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ORIGINAL SCIENTIFIC REPORT

The Effectiveness of Radioactive Iodine Remnant Ablation for Papillary Thyroid Microcarcinoma: A Systematic Review and Meta-analysis

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Abstract

Background This systematic review and meta-analysis aimed to evaluate the effectiveness of radioactive iodine (RAI) remnant ablation for thyroid cancer-related outcomes of patients with papillary thyroid microcarcinoma (PTMC).

Methods A systematic literature search of PubMed, EMBASE OvidSP, and EBSCO was conducted. Studies were selected that provided multivariable analysis of the effectiveness of RAI ablation or provided specific data of a 10 years history of thyroid cancer-related outcomes in patients that presented with PTMC.

Results Nineteen studies met the inclusion criteria. A multivariable analysis of the effectiveness of RAI ablation for any recurrence or thyroid cancer-related mortality in patients with PTMC was performed in several studies, among which only one study reported a positive result. Furthermore, for PTMC patients treated by total or near-total thyroidectomy (TT/NT), with or without RAI ablative therapy, the meta-analysis suggested that RAI ablation did not decrease the 10 years history of any tumor recurrence (relative risk [RR] 0.96; 95 % confidence interval [CI] 0.63–1.48; $P = 0.87$), locoregional recurrence (RR 1.15; 95 % CI 0.75–1.76; $P = 0.51$), distant metastases (RR 0.32; 95 % CI 0.08–1.32; $P = 0.11$) or thyroid cancer-related mortality (RR 0.76; 95 % CI 0.22–2.63; $P = 0.66$).

Conclusions With regard to multivariable analyses, there was almost no positive treatment effect of RAI ablation noted for patients with PTMC. For PTMC patients already treated by TT/NT, incremental RAI ablation may not be beneficial at decreasing the 10 years recurrence of PTMC or incidence of thyroid cancer-related mortality.

Introduction

The incidence of papillary thyroid microcarcinoma (PTMC), defined by the World Health Organization (WTO) as papillary thyroid cancer (PTC) with greatest dimensions of 10 mm or less [1], has increased

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dramatically in recent years. [2]. Considerable debate has focused on the clinical significance of PTMC and whether this condition should be managed as aggressively as other thyroid malignancies [3]. The optimal therapeutic strategy, and especially the role of RAI ablation for PTMC remains controversial [4].

Radioactive iodine (RAI) ablation is often administered after total or near-total thyroidectomy (TT/NT), with the intention of ablating any residual thyroid tissue and potential microscopic residual tumor. It is also administered to facilitate long-term surveillance based on serum thyroglobulin (T_g) measurement and diagnostic ^{131}I total-body scanning radioiodine [5]. According to several guidelines [6, 7], it is recommended that RAI ablation is modulated on the basis of risk factors irrespective of the tumor size. There is little controversy over the value of RAI for higher risk thyroid cancer [8]. In addition, a systematic review and meta-analysis of the data have demonstrated that RAI ablation might benefit clinical management by decreasing the recurrence of well-differentiated thyroid cancer [9]. However, in a systematic review of a majority of patients presenting with very low-risk, low-risk, and other select cases of patients with moderate risk thyroid cancer; RAI therapy did not demonstrate any survival or disease-free survival benefit [10].

In regard to PTMC, some studies indicate that this condition has after all, the characteristics of a malignant tumor, and is often multifocal and prone to central lymph node metastasis, and thus requires aggressive surgery, and even post-operative RAI ablation [3, 11]. Moreover, some studies indicate that PTMC is mostly an inert carcinoma or has little or no impact on long-term outcome, wherein aggressive surgical treatment, RAI ablation or even any other treatment option is not recommended [12–14]. The many single-center studies described above could not accurately assess the impact of RAI treatment on the final outcome due to the small number of patients and event rates. Nevertheless, up to now, there is currently no special systematic review or meta-analysis of the effectiveness of RAI therapy for PTMC.

Thus, we aimed to carry out a systematic review and meta-analysis of the literature to determine whether RAI ablation decreases either the risk of recurrence or thyroid cancer-related mortality for patients that presented with PTMC, and that did not receive TT/NT surgery.

Materials and methods

The guidelines presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were used in this study [15, 16].

Search strategy

Two trained investigators (i.e., G.H. and W.Z.) independently conducted a search of the following databases: PubMed, EMBASE, OvidSP, and EBSCO for English-language studies that were published between January 1966 and June 2015. The search was conducted using Medical Subject Headings (MeSH) or keywords, and when appropriate as search terms. Search terms were Boolean search criteria and included "papillary thyroid microcarcinoma", "papillary microcarcinoma", "thyroid microcarcinoma" OR "PTMC" and "RAI remnant ablation", "RAI", "iodine radioisotopes" OR "iodine radioisotopes". The reference lists of the articles that we retrieved and previous reviews were manually searched to identify and aggregate suitable studies. The last search was performed on June 4, 2015. Detailed search methods are included in Supplementary Table 1.

Eligibility criteria

Two trained reviewers (i.e., G.H. and W.Z.) independently screened all of the retrieved abstracts and titles to determine articles that were "potentially" and deemed "relevant" references. The same two reviewers then independently reviewed the full articles, using the following inclusion criteria: (1) studies that provided multivariable analysis for the benefit of RAI ablation for any recurrence or thyroid cancer-related mortality in patients with PTMC; (2) studies that provided specific data of the 10 years outcome of recurrence or thyroid cancer-related death in patients that presented with PTMC treated by TT/NT, with or without RAI ablation therapy. Studies were excluded if (1) they were single case reports, regular review or systematic review articles; (2) a median or mean follow-up period less than 5 years; (3) a cohort size smaller than 50 patients; (4) studies that lacked a control or non-exposed group; (5) studies that included PTMC that were associated with medullary, or only high-risk or very low-risk PTMC. Disagreements were resolved by consensus discussion. When studies of overlapping groups of patients were identified, only the most recent studies were retained, with the notable exception of earlier studies presenting analyses that were not repeated in the most recent study.

Quality assessment

Two reviewers (i.e., G.H. and L.S.) independently conducted the quality assessment of studies with the Newcastle-Ottawa Scale (NOS) [17, 18]. The NOS was developed to assess the quality of case–control and cohort studies, containing three parameters of quality that included: (1) selection; (2) comparability; and (3) exposure/outcome assessment. Studies that achieved five or more points were considered to be of high quality. Any

discrepancies between reviewers were addressed by a joint reevaluation of the original article. In addition, the publication bias was assessed using the funnel plot [19, 20].

Data abstraction

Two trained investigators (i.e., W.Y. and H.W.) independently abstracted the data from the finally included articles. First author's name, publication year of the article, demographics, pathological characteristics of PTMC, surgical procedure and RAI ablation were extracted from each study. Any multivariable analysis for effectiveness of RAI therapy for tumor recurrence or thyroid cancer-related mortality was tabulated, respectively. Whenever possible, the numbers of patients with any recurrence, locoregional recurrence, distant metastases, and death from thyroid cancer at 10 years following TT/NT treatment with or without RAI ablation were extracted. If the numbers of events were missing, data were extrapolated from graphs, tabulated proportions of events or by subgroup analyses. Any disagreements were discussed to reach a consensus agreement. Studies that provide multivariable analyses or meta-analysis for effectiveness of RAI ablation for 10 years thyroid cancer-related outcomes are included in Supplementary Table 2.

Data analysis

Data from multivariable analyses that were adjusted for prognostic factors were tabulated as presented in the primary studies. An alpha value of $P < 0.05$ was defined statistically significant for multivariate analyses. Meta-analyses were performed for the 10 years outcomes of any recurrence, locoregional recurrence, distant metastases and thyroid cancer-specific mortality, respectively. The X^2 test and I^2 statistic were performed to assess the statistical heterogeneity of the RAI effect for each treatment outcome. Values of $P > 0.10$ and $I^2 < 50$ % suggested that the observed heterogeneity might be accepted, and thus meta-analysis was performed. The relative risk (RR), with a 95 % confidence interval (CI), was used to estimate the RAI effect for 10 years thyroid cancer-related outcomes. All of the statistical analyses were conducted using the RevMan version 5.2 statistical software package (Cochrane Collaboration, RevMan software, Oxford, UK).

Results

Results of the search

The search strategy above yielded no randomized controlled trials. We obtained 1101 abstracts and titles through electronic searches, and of these, one full-text article was identified and retrieved through manual hand searches. After reviewing the titles, abstracts, and full text, 19 studies met the inclusion/exclusion criteria for this review [21–39] (Fig. 1).

Patient demographic characteristics, tumor pathological findings and details of TT/NT surgery with or without RAI ablation of patients in the included studies are shown in Table 1. The dose of RAI that was administered was unavailable in seven studies [25, 27, 28, 31, 33–35] and ranged from 30 to 150 mCi in the remaining included studies. The use of thyroid hormone suppressive therapy was clearly reported in the majority of studies, with the exception of seven other studies [22, 26, 27, 31, 32, 34, 35]. The mean or median follow-up period in the 19 selected studies ranged from 5.1 to 17.2 years.

Assessment of methodologic quality

The results of quality assessment according to the NOS are included in Supplementary Table 3. In total, the detailed search strategies yielded 19 cohort studies, and 100 percent of the studies were assessed as high quality: nine studies had a NOS score of seven, eight studies had a NOS score of eight, and two studies had a NOS score of nine.

Furthermore, funnel plots for 10 years any tumor recurrence, and locoregional recurrence included in the meta-analysis suggested little publication bias, respectively. Funnel plots for 10 years distant metastases and thyroid cancer-related mortality did not suggest any publication bias (Supplementary Fig. 1).

Summary of multivariable analysis for effectiveness of radioiodine for thyroid cancer-related outcomes

Multivariable analysis of any thyroid cancer-related recurrence is shown in Table 2. In addition, eight of the studies included in the review were subjected to a multivariable analysis of the effectiveness of RAI ablation for any tumor recurrence [21–24, 26, 31, 33, 39]. Post-operative RAI ablation decreased the adjusted risk of any thyroid cancer-related recurrence to just one small study (i.e., 130 patients; $P = 0.005$) [22]. This positive study had any thyroid cancer-related recurrence rates of 10.8 % with a median follow-up period over 10 years. A positive treatment effect of RAI ablation was not noted in the other six remaining largest studies [21, 23, 26, 31, 33, 39] as well as in one other small study [24]. In addition, another study reported a statistically significant benefit of RAI ablation in decreasing locoregional recurrence ($P = 0.01$, RR = 0.2, 95 % CI 0.07–0.7) [37].

Multivariable analysis of thyroid cancer-related mortality is shown in Table 3. Four of the included studies in

the review performed a multivariable analysis of the benefits of RAI ablation in terms of the outcomes of cause-specific mortality [22, 31, 33, 37]. These four studies examined 130–892 patients, with a median follow-up period that ranged from 8.4 to 17.2 years, with an overall thyroid cancer-related mortality rate that ranged from 0.2 to 3.1 %. None of these studies reported a mortality advantage for the ablated patients, after adjusting for prognostic factors and cointerventions.

Summary of the meta-analysis for effectiveness of radioiodine for 10 years thyroid cancer-related outcomes

Meta-analysis of a 10 years any tumor recurrence is shown in Fig. 2. The numbers of patients with a 10 years any recurrence after TT/NT and treated with or without RAI ablation could be extracted from ten of the studies that were included in the review. Upon pooling the 10 years data for any tumor recurrence of 2295 patients, there was no evidence of any marked statistical heterogeneity ($P = 0.10$, $I^2 = 39$ %), thus the results were pooled. The pooled estimate suggested that there was no significant benefit of RAI ablation on any tumor recurrence ($P = 0.87$). The pooled 10 years any recurrence rates in the selected studies were determined as follows: 49 of 1536 (3.19 %) in the TT/NT- and RIA-treated patients, and 36 of 759 (4.74 %) in the TT/NT-treated patients (relative risk [RR] = 0.96, 95 % confidence interval [CI] 0.63–1.48).

Meta-analysis of the 10 years locoregional recurrence is shown in Fig. 3, and the 10 years distant metastases are shown in Fig. 4. Further pooled analyses were performed by examining the effect of radioiodine on the 10 years locoregional recurrence or distant metastases in 11 different studies that were included in the review. Statistical heterogeneities were not significant by either test ($P = 0.15$, $I^2 = 31$ %, $P = 0.63$, $I^2 = 0$ %, respectively). For the outcome of locoregional recurrence in 2509 patients, the event rate in the TT/NT- and RIA-treated patients was 66 of 1703 (3.87 %) and in TT/NT-treated patients it was 35 of 806 (4.34 %), such that the pooled RR for locoregional recurrence was 1.15 (95 % CI 0.75–1.76) in ablated patients (Fig. 3). For the outcome of distant metastases in 2711 patients, the rate of distant metastases was 5 of 1925 (0.25 %) in TT/NT- and RIA-treated patients as compared with 4 of 786 (0.50 %) in TT/NT-treated patients. Moreover, there was no significant benefit of radioiodine ablation on distant metastases between either group (RR = 0.32; 95 % CI 0.08–1.32; $P = 0.11$; Fig. 4).

Meta-analysis of the 10 years thyroid cancer-related mortality is shown in Fig. 5. The numbers of patients with a 10 years thyroid cancer-related mortality after TT/NT with or without RAI remnant ablation could be extracted in

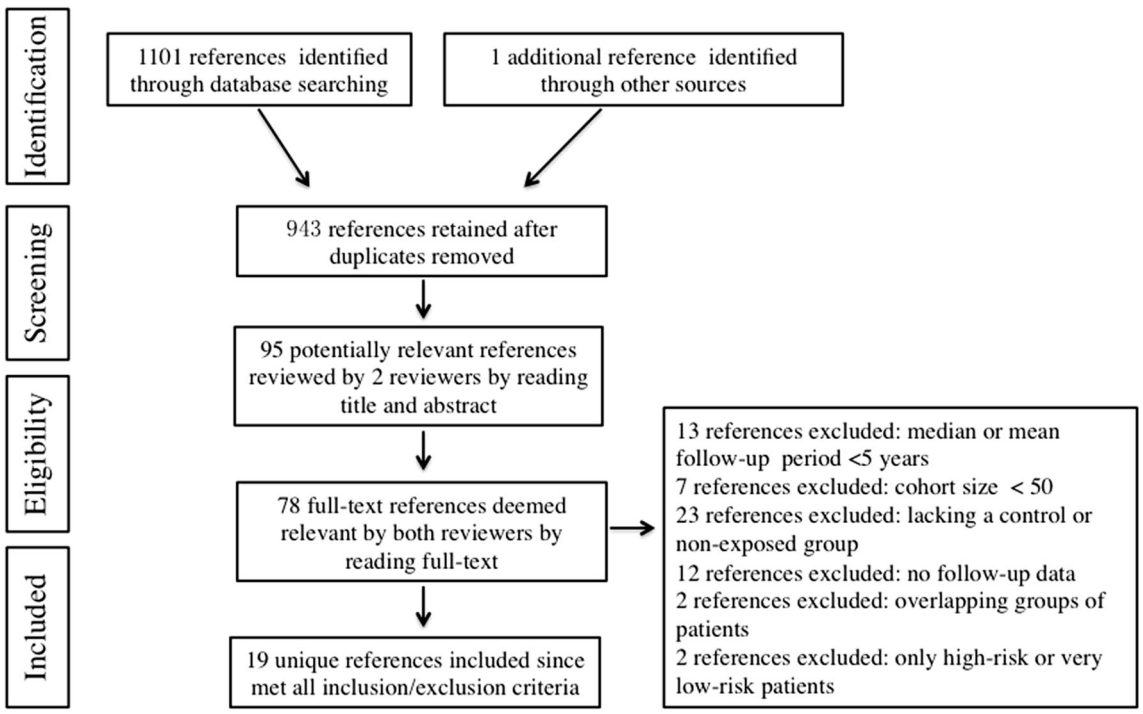

Fig. 1 PRISMA flow diagram detailing the strategy adopted for the literature search described in this article

Table 1 Cohort characteristics of included studies

Study	Year	Country	*N*	Mean age	Male/female	Mean tumor size (mm)	Histology	MF (%)	ETE (%)	LNM (%)	Incidental (%)	Treat with TT/NT	Treat with RAI	RAI dose (mCi)	Median F/U year
Pedrazzini [21]	2013	Italy	231	45.7	54/177	NA	NA	30.7	15	31.6	61.1	177	136	100	12 (5–35)
Mihailovic [22]	2013	Serbia	130	44	22/108	NA	P, F	NA	NA	NA	NA	121	63	100 for N0 150 for N1	10 (0.7–25)
Kim [23]	2013	Korea	704	47	73/631	6.0	P	32	46	24	NA	704	128	<100 or >100	5.3 (0.1–15.4)
Riss [24]	2012	France	160	47.8	27/133	6.8	NA	37	5	28	61.8	160	129	100	NA (> 5)
Gershinsky [25]	2012	Israel	293	50.7	41/252	6.3	NA	45.4	9.6	18.4	NA	214	167	NA	7.2 (0.4–14)
Neuhold [26]	2011	Austria	759	53	173/586	3.8	P, H	31.2	NA	NA	99.3	312	173	30	7.3 (1–53)
Moon [27]	2011	Korea	288	46.6	26/262	6.9	NA	20.5	30.9	33.7	NA	181	114	NA	6 (5–7.4)
Mercante [28]	2009	Italy	445	48.2	98/347	7.0	P, F, H	35	30	25.6	50	404	389	NA	5.3 (1–26)
Pisanu [29]	2009	Italy	149	NA	23/126	NA	P, F, S	40	4.7	11	49	131	125	100	5.4
Kim [30]	2008	Korea	307	46	32/275	8.0	P, F	31.9	37.8	45.3	93.4	173	163	75 –150	5.4 (0.42–15.6)
Hay [31]	2008	America	892	46	373/627	7.0	P	23	2	30	13	765	155	NA	17.2 (0.1–54)
Gülben [32]	2008	Turkey	81	37	15/66	6.0	P, F	11.1	NA	15	12.3	81	30	100–150	6.9 (2.3–16)
Pellizzo [33]	2006	Italy	403	NA	66/337	NA	P, F, H	14.9	4	11.7	10.9	359	260	NA	8.5
Cheema [34]	2006	America	74	42	17/57	5.7	NA	24	NA	16	NA	48	45	NA	NA (> 5, 0.5–11.2)
Lo [35]	2006	China	185	45	37/148	6.2	NA	23.8	11.4	21	40.5	129	53	NA	8.2 (0.1–38)
Roti [36]	2006	Italy	243	52	46/197	6.0	P, F, H, S	32	17	13	21.4	243	235	50–100	5.1 (2.4–10.6)
Chow [37]	2003	China	203	46.8	27/176	7.0	NA	31	20.7	24.6	NA	187	137	80–150	8.4
Appetecchia [38]	2002	Italy	120	45.2	24/96	NA	NA	20	15	22	66.6	106	62	75–150	8 (5–15)
Baudin [39]	1998	France	281	NA	74/207	5.9	P, F	40	15	43	67.3	195	124	100	7.3

P Papillary, *F* follicular, *H* Hurthle cell, *S* sclerotic, *NA* not available, *MF* multifocality, *ETE* extrathyroidal extension, *LNM* lymph node metastasis, *TT* total thyroidectomy, *NT* near-total thyroidectomy, *RIA* radioiodine ablation, *F/U* follow-up

Table 2 Summary of multivariable analysis for effectiveness of RAI ablation for any tumor recurrence

Study	*N*	Median follow-up (years)	Event rate (%)	Independent variables in the model	Effectiveness of radioiodine ablation for any tumor recurrence[a]
Pedrazzini [21]	231	12	6.5	Age, surgical extent, tumor characteristics, local or distant metastasis at presentation	NS
Mihailovic [22]	130	10	10.8	Age, gender, tumor characteristics, regional metastases at presentation, initial treatment	RR < 1, $P = 0.005$
Kim, HJ [23]	704	5.3	0.85	Age, gender, tumor characteristics, extrathyroidal invasion, cervical lymph node metastasis	NS, $P = 0.17$
Riss [24]	160	NA	6.3	Age, gender, tumor characteristics, extrathyroidal invasion, lymph node metastasis	NS
Neuhold [26]	759	7.3	0.52	Patient characteristics, therapeutic procedures, pathologic characteristics	NS
Hay [31]	892	17.2	8	NA	NS (LR, $P = 0.34$; DM, $P = 0.84$)
Pellizzo [33]	403	8.5	1.5	Age, gender, tumor characteristics, co-existence of thyroid diseases, extent of surgery	NS
Baudin [39]	273	7.3	4	Age, gender, surgical extent, tumor characteristics, mode of diagnosis, type of surgery	NS

LR locoregional recurrence, *DM* distant metastasis, *ERT* external radiotherapy, *NA* not available, *NS* not significant

[a] Excluded patients with distant metastases at presentation from analysis

Table 3 Summary of multivariable analysis for effectiveness of RAI ablation for thyroid cancer-related mortality

Study	*N*	Median follow-up (years)	Event rate (%)	Independent variables in the model	Effectiveness of radioiodine ablation for thyroid cancer-related mortality[a]
Mihailovic [22]	130	10	3.1	Age, gender, tumor characteristics, metastases at presentation, initial treatment, risk categories, recurrence	NS, $P = 0.5$
Hay [31]	892	17.2	0.3	Age, gender	NS $P = 0.96$
Pellizzo [33]	403	8.5	0.2	Age, gender, tumor characteristics, co-existence of thyroid diseases, extent of surgery	NS
Chow [37]	203	8.4	1	Age, gender, tumor characteristics, type of surgery, cervical lymph nodes metastases at presentation, ERT	NS

ERT external radiotherapy, *NS* not significant

[a] Excluded patients with distant metastases at presentation from analysis

17 of the included studies. The 10 years thyroid cancer-related mortality for PTMC was calculated as 0–3.77 % [35] for TT/NT- plus RIA-treated patients, and from 0 to 5.17 % [22] in TT/NT-treated patients. Significant statistical heterogeneity of the treatment effect was not observed ($P = 0.57$, and $I^2 = 0$ %), and thus pooling was performed. The pooled 10 years thyroid cancer-related mortalities in the studies were 4 of 2516 (0.16 %) in the TT/NT- plus RIA-treated patients and 5 of 1502 (0.47 %) in the TT/NT alone treated patients (RR = 0.76, 95 % CI 0.22–2.63; $P = 0.66$).

Discussion

Our systematic review of the literature revealed that any tumor recurrence was adjusted to a variable degree for prognostic factors or cointerventions in eight cohort studies, among which only one study appeared to have a positive result. Four cohort studies examined the thyroid cancer-related mortality; however, none of them appeared to have a positive result. Demographics and tumor pathological characteristics were adjusted in the majority of the multivariable models. Furthermore, for patients already

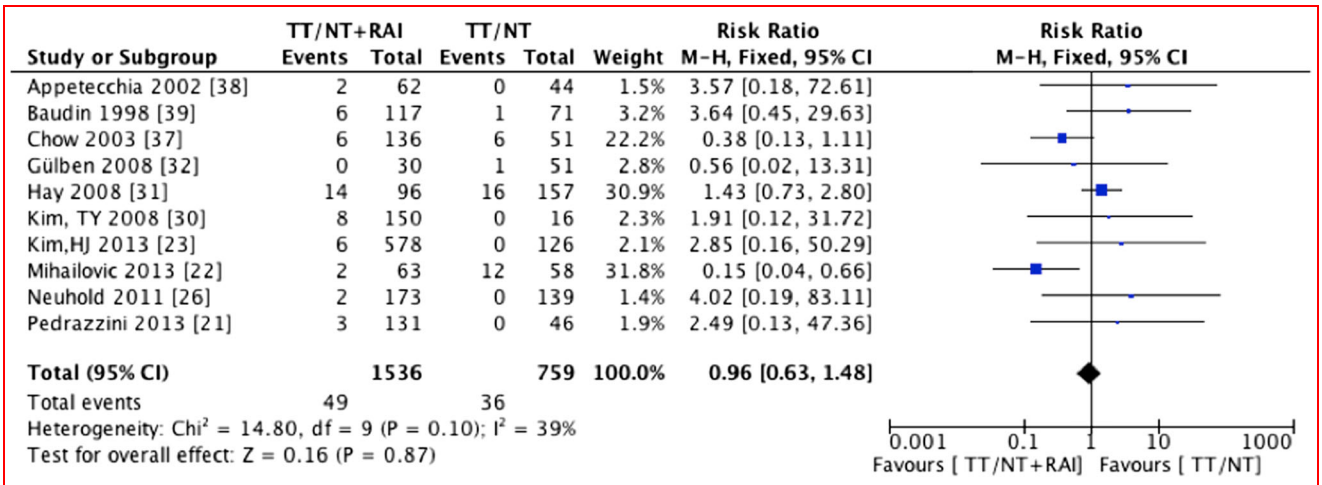

Fig. 2 A Forest plot that details the 10 years history of any tumor recurrence. *TT* total thyroidectomy, *NT* near-total thyroidectomy, *RAI* radioiodine ablation. *Note*: In Hay 2008 [31], the data were extrapolated from the survival curve for node-positive PTMC

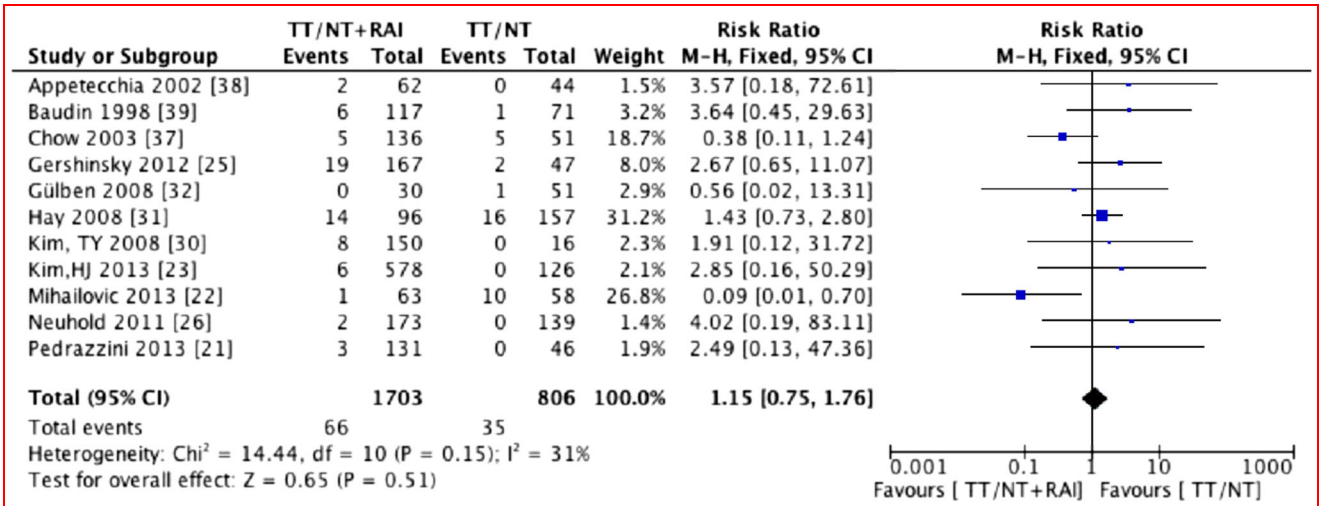

Fig. 3 A Forest plot that details the 10 years history of locoregional recurrence of a tumor. *TT* total thyroidectomy, *NT* near-total thyroidectomy, *RAI* radioiodine ablation. *Note*: In Hay 2008 [31], the data were extrapolated from survival curve for node-positive PTMC

treated by TT/NT, the pooled analysis suggested that any tumor recurrence, locoregional recurrence, distant metastases, and thyroid cancer-related mortality at 10 years did not decrease with incremental RAI ablation.

It is a remarkable fact that the prevalence of regional nodal metastases in PTMC is known to be high [40, 41]. All studies, with the exception of one article [26] in our review, described a central neck node dissection being performed, which was combined with a lateral cervical node dissection in patients with intraoperative suspect lymph node. In addition, the rates of lymph node metastases ranged from 11 to 43 % in all studies, respectively. Since it was not possible to extract the prognostic data of the PTMC patients with lymphatic metastases, the meta-analysis of this subgroup of patients could not be conducted.

However, our meta-analysis suggested inferentially that in TT/NT therapy with lymph nodes resected, the vast majority of these lymphatic metastases did not progress to clinical recurrence without RAI treatment.

Our systematic review and meta-analysis were subject to some methodologic limitations too. The systematic review yielded totally retrospective cohort studies. Patients were often not stratified into low-risk, intermediate-risk, and high-risk groups in the statistical analysis, and patient demographics and tumor characteristics were inconsistent

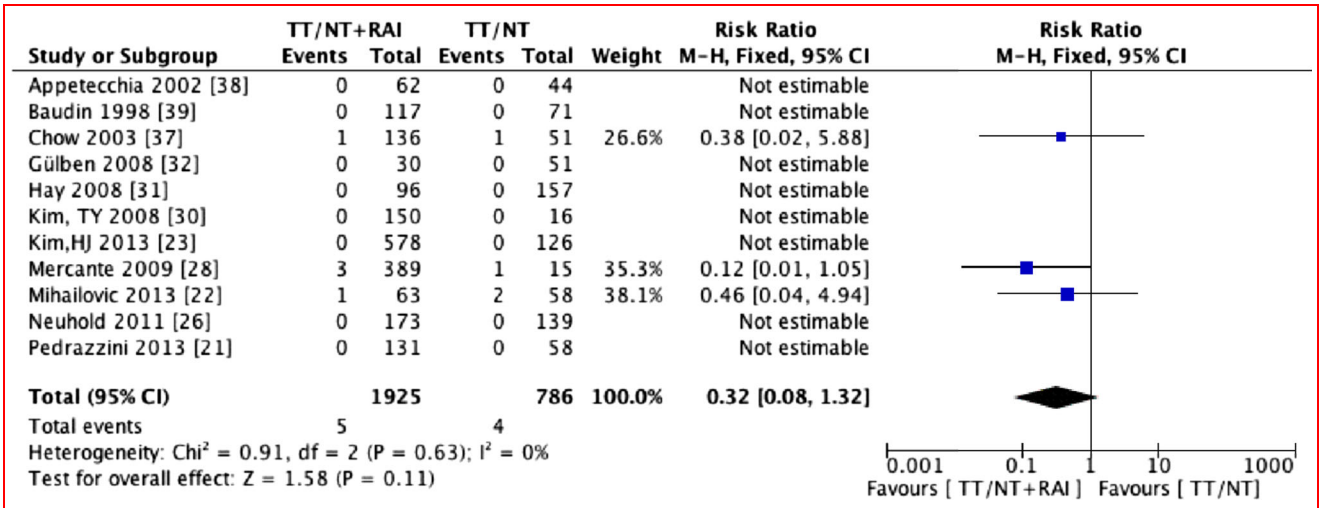

Fig. 4 A Forest plot that details the 10 years history of distant metastases. *TT* total thyroidectomy, *NT* near-total thyroidectomy, *RAI* radioiodine ablation. *Note*: In Hay 2008 [31], the data were extrapolated from survival curve for node-positive PTMC

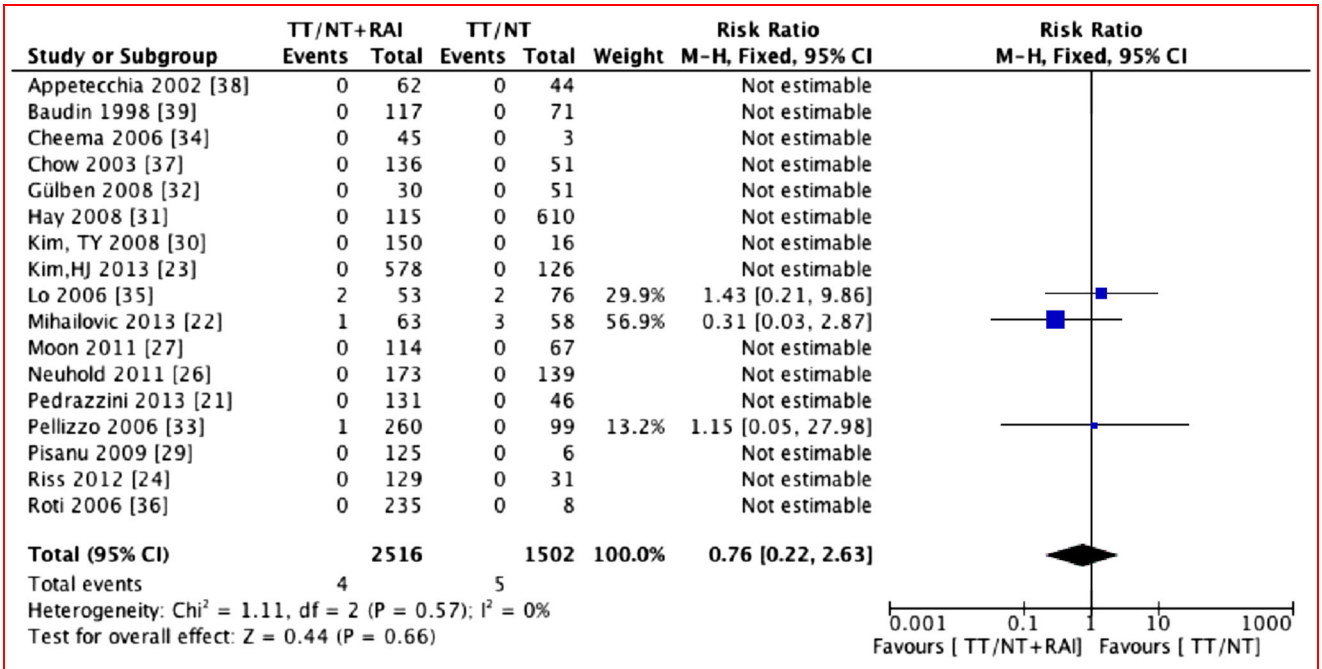

Fig. 5 A Forest plot details the 10 years history of thyroid cancer-related mortality. *TT* total thyroidectomy, *NT* near-total thyroidectomy, *RAI* radioiodine ablation

from study to the next. Furthermore, the multivariate analyses were limited by the inconsistency of independent variables in the model among studies, the lack of adjustment for the cointervention of thyroid hormone suppressive therapy, and particularly, under-powering of studies due to the small sample sizes or event rates. Moreover, with regard to the meta-analysis, about half of the studies lacked a complete 10 years dataset due to the follow-up period being of insufficient time or because subjects were lost to follow-up during the 10 years period after their initial treatment. Although the 20 years data could be abstracted in five studies [21, 22, 26, 28, 31], significant statistical heterogeneity was present when pooling was performed. Our meta-analysis was also limited by the fact that some patient data had to be extrapolated from graphs, tabulated proportions of events, subgroup analyses or it had to be

calculated from information derived directly from selected articles, possibly resulting in some human error.

In sum, our systematic review and meta-analysis supports the finding of several previous studies [23, 31, 39] that RAI ablation does not result in superior outcomes for PTMC.

Recurrences were localized mostly to the locoregional sites, and rarely to distant sites, and thus the post-operative follow-up period by clinical examination, ultrasound of the neck, assessment of serum T_g levels and T_g antibodies, and TSH suppressive therapy without RAI ablation, might already represent an adequate management strategy for PTMC patients treated by TT/NT.

Given the methodologic limitations of the meta-analysis of retrospective data, a long-term, prospective, randomized controlled trial with a larger sample size of selected patients may definitively resolve this issue. In addition, in this unprecedented gene-molecular era, the novel gene-molecular-based management strategies might also be used to select RAI-required patients with PTMC in the near future [42, 43].

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Compliance with ethical standards

Conflicts of interest Authors declare that there are no conflicts, either perceived or real, with respect to this article.

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