REVIEW ARTICLE

Royal Australasian College of Surgeons

Effectiveness of prophylactic central compartment neck dissection following hemithyroidectomy in papillary thyroid cancer: a meta-analysis

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Key words
disease-free survival, hemithyroidectomy, locoregional recurrence, neck dissection, papillary thyroid carcinoma.

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Accepted for publication 6 August 2024.

doi: 10.1111/ans.19210

Abstract

Introduction: In this study, we aimed to assess the effect of prophylactic central compartment neck dissection (pCCND) in conjunction with hemithyroidectomy (HT) for clinically low-risk node-negative (cN0) papillary thyroid carcinoma (PTC).
Methods: A thorough literature search was performed utilizing PubMed and EMBASE for articles published until October 2023. Subsequently, a meta-analysis was performed on studies involving patients with cN0 PTC, with postoperative locoregional recurrence (LRR) and survival data, treated with HT + pCCND or HT. The study was registered with PROSPERO (CRD42024560962).
Results: We included seven studies in this meta-analysis, including 2132 patients who met the inclusion criteria: six retrospective cohort studies and one randomized controlled trial. The HT + pCCND group consisted of 1090 cases, and the HT group had 1042 cases. The LRR rates after HT with or without pCCND were similar (3.58% vs. 4.51%; odds ratio (OR) = 0.65; 95% confidence interval (CI) = 0.41–1.03). Five of the seven studies provided prognostic and survival data, particularly the log hazard ratio (log HR) of disease-free survival (DFS) between the two groups. There was also no significant difference in terms of DFS between the HT + pCCND and HT groups (OR = 0.67; 95% CI = 0.42–1.07).
Conclusions: There was no significant difference in LRR and DFS between the HT + pCCND and HT groups. pCCND did not demonstrate significant efficacy in improving oncological outcomes for low-risk patients with cN0 PTC. Therefore, for patients with low-risk cN0 PTC, thyroid surgeons should make reasonable and individualized decisions regarding the extent of surgical removal.

Introduction

Papillary thyroid carcinoma (PTC) is a well-differentiated, slow-growing malignancy that accounts for most thyroid malignancies. The prognosis is favourable with surgical therapy, and the 10-year survival rate has consistently exceeded 90% in recent decades.[1] However, the rate of occult lymph node metastasis in PTC is high, ranging from 26.6% to 61.2%, depending on the tumour size, especially in the central compartment of the neck.[2–4] Many studies have shown that this increases the risk of local tumour recurrence.[5,6] However, ultrasound as the primary examination for PTC does not have satisfactory sensitivity (36.7–61%) to distinguish occult central lymph node metastasis (CLNM).[7] Since the American Thyroid Association (ATA) guidelines were revised in 2015, surgery has been the first choice of treatment for PTC and CLNM. The guidelines state that thyroid lobectomy or hemithyroidectomy (HT) may be sufficient for clinically low-risk node-negative (cN0) DTC with no extrathyroidal extension (ETE) in 1–4 cm DTCs.[8] However, the significance of prophylactic central compartment neck dissection (pCCND) in patients with low-risk cN0 PTC, who are assumed to have a lower cancer-specific mortality, remains controversial. Several studies have reported that, for cN0 PTC, pCCND does not improve oncological outcomes in patients randomized to receive total thyroidectomy (TT) with or without pCCND.[9,10]

Conversely, some studies have suggested that, given the high incidence of central compartment lymph node metastasis in PTC and the challenges in protecting the recurrent laryngeal nerve (RLN) and parathyroid function during secondary operations, pCCND is a significant primary surgical strategy.[11,12]

To the best of our knowledge, only one existing meta-analysis has compared the recurrence outcome of HT + pCCND with that of HT for cN0 PTC.[13] This meta-analysis was published 3 years ago and included only two comparative studies. Therefore, in this study, we aimed to evaluate the effectiveness of HT + pCCND and HT for low-risk cN0 PTC using current literature, including a comparison of DFS between the two operative strategies.

Materials and methods

Search strategy

This meta-analysis was conducted according to the PRISMA 2020 statement.[14] This review of previously published studies did not require approval from the institutional review board or informed consent. The full study protocol was registered at PROSPERO (CRD42024560962).

Two authors (P.Z. and L.L.) independently completed the literature selection process flowchart (Fig. 1). We searched PubMed and EMBASE for literature published in English until October 2023. The following keywords constituted the search strategy across all fields: papillary thyroid carcinoma AND (hemithyroidectomy OR lobectomy) AND lymph node.

Selection of articles

Articles were screened based on the following criteria: (i) studies including patients with low-risk cN0 PTC; (ii) the scope of thyroidectomy was defined, with data reported separately; (iii) patients in the experimental group received HT+ pCCND, while the control group received HT alone; (iv) the article provided complete information about survival, such as locoregional recurrence (LRR) rate, DFS, and the number of participants; and (v) retrospective and prospective cohort studies or randomized controlled trials (RCTs), and the mean or median follow-up period was over 5 years. Studies were excluded as follows: (i) the full text could not be accessed online, and clinical data extraction was not possible; (ii) reviews, case reports, letters to the editor, and conference abstracts; and (iii) studies not published in English.

Data extraction

The primary data extracted from each article included the year, country, type or design, follow-up, number of cases, and recurrence. Data were extracted independently by two reviewers (P.Z. and L.L.). Locoregional recurrence (LRR) was defined as a recurrence occurring in the thyroid bed, contralateral thyroid, or central and/or lateral compartments. The Kaplan–Meier curves from each study were digitized using the Engauge Digitizer (v11.3), and survival data along with follow-up times were extracted to reconstruct and estimate the logHR of DFS.

Data analysis

The rate of LRR was calculated for all patients in both groups, and odds ratios (OR) with 95% confidence intervals (CIs) were computed using both fixed-effects and random-effects models by the mean command in STATA (version 17.0; StataCorp, USA). Statistical heterogeneity among studies was evaluated using I^2 statistics. A threshold of $I^2 > 50\%$ indicated high heterogeneity, prompting the use of the random-effects model, whereas $I^2 < 50\%$ guided the choice of the fixed-effects model.

Publication bias and quality assessment

Publication bias was assessed using funnel plots generated by Review Manager 5.3 and Begg's tests in STATA version 17.0. Publication bias was not evident with a symmetrical graph but was suggested to be asymmetrical. The statistical significance cutoff was set at $P < 0.05$. The quality of articles was assessed using two evaluation systems. Retrospective studies were evaluated using the Newcastle–Ottawa scale,[15] in which scores ranging from zero to nine stars were used to assess each study. A study that received more than six stars was considered a high-quality study. RCT was assessed using Cochrane's Risk of Bias 2.0 tool,[16] consisting of five dimensions: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. All quality assessments were performed by two independent reviewers (P.Z. and L.L.).

Results

Literature search results

The study identification process flowchart illustrates the inclusion of seven studies comprising 2132 patients (Fig. 1). These studies met the predefined inclusion criteria and were included in the meta-analysis, focusing on LRR and DFS. We started with an initial search of 1050 potentially eligible studies and reduced the number to 874 after removing duplicate studies. After reviewing the titles and abstracts, 46 articles were eligible for full-text evaluation. Finally, this study included six retrospective cohort studies (CS)[17–22] and one RCT,[23] all of which provided comparative data between HT + pCCND and HT.

Study characteristics

Table 1 depicts the features of the seven studies published between 2012[22] and 2022.[17] The sample sizes ranged from 58[18] to 1071,[19] and the median duration of follow-up varied from 47 months[22] to 79 months.[19] Among these studies, five were conducted in Korea, with one each in China and Italy. Further analysis of DFS was possible in five studies,[19–23] and the logHR could be acquired from the studies directly or indirectly. As per the Newcastle–Ottawa Scale, the quality scores of the included retrospective cohort studies ranged from 7 to 8 (Table 1), and the quality assessment of the RCT is shown in Figure 2.

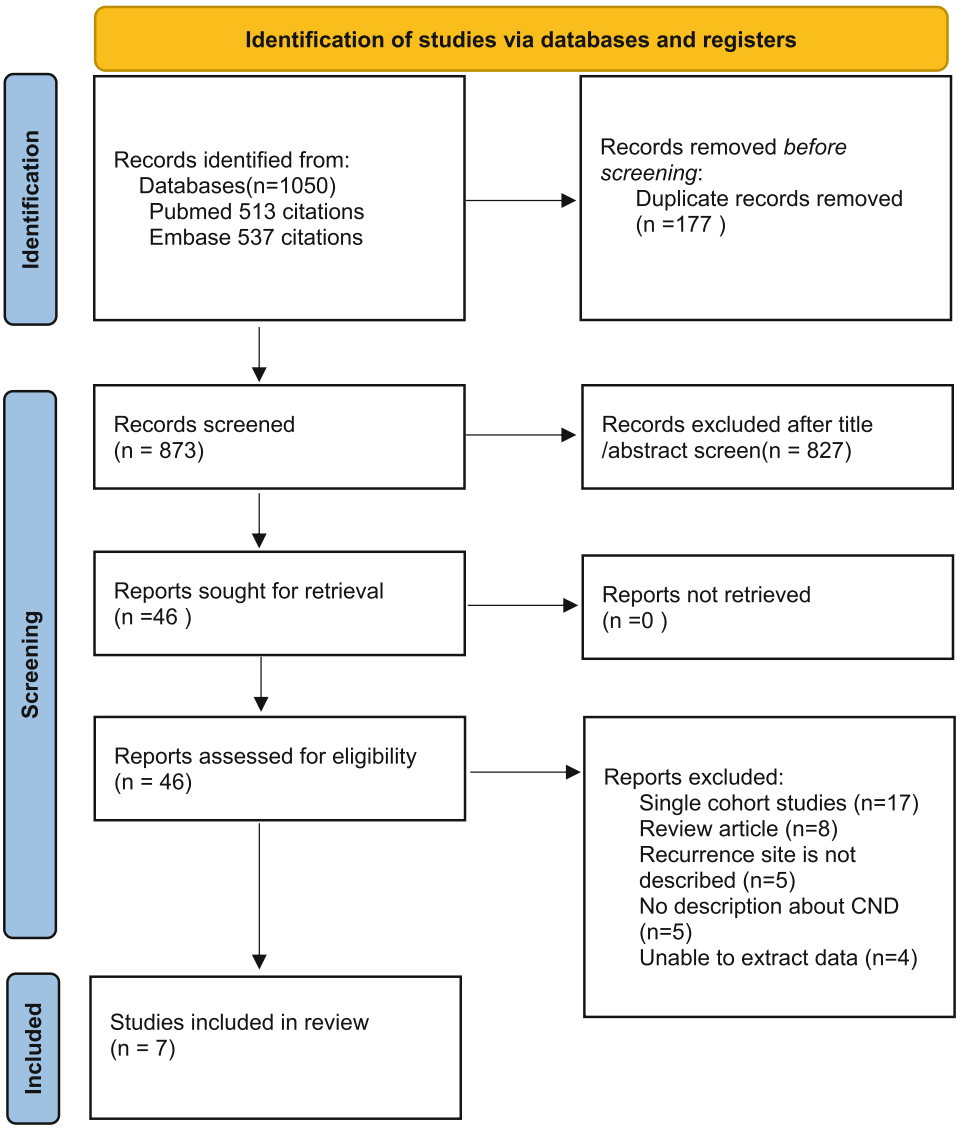

Fig. 1. Flowchart of study inclusion criteria.

Outcomes of the LRR

All seven studies reported the number of patients with LRR (Table 1). The rate of LRR in the HT + pCCND group was lower than that in the HT group (3.58% vs. 4.51%), but there was no significant difference between the two groups (OR = 0.65, 95% CI = 0.41–1.03, Fig. 3a) and no significant heterogeneity between these studies ($I^2 = 0\%$ and $P = 0.58$). The publication bias of this comparison was confirmed by the funnel plot (Fig. 3b) as well as Begg's tests, which did not show any significant difference ($Pr > |z| = 0.230$).

Outcomes of DFS

Five studies acquired the logHR of DFS between the two groups. No significant differences in terms of DFS were observed between the two groups (HR = 0.67, 95% CI = 0.42–1.07, Fig. 4a). Heterogeneity between studies was low ($I^2 = 0\%$ and $P = 0.44$), and no significant difference in publication bias was observed from the funnel plot (Fig. 4b). Begg's tests, which did not show any significant difference ($Pr > |z| = 0.806$).

Discussion

Global discussions persist regarding the impact of pCCND on postoperative quality of life and prognosis in patients with PTC. The 2015 ATA guidelines suggest that for cN0 T1 or T2 stage-differentiated thyroid cancers with low-risk factors, such as unifocal, intrathyroidal carcinomas without a history of head and neck radiation or familial history of thyroid carcinoma, HT might be sufficient as an initial treatment approach.[8] An alternative perspective considers the high rate of lymph node metastasis in the central compartment of PTC and reduces the risk of intraoperative complications in cases of recurrence; ipsilateral pCCND should be performed during the initial operation.[24] Most meta-analyses exploring this issue have focused on TT and TT + pCCND, with different outcomes. In studies by Chen *et al.*[25] and Liang *et al.*,[26] it was observed that TT + pCCND could reduce the likelihood of

Table 1 Characteristics of seven included studies

Study	Year	Country	Study design	Follow-up	No. of cases	pCCND pCCND (+)	pCCND pCCND (−)	LRR pCCND (+)	LRR pCCND (−)	OLNM (%)	NOS
Giordano *et al.* (2022)[17]	2000–2018	Italy	CS	75 months (36–207 months)	89	16	73	1	4	1 (6.25%)	7
Hyun *et al.* (2012)[22]	2002–2009	Korea	CS	51.3 ± 25.89 months	105	42	63	1	9	19 (21.84%)	8
Son *et al.* (2018)[20]	2005–2015	Korea	CS	56 months (24–117 months)	537	399	138	22	10	N/A	7
Ryu *et al.* (2020)[19]	2004–2012	Korea	CS	79 months (12–176 months)	1071	458	613	8	19	95 (20.74)	8
Jin *et al.* (2019)[21]	2002–2015	Korea	CS	HT + pCCND:59 ± 30 months; HT:66.7 ± 32.7 months	108	54	54	2	4	10 (18.5%)	8
Zhang *et al.* (2020)[18]	2013.1–11	China	CS	63.6 ± 3.6 months	58	39	19	2	0	9 (23.1%)	7
Kim *et al.* (2019)[23]	2011–2014	Korea	RCT	HT + pCCND:74.2 months; HT: 72.6 months	184	82	82	3	1	41 (50%)	-

CS, cohort studies; HT, hemithyroidectomy; LRR, locoregional recurrence; mo, month; NOS, Newcastle–Ottawa scale; OLNM, occult lymph node metastasis; pCCND, prophylactic central compartment neck dissection; RCT, randomized controlled trial.

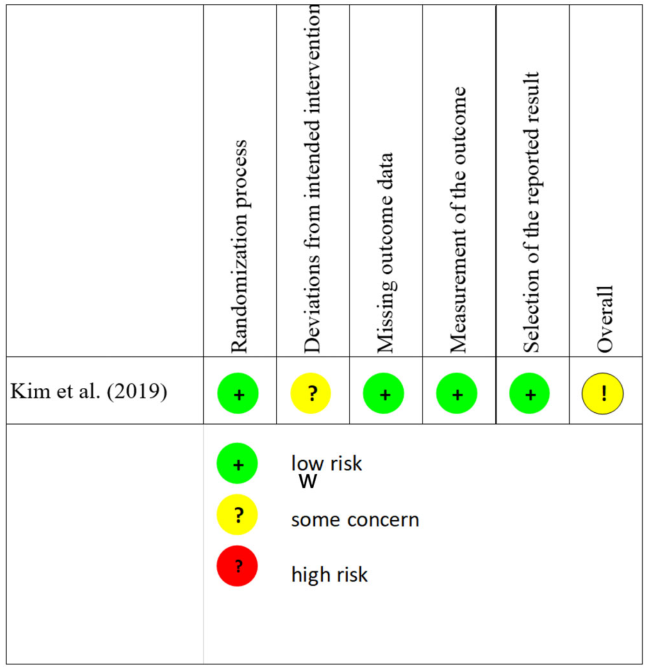

Fig. 2. Risk of bias assessment for RCTs.

LRR compared to TT alone but was associated with a higher occurrence of temporary hypoparathyroidism and RLN injury postoperatively. In contrast, Yang *et al.*[27] found no statistical difference in LRR between the TT + pCCND and TT groups; however, pCCND increased the incidence of postoperative complications. Lang *et al.* suggested that pCCND did not significantly lower LRR after TT, emphasizing the importance of considering the impact of radioactive iodine ablation after surgery.[28] In summary, debate persists on whether pCCND can decrease postoperative LRR and the prognosis of patients with PTC. However, as follow-up ultrasound diagnostic technology advances and public awareness of thyroid physical examinations have increased, the diagnosis rate of early PTC, particularly among patients with unilateral low-risk PTC, has increased dramatically. HT has become the most common surgical procedure for these patients since the 2015 ATA guidelines were published. However, there is a relative scarcity of meta-analyses on whether HT combined with pCCND can improve prognosis after surgery. A proportional meta-analysis in Korea demonstrated that the risk of recurrence in the central compartment among patients in the HT group was lower in patients who underwent HT+ pCCND than in those who underwent HT (0.17% vs. 1.78%).[13] In this meta-analysis, we aimed to assess the impact of pCCND following HT on LRR and DFS in patients with cN0 low-risk PTC through comparative studies, with the goal of evaluating the necessity of this surgery.

There was no significant difference in postoperative LRR between the HT + pCCND and HT groups (OR = 0.65, 95% Cl = 0.41–1.03). This conclusion was different from that of Ahn's study.[13] This may be related to variations in the number of included studies and differences in the total sample size. Moreover, our meta-analysis mainly focused on comparative studies, differing

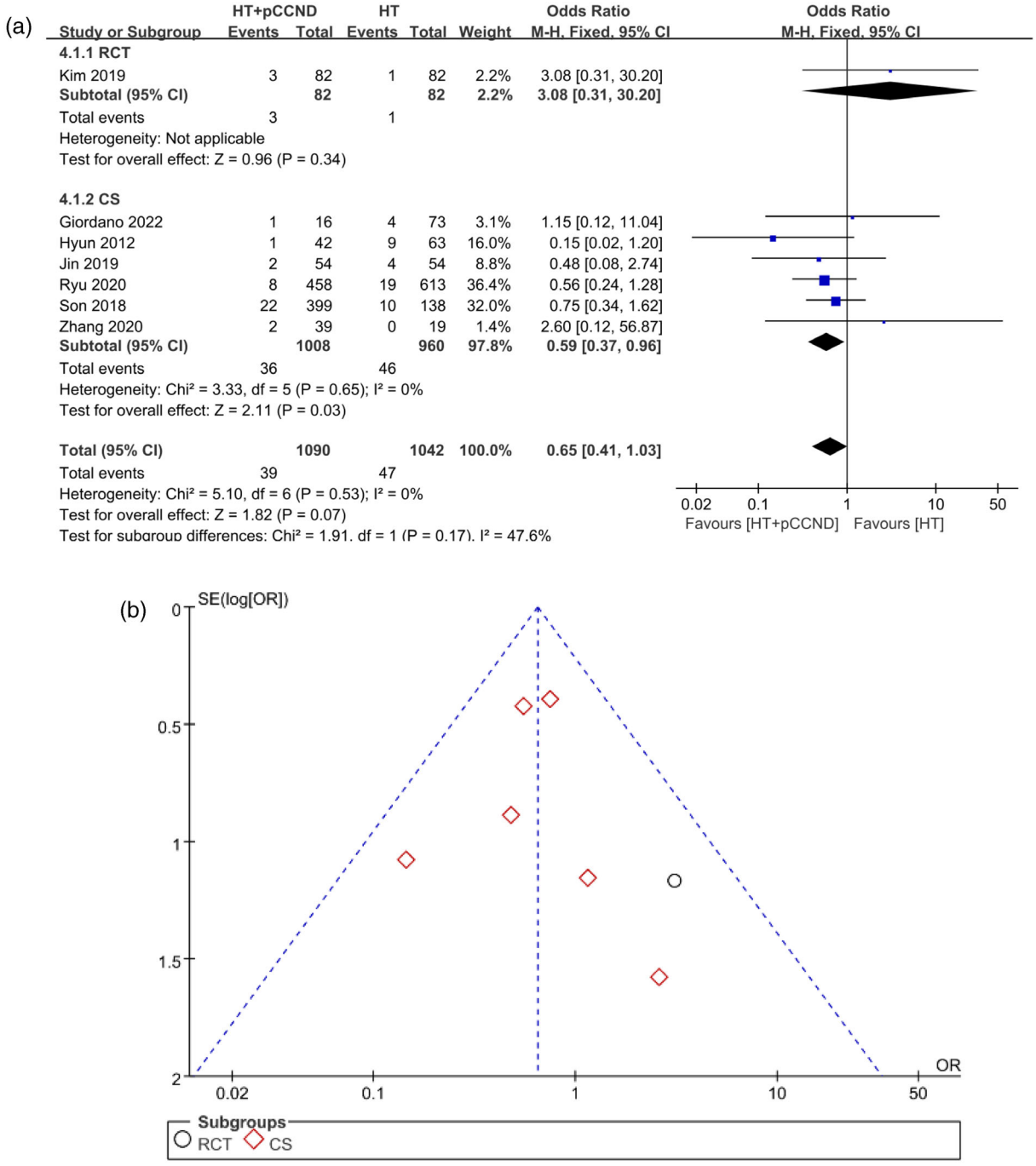

Fig. 3. (a) Forest plot of local recurrence in HT with pCCND and HT alone groups. (b) Funnel plot of local recurrence in HT with pCCND and HT alone groups.

from the types included in other analyses, which could reduce the risk of selection bias. In addition, the reasons for LRR after surgery in patients with PTC were probed by numerous studies, such as the patient's age (paediatric or geriatric), the male sex, tumour size, the ETE, the number of lymph node metastases, and the LN ratio >0.26.[6,8,19,29,30] All studies included in this meta-analysis focused on cN0 low-risk PTC or PTMC, and the participants had fewer risk factors. Thus, the LRR rate was similar in both groups. Our analysis revealed no significant difference in terms of DFS between the two groups (HR = 0.67, 95% CI = 0.42–1.07), similar to multiple RCTs[10,23,31] that investigated whether pCCND was significant for prolonging DFS in patients with PTC after TT or HT. Ryu *et al.*[19] reported that, for PTMC, pCCND performance was not associated with DFS after HT (HR = 0.56, 95% CI = 0.24–1.27). Son *et al.*[20] compared the HT + pCCND and HT groups and found no correlation between pCCND and DFS among 537 patients with

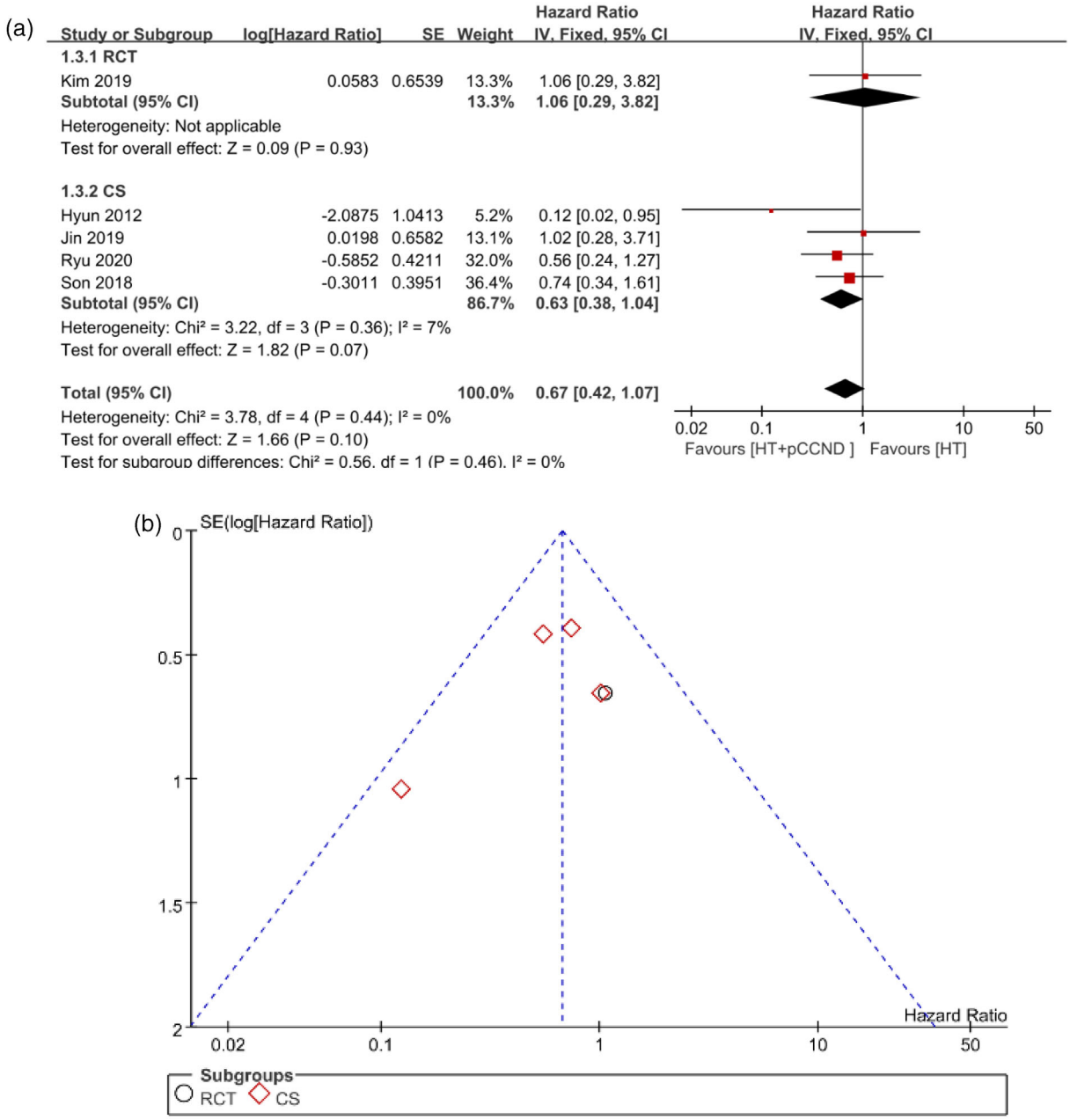

Fig. 4. (a) Forest plot of disease-free survival in HT with pCCND and HT alone groups. (b) Funnel plot of DFS in HT with pCCND and HT alone groups.

PTMC (HR = 0.74, 95% CI = 0.35–1.57). These trials emphasize the importance of cautious selection when applying pCCND in cN0 low-risk PTC cases to prevent overtreatment because it may not improve the oncological outcomes for patients with PTC.

The quality of the included literature was assessed as acceptable. Although the RCT by Kim *et al*. showed some differences in the sex distribution and tumour size post-randomization, potentially imposing bias and influencing the current conclusions to some extent, the cohort studies included in the present research, assessed using the Newcastle–Ottawa Scale, consistently scored between 7 and 8 points, indicating high quality. Therefore, the overall study conclusions are considered reasonably credible.

The current meta-analysis has some strengths. To our knowledge, it is the first to explore the association between HT and pCCND in patients with low-risk PTC with respect to LRR and DFS that includes comparative studies. This may provide direct instructions for clinical surgeons and institutions. Additionally, the observed low heterogeneity among the comparison groups and the absence of apparent publication bias enhanced the credibility and robustness of our findings.

This study also has some limitations. Six of the seven articles in this study were retrospective cohort studies, with potential selection and review biases, compromising the reliability of the analysed outcomes. In addition, the small sample size in the current study

included fewer patients than other recently published reports, which would affect the reliability of our research. The included studies span an 18-year period, during which surgical techniques and equipment have changed dramatically, which may influence the effect of surgical treatment.

Conclusion

There are no significant differences in the rate of LRR or improvements in DFS in patients undergoing HT + pCCND for cN0 low-risk PTC compared to those undergoing HT alone. The inclusion of pCCND does not improve the oncological outcomes for these patients. Therefore, thyroid surgeons should carefully assess the patient's condition and select the most suitable surgical method. Future research should incorporate additional prospective data and high-quality RCTs to further clarify this association.

Conflicts of interest

None declared.

Acknowledgements

We would like to thank Editage (www.editage.cn) for English language editing.

Author contributions

Peng Zhao: Data curation; methodology. **Lulu Liang:** Data curation; methodology. **Yongbiao Luo:** Methodology. **Quankun Liang:** Software. **Bangde Xiang:** Conceptualization.

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