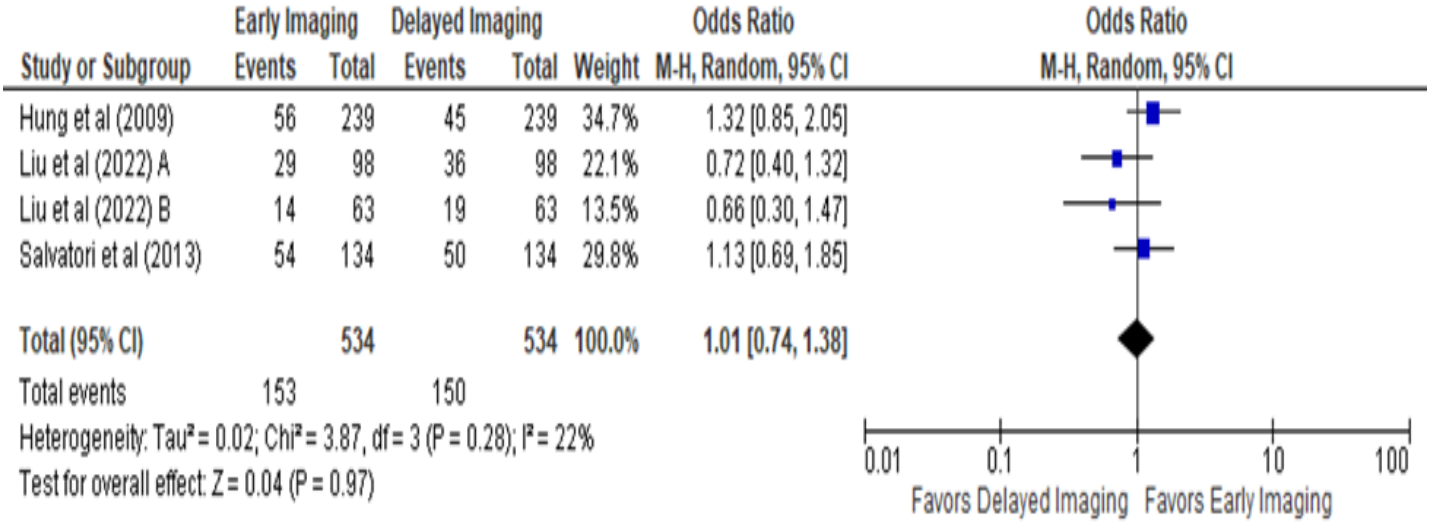

FIGURE 3. Nodal metastases meta-analysis of early and delayed post-therapy WBS

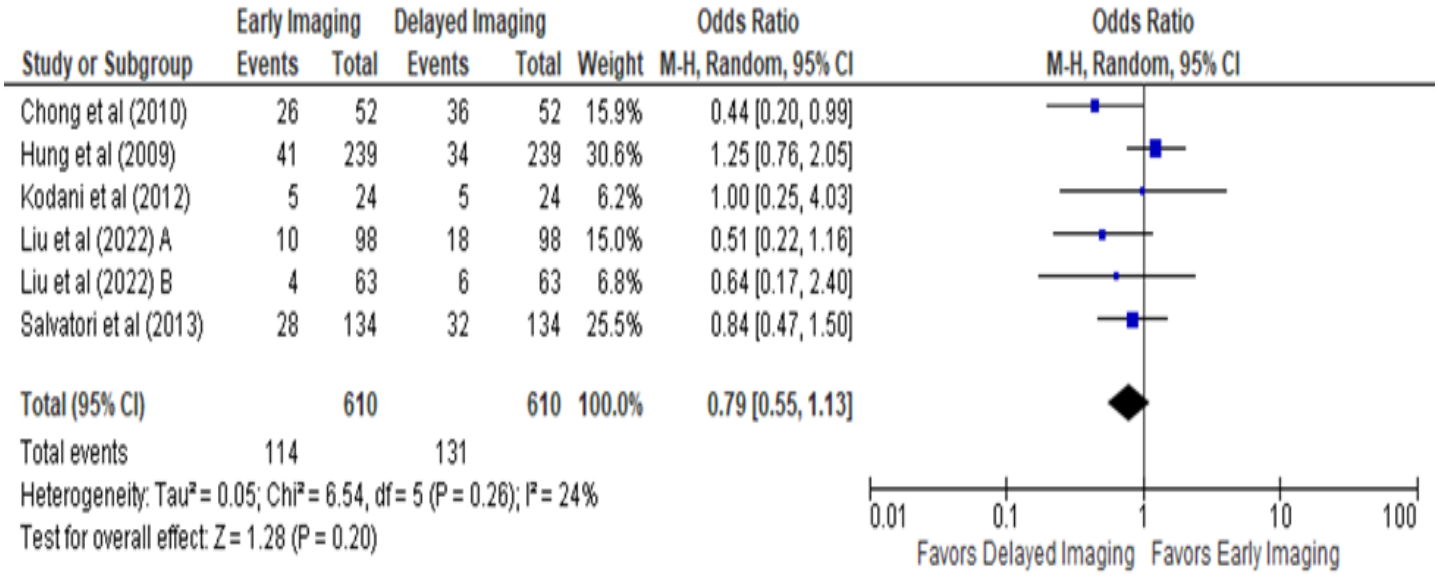

FIGURE 4. Lung metastases meta-analysis of early and delayed post-therapy WBS

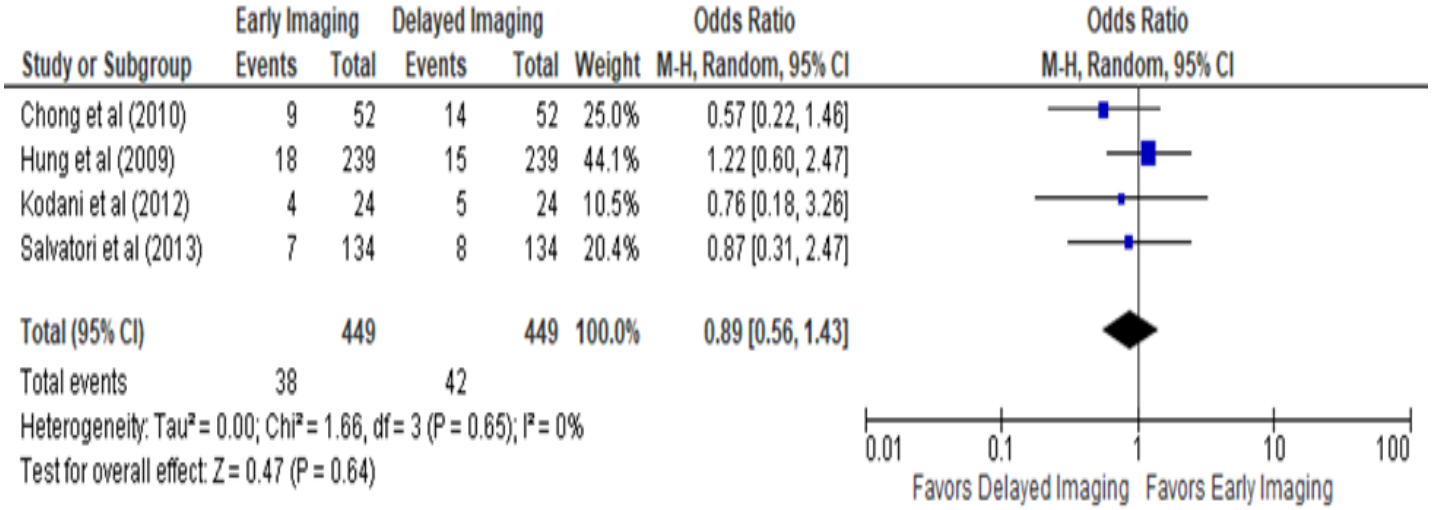

FIGURE 5. Bone metastases meta-analysis of early and delayed post-therapy WBS

Nodal Metastases

Among the six included studies, there were 3 studies that reported detected nodal metastatic lesions, particularly cervical and mediastinal lymph nodes, using post-therapy WBS at both early and delayed imaging times. Of the 534 patients with well-differentiated thyroid cancer involved in this analysis, early imaging detected 153 nodal metastases (29%) while 150 lesions (28%) were detected using delayed imaging. Figure 3 shows that there is no evidence to support that conducting WBS at either an early or delayed time after RAI therapy is superior to the other in detecting nodal metastatic lesions (OR 1.01; 95% CI 0.74–1.38; p = 0.97). Low heterogeneity was noted in the analysis of nodal metastasis detection (I^2= 22%; Tau^2 = 0.02; p = 0.28).

Lung Metastases

Lung metastatic lesions detected using post-therapy WBS at both early and delayed imaging times were reported in 5 of 6 included studies, involving a total of 610 thyroid carcinoma patients who underwent RAI therapy. Early imaging was able to detect 114 lung metastases (19%), while delayed imaging detected 131 lesions (21%). Figure 4 shows that there is no evidence to support that conducting WBS at either an early or delayed time after RAI therapy is superior to the other in detecting lung metastases (OR 0.79; 95% CI 0.55 – 1.13; p = 0.20). Low heterogeneity was noted in the analysis of lung metastasis detection (I^2= 24%; Tau^2 = 0.05; p = 0.26).

TABLE 3. Subgroup analysis of detected thyroid remnant and metastatic lesions based on collimator

	Thyroid Remnant		Nodal Metastases		Lung Metastases		Bone Metastases	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
HEPH	0.98 (0.69, 1.41)	0.93	0.89 (0.63, 1.25)	0.49	0.73 (0.48, 1.11)	0.14	0.83 (0.36, 1.94)	0.67
MEPH	1.24 (0.88, 1.75)	0.22	-	-	0.78 (0.29, 2.14)	0.63	0.89 (0.43, 1.85)	0.75

Bone Metastases

There were 4 out of the 6 included studies that reported on detected bone metastatic lesions using post-RAI therapy scans at both early and delayed imaging times. This analysis involved 449 patients with well—differentiated thyroid cancer, and among them, early imaging detected 38 bone metastatic lesions (8%) while 42 lesions (9%) were detected using delayed imaging. Figure 5 demonstrates that there is no evidence to support that conducting WBS at either an early or delayed time is superior to the other in detecting bone metastases (OR 0.89; 95% CI 0.56 – 1.43; p = 0.64). Low heterogeneity was noted in the analysis of bone metastasis detection (I^2= 0%; Tau^2 = 0.00; p = 0.65).

D. Subgroup analysis

Subgroup analysis was done based on the type of collimator used in performing the post-therapy WBS. There were 3 studies that used high-energy parallel hole (HEPH) collimators, while the other 3 studies made use of medium-energy parallel hole (MEPH) collimators. There is no evidence to support that conducting WBS at either an early or delayed time is superior to the other in detecting thyroid remnants as well as nodal, lung, and bone metastatic lesions (all p values >0.05) for both the HEPH and the MEPH groups. The results of the subgroup analysis according to collimator used are summarized in Table 3.

E. Sensitivity analysis and publication bias

None of the studies were determined to be overly influential on the results of the analyses conducted. Neither the rank correlation nor the regression tests suggested strong evidence for publication bias for all the meta-analyses done (all p values > 0.05).

DISCUSSION

The utility of post-therapy whole body scintigraphy (WBS) has been attested to by several studies with its superior sensitivity that allows the detection of more tumors and metastases than would pre-therapy diagnostic scans [20, 21]. Such information would contribute to prognostication and management of patients with thyroid carcinoma, guiding clinicians as to which patients would need further diagnostic imaging, closer monitoring, repeat radioactive iodine (RAI) therapy, and even other forms of treatment outside RAI [20, 22].

The question remains, however, whether there exists an ideal time for conducting the post-therapy WBS. As in any scintigraphic study, proper timing is crucial in obtaining quality images. Imaging early may avoid missing lesions due to washout [9], but a longer delay helps in achieving optimal target-to-background ratios, which may also improve lesion detection [21]. Because the presence of a single metastatic lesion is enough to change the staging and prognosis of a patient, as well as influence monitoring and management, the ability of I-131 whole body scintigraphy in detection of such lesions must be optimized. Therefore, this meta-analysis aims to compare early versus delayed imaging in well-differentiated thyroid carcinoma patients who received RAI therapy in terms of lesion detection rate. To the best knowledge of the researchers, this is the first attempt made in this matter.

Based on the results of the conducted analyses, there is currently no evidence to support that early or delayed post-therapy WBS was superior to the other in identifying thyroid remnants as well as metastatic lesions in the lymph nodes, lungs, and bones. Subgroup analysis according to the type of collimator used, whether

high-energy parallel hole (HEPH) or medium-energy parallel hole (MEPH), likewise revealed no statistically significant difference between lesion detection rates of early and delayed scanning across all 4 sites analyzed.

Although no evident overall difference was demonstrated in thyroid remnant and metastatic lesion detection rates of early and delayed post-therapy WBS, these results should be interpreted while factoring in certain conditions. Firstly, the influence of using single photon emission computed tomography (SPECT) was not assessed, given that it was utilized in only one of the included studies [17]. The addition of SPECT, particularly when combined with computed tomography (CT), has been shown to be beneficial in the post-RAI setting by improving lesion detection and increasing confidence in diagnostic interpretation [23, 24], compared to planar scintigraphy alone. Additionally, the effect of previous RAI therapy was likewise not explored. In a study by Oh et al. [25], there were considerable differences in the diagnostic performances of the post-therapy WBS in patients who have undergone multiple RAI therapies compared to those on their first treatment session, with the latter showing greater sensitivity and specificity than the former.

Proper patient preparation is vital to the satisfactory conduction of any diagnostic test as well as the success of any treatment procedure. For instance, following a low iodine diet prior to RAI administration has been shown to be associated with an increase in remnant uptake [26]. Not all studies included in this analysis had mention of the kind of patient preparation done as well as the uniformity of preparation across patients (i.e. whether all patients were compliant, and for how long); and this may influence whether certain lesions may be more visible on scanning or remain undetected.

In relation to other pretreatment processes that may affect tracer uptake, most of the included studies in this analysis did not mention whether patients underwent diagnostic WBS prior to RAI therapy or not. Pre-therapy WBS has been postulated to cause thyroid stunning and though much controversy still exists regarding this phenomenon, it has been associated with variable degrees of reduced iodine-131 (I-131) uptake on the post -therapy scan [27]. It is uncertain whether this may have affected detection rates on the scans involved in this analysis.

Furthermore, it should be noted that the visual interpretation of a diagnostic scan such as the post-therapy WBS may be influenced by several factors including but not limited to individual reader experience and fatigue, individual patient characteristics such as co-morbidities, technical aspects affecting image quality,

and availability of other diagnostic test results for correlation. Several non-thyroid conditions may also manifest with I-131 tracer uptake and thus, potentially cause false positive scan interpretation [28].

This study possesses several limitations. There were only a limited number of studies derived, of which a number had small sample sizes. Included only were studies written in the English language. This study also focused primarily on lesion detection rate involving thyroid remnants and nodal, lung, and bone metastases, and did not account for the intensity of uptake of such lesions. Lesion detection was based mostly on the ability of expert physician readers in interpreting the scans. Not all the studies did confirmatory work-up via pathologic biopsy or correlation with anatomic imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI). Finally, the imaging hardware and protocols used were varied across the studies included, depending on specific country guidelines, respective institutional preferences, and equipment availability.

CONCLUSION

This meta-analysis did not show a significant difference between early and delayed post-therapy whole body scintigraphy in terms of detecting thyroid remnants and nodal, lung, and bone metastases in patients with well-differentiated thyroid carcinoma. This finding supports the recommended timing range provided by current practice guidelines.

Acknowledgment

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Appendix 1: MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	3
2	Hypothesis statement	-
3	Description of study outcome(s)	3
4	Type of exposure or intervention used	3
5	Type of study designs used	3-4
6	Study population	3-4
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	Title, 4
8	Search strategy, including time period included in the synthesis and key words	4
9	Effort to include all available studies, including contact with authors	4
10	Databases and registries searched	4
11	Search software used, name and version, including special features used (eg, explosion)	4
12	Use of hand searching (eg, reference lists of obtained articles)	4
13	List of citations located and those excluded, including justification	4
14	Method of addressing articles published in languages other than English	-
15	Method of handling abstracts and unpublished studies	4
16	Description of any contact with authors	-
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	3-4
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	3-4
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater relia-	3-4
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	-
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	4-5
22	Assessment of heterogeneity	5
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	5
24	Provision of appropriate tables and graphics	6-7;
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	6-7;
26	Table giving descriptive information for each study included	7,
27	Results of sensitivity testing (eg, subgroup analysis)	10-11
28	Indication of statistical uncertainty of findings	8-11

Item No	Recommendation	Reported on Page
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	11
30	Justification for exclusion (eg, exclusion of non-English language citations)	13
31	Assessment of quality of included studies	7
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	11-12
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the	11-12
34	Guidelines for future research	-
35	Disclosure of funding source	-

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.