Original Article

Impact of completion thyroidectomy timing on post-operative complications: a systematic review and meta-analysis

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Despite a number of studies, the optimal timing of completion thyroidectomy is still controversial. This systematic review and meta-analysis aims to compare the outcomes of early versus delayed completion thyroidectomy regarding post-operative complications.

Methods: We performed a systematic review in electronic databases including: bumped, Scopus, Medline and Google Scholar to identify relevant studies. Eligibility criteria included studies comparing the outcomes of early versus delayed completion thyroidectomy with no language restriction. Publication bias was assessed by funnel plot, and Heterogeneity was assessed using I^2 statistic. Finally, pooled odds ratios (OR) with a 95% confidence interval (CI) was reported for comparing the overall complications rate.

Results: Eventually 7 studies were included. Delayed completion thyroidectomy was found to be associated with significantly lower rates of post-operative complications (OR =1.55; 95% CI, 1.00–2.42; Z=1.95; P=0.05) with low heterogeneity (I^2=0%, P=0.55), and low risk of publication bias. The rate of transient hypocalcemia and persistent hypocalcemia were 8.97% and 1.52% in early completion thyroidectomy group, and 8.2% and 0.72%, in delayed completion thyroidectomy group. Transient vocal cord paresis occurred in 5.38% of the early CT group versus 3.27% in the delayed CT group.

Conclusions: This review is the first to summarize the outcome of early verse delayed completion thyroidectomy. The result of our systematic review and meta-analysis suggest that delayed completion thyroidectomy is associated with lower rate of post-operative complications compared to early completion thyroidectomy.

Keywords: Completion thyroidectomy; postoperative complication; thyroidectomy; thyroid carcinoma

Submitted Aug 19, 2018. Accepted for publication Sep 04, 2018.
doi: 10.21037/gs.2018.09.03
View this article at: http://dx.doi.org/10.21037/gs.2018.09.03

Introduction

Completion thyroidectomy is the removal of the remaining thyroid tissues with a second operation in patients who have had a lobectomy as the primary operation that revealed thyroid malignancy (1). The indication of completion thyroidectomy fall under three categories. These are: postoperative diagnosis of cancer, residual or recurrent cancer, and symptomatic recurrent multinodular goiter (2,3).

Completion thyroidectomy is thought to carries a higher risk of post-operative complications Due to the issues of tissue inflammation, adhesions, edema, and development of scar tissue after the primary operation (4-8). The risks of complications usually occurs during dissection of the scar tissue that surround the recurrent laryngeal nerve or the vascular pedicle of the parathyroid glands (9,10), due to loss

of landmarks. As in the primary thyroid surgery, recurrent laryngeal nerve palsy and hypoparathyroidism are the major complications in completion thyroidectomy operation.

In this study early completion thyroidectomy is the procedure done between 7 to 90 days, whereas delayed completion thyroidectomy is done after 90 days. Performing completion thyroidectomy in the time period between 7 and 90 days has been suggested to be associated with higher risk of complications compared to completion thyroidectomy done after 90 days (11-14).

The best timing of completion thyroidectomy remains uncertain. In view of this, we aim to present a comprehensive systematic review and a meta-analysis to compare the result of early completion thyroidectomy (7–90 days) versus delayed completion thyroidectomy (>90 days) from the reported studies.

Methods

This systematic review and Mata analysis was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (15).

Electronic literature databases

A literature search was conducted in September 2017 using the following databases: PubMed, Ovid MEDLINE(R) (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Cochrane library (Issue 7 of 12, July 2017), Elsevier Scopus and google scholar, identifying all related articles from 1995 until 2017. The key word combinations used for the search were: ("completion thyroidectomy" OR "thyroid reoperation") AND ("timing"). The cited articles in the included articles were also screened to identify relevant articles not found by our literature search. The first search yielded 146 articles. Concrete reviews of abstracts were performed by two authors independently to select appropriate studies for full-text review. Disagreements regarding selected articles were resolved by through discussion.

Inclusion and exclusion criteria

All studies comparing the outcomes of completion thyroidectomy done within 7–90 days versus after 90 days of the primary surgery, either prospective randomized or retrospective, in any language were considered candidates. The included studies had to contain specific complication rate data to allow for their calculation.

Exclusion criteria were reviews, case reports or series, comments or letters, and duplicate publication, we also excluded studies with incomplete initial data. The full text of articles that survived the abstract review were retrieved and examined for further selection based on the criteria mentioned above. Finally, 7 articles passed the full-text review and were thus included in this analysis (*Figure 1*).

Study quality assessment

Two authors independently judged the methodological quality of all the selected studies using the Newcastle-Ottawa scale (NOS) for cohort studies (16). The checklist contained 9 items (regarding patient selection, comparability of the study and exposure) with every item accounting for 1 point. The scores were evaluated as follows: ≤5, low quality; 6–7, medium quality; 8–9, high quality. Article with a final score of 5 or more points were included. The quality score average was medium with 6 studies obtaining a score of 6 or more (ranging between 5 and 7) (*Table 1*) the proportion of agreement was measured by using the intraclass correlation coefficient. A coefficient of 0.7 or greater was considered adequate.

Data extraction

Full text articles were obtained for studies that fulfilled the inclusion criteria or for which sufficient information was given. Two authors independently reviewed the included articles to extract data on excel spreadsheet. The extracted data sets were compared to confirm accuracy, any discrepancies in extracted data were resolved by through discussion. The following data were extracted from the articles: first author's last name, publication year, country, number of patient, mean age, sex, study design and the timing of CT (*Table 2*). The primary outcome measure incidences of postoperative complication, including Transient and persistent: hypocalcemia, vocal cord paresis and hypoparathyroidism.

Statistical analysis

Seven articles were analyzed using Revman 5.3 (RevMan version 5.3., Copenhagen: the Nordic Cochrane collaboration, 2012) to estimate the overall pooled effect size. The incidence of post-operative complication was calculated based on the number of events. The pooled risks

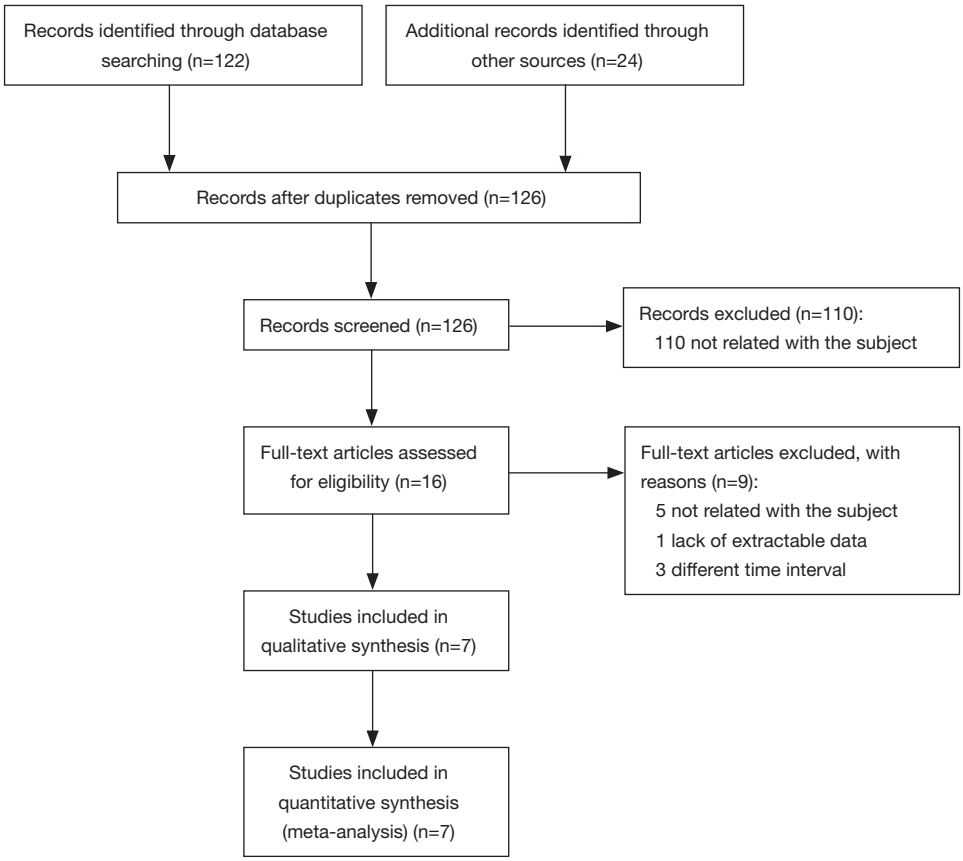

Figure 1 Flow diagram for study identification.

Table 1 Quality of the selected studies by using the Newcastle-Ottawa scale

Authors	Year	Study	Selection	Comparability	Outcome	Final score
Walgenbach	2002	Retrospective	4		3	7
Baloch	2007	Retrospective	4		1	5
Erbil	2008	Retrospective	4		2	6
Kepenekçi	2009	Retrospective	4		2	6
Glockzin	2012	Retrospective	4		3	7
Kısaoğlu	2014	Retrospective	4		2	6
Salem	2017	Retrospective	4		3	7

Under comparability, all of the study did not control for confounders, such as sex, age, and comorbidities.

for the overall complications include transient and persistent hypocalcemia, vocal cord paresis and hypoparathyroidism. The overall complication was estimated and compared between the early completion thyroidectomy and delayed completion thyroidectomy groups.

The result of the Mata-analysis were presented using the fixed effect model, odds ratio and corresponding 95% confident intervals (CIs) and the Z test for pooled effect size estimate. Forest plots were used for graphical display of the results.

To assess the heterogeneity among studies, we calculated using the I^2 statistic: 25% to 50% indicates

Table 2 Data and characteristics of the included studies

Author	Year	Country	Number of patient	Mean age (years)	Sex		Study design	Time of Ct
					Women	Men		
Walgenbach	2002	Germany	230	Women: 52±18.4; men: 49±15.6	151	79	Retrospective	Group A: <7 days; group B: >8 days and <3 months; group C: >3 months
Baloch	2007	Pakistan	114	21–76	81	33	Retrospective	Group A: >10 days and <3 months; group B: >3 months
Erbil	2008	Turkey	60	Group A: 46; group B: 48	57	3	Retrospective	Group A: <90 days; group B: >90 days
Kepenekçi	2009	Turkey	241	40.8±12.8	179	62	Retrospective	Group A: >90 days; group B: 10–90 days
Glockzin	2012	Germany	128	44.5	54	74	Retrospective	Group A: first 3 days; group B: >4 days and <7 days; group C: >1 week and <7 weeks; group D: >1 week and <3 months; group E: > 3 months
Kısaoğlu	2014	Turkey	66	36.4 [24–70]	14	52	Retrospective	Group A: >10 days and <3 months; group B: >3 months
Salem	2017	Egypt	118	41.7 [13–79]	90	28	Retrospective	Group A: 1 week to 3 months; group B: 3–6 months; group C: more than 6 months

low heterogeneity, 50% to 75% indicate moderate heterogeneity, >75% indicate high heterogeneity.

A (P value) equal to or less than 0.05 was consider statistically significant different. Potential publication bias was assessed by performing visual inspection of funnel plot for asymmetry, based on the primary outcome, that is, postoperative complication.

Results

Search result

Our searched yield 126 studies from searching all the data bases mentioned above (*Figure 1*) present a flowchart that briefly overviews the search process for the studies included in the meta-analysis. Out of a total of 126 studies, we excluded 119 studies. After a thorough evaluation of the final studies, we selected 7 studies that met eligibility criteria.

Basic characteristics and quality assessment

The included studies were published between 2002 and 2017. The characteristics of the included studies are summarized in (*Table 2*). All included studies were retrospective cohort design. The sample size ranged from 26 to 113 patients. Three of the studies were conducted in Turkey, two in Germany, one in Egypt and one in Pakistan. We judged 6 studies of moderate methodology quality, and 1 study to be low quality (*Table 1*).

Meta-analysis of primary outcomes

A total of 7 studies were included in this analysis to estimate the pooled risk of complication.

Transient hypocalcemia occurred in 8.97% (27/301) and 8.2% (20/244) of the patient in the early CT and delayed CT, respectively. The persistent hypocalcemia rates were 1.52% and 0.72% in the early CT (5/330) and delayed CT (2/276), respectively. There were no significant difference in the occurrence of transient hypocalcemia (OR =1.21; 95% CI, 0.65–2.25; Z=0.60; P=0.55) or persistent hypocalcemia (OR =1.95; 95% CI, 0.40–9.49; Z=0.83; P=0.41) (*Figure 2*).

The prevalence of Transient vocal cord paresis was 5.38% (21/390) in early CT group versus 3.27% (11/336) in the delayed CT group, without significant deference

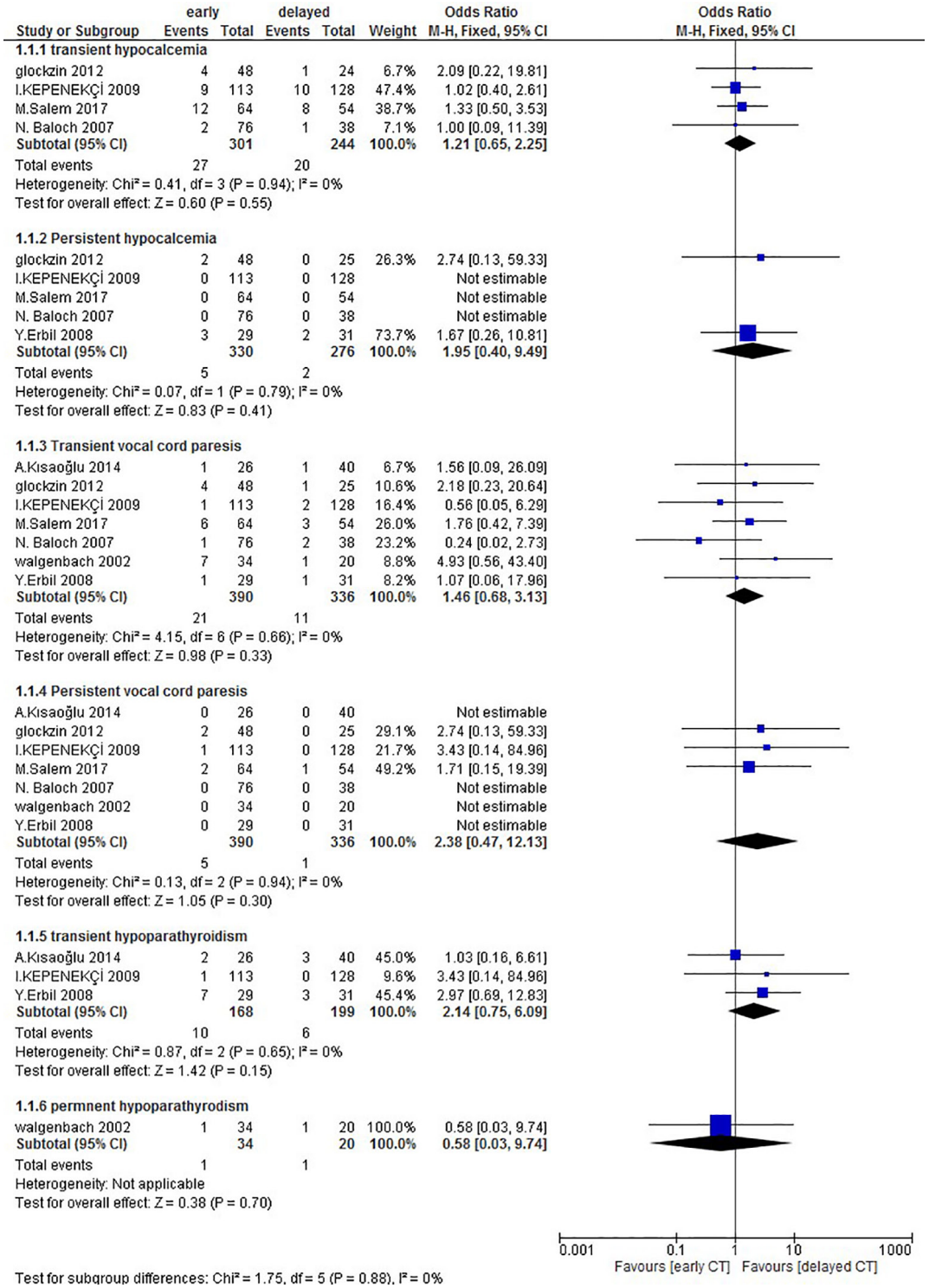

Figure 2 Forest plot presenting the pooled ORs of complications for early CT versus delayed CT. A fixed-effects meta-analysis model was used. CT, completion thyroidectomy.

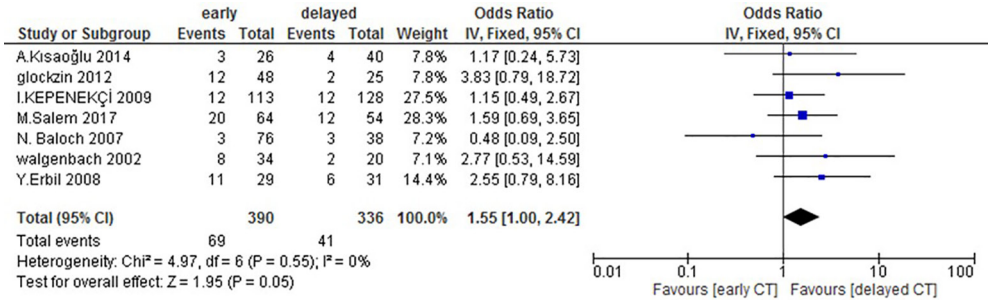

Figure 3 Forest plot presenting the pooled ORs risk of overall complications.

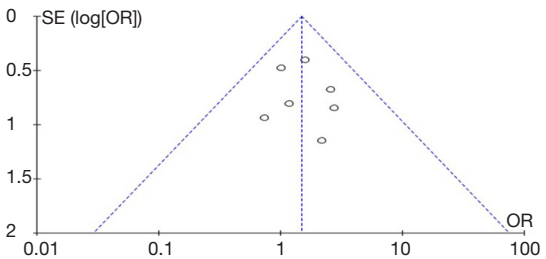

Figure 4 Funnel plot of the primary outcomes for assessing publication bias.

(OR =1.46; 95% CI, 0.68–3.13; Z=0.98; P=0.33). The prevalence of Persistent vocal cord paresis was 1.28% (5/390) in early CT group versus 0.3% (1/336) in the delayed CT group, without any significant deference (OR =2.38; 95% CI, 0.47–12.13; Z=1.05; P=0.30) (*Figure 2*).

Three studies reported transient hypoparathyroidism, and there was no significant differences in the occurrences between the groups (OR =2.14; 95% CI, 0.75–6.09; Z=1.42; P=0.15) (*Figure 2*).

One study reported permanent hypoparathyroidism, with no significant differences in the occurrences between the groups (OR =0.58; 95% CI, 0.03–9.74; Z=0.38; P=0.70).

Pooled analysis revealed significant reduction in the overall complications in the delayed surgery group compared too early surgery group (OR =1.55; 95% CI, 1.00–2.42; Z=1.95, P=0.05) (*Figure 3*). A similar result for the test of overall effect was obtained when the random-effect model was used. No significant heterogeneity was detected between the studies (I^2=0%, P=0.55) (*Figure 3*).

Funnel plots of the studies showed symmetry of the study distribution, indicating low possibility of publication bias in this analysis (*Figure 4*). However, the result is unreliable, since there is limited number of studies in this analysis.

Discussion

We performed a systemic review and meta-analysis of reported outcomes to compare the result of early completion thyroidectomy versus delayed completion thyroidectomy. A total of 7 studies were included in the current study. All of which were retrospective cohort studies including 957 patients. Most common complications reported were transient hypocalcemia, persistent hypocalcemia, transient vocal cord paresis, persistent vocal cord paresis and transient hypoparathyroidism. In Most patients the histopathologic examination of the restricted thyroid gland, after the primary procedure showed papillary cancer (1,13,17,18). The heterogeneity in our meta-analysis was low (I^2=0), indicating that the studies included in our systematic review and meta-analysis were statistically reliable.

The included studies comparing complication rates between early and delayed completion thyroidectomy have shown mixed results. Some conclude that delayed completion thyroidectomy have lower rates of postoperative complications, including transient hypocalcemia, persistent hypocalcemia, transient vocal cord paresis, persistent vocal cord paresis and transient hypoparathyroidism, compared to early completion thyroidectomy (11,13,18,19), other studies suggest the Timing of completion thyroidectomy did not significantly affect the incidence of post-operative complication (1,13,19).

The result of our meta-analysis suggested that delayed completion thyroidectomy surgery was significantly associated with lower odds of post-operative complications (P=0.05) compared to early completion thyroidectomy surgery.

Limited studies reported the incidence of post-operative complications In patients who had the completion thyroidectomy in the first week after the initial surgery,

which might be due to restriction of timing in Establishing the diagnosis and recovery from the first operation often goes beyond the first week to 10 days deadline (20), therefore these periods in the studies were exclude from this meta-analysis, and there is a need for additional well designed studies to clear the insights into the effects of this timing period

This study has some limitations. First, all of the studies in our meta-analysis were retrospective cohort studies, and is therefore subject to the individual limitation of the included studies. Second, the type of cancer, the operation, operation technique and definitions for hypocalcaemia and RLN palsies varies between the studies. These variations may limit the effective comparison of the outcomes. Therefore For meaningful comparisons a standardization of definitions and protocols for hypocalcaemia and RLN palsies is required.

Despite these limitations, this review is the first to summarize the outcome of early verse delayed completion thyroidectomy.

Conclusions

On the basis of current evidence, delayed completion thyroidectomy is associated with lower rate of post-operative complications compared to early completion thyroidectomy. Further studies are needed for definite conclusion.

Acknowledgements

This project was supported by the Health Science Research Center at Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia.
Supporting Information: PRISMA Checklist (DOC).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Bin Saleem R, Bin Saleem M, Bin Saleem N. Impact of completion thyroidectomy timing on post-operative complications: a systematic review and meta-analysis. Gland Surg 2018;7(5):458-465. doi: 10.21037/gs.2018.09.03

