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Thyroidectomy for thyroid cancer in the elderly: A meta-analysis

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ABSTRACT

Thyroid cancer, the most common endocrine malignancy, has patients who generally have excellent prognosis. It has been shown that elderly patients are more likely to undergo sub-therapeutic management, despite having more aggressive disease, resulting in increased mortality and morbidity. The present study aimed to quantitatively investigate the risks of elderly patients who underwent thyroidectomy for thyroid cancer regarding mortality/survival, recurrence of disease, and complications arising from thyroidectomy. A systematic search and meta-analysis was carried out using the electronic databases PubMed and Medline. We searched for articles containing epidemiological evidence of mortality and recurrence of disease in patients above the age of 60, who are treated for operatively thyroid cancer and data involving complications following total thyroidectomy. The meta-analysis consisted of a total of 16 studies meeting the inclusion and exclusion criteria. The current study confirmed that patients have increased risk of recurrence (HR 4.84; 95% CI = 22.2–10.52; $I^2 = 0.00$; P = 0.98) including increased risk of lymph node recurrence and distant metastases. Additionally these patients had an increased risk of complications (OR 1.82; 95% CI = 0.88–3.77; $I^2 = 77.01$; P = 0.005) following thyroidectomy compared to patients in the younger cohort. The current study also qualitatively compared survival data between the different age cohorts, and identified a reduced overall survival and disease free survival for elderly patients. The current study suggests that elderly patients should be classified as higher risk following total thyroidectomy for thyroid cancer and puts an emphasis is early detection and intervention.

Introduction

Thyroid cancer is the most common endocrine malignancy with the papillary variant being the most common. In recent years there has been an increase in the incidence of papillary thyroid cancer [1–4]. There have been a number of opinions as to the cause, however, most clinicians attribute the rise in numbers to an increase in surveillance techniques and better accessibility to ultrasound investigation [4–7]. Alternatives to this theory include reduction in iodine from diet and increase in ambient electromagnetic radiation levels. Papillary thyroid cancer is one of the best curable cancers and with good overall prognosis following treatment with overall 10 year survival rate exceeding that of 80–95%. Despite the good overall prognosis for thyroid cancer, recurrences are common, and active surveillance is necessitated throughout such patient's lives [8,9].

There has been a number of suggestions by clinicians and researchers alike about an indolent natural history to papillary thyroid cancer and the possibility of avoiding surgical treatment altogether, particularly for patients who have papillary thyroid microcarcinoma (defined as having a nodule size of <1 cm) [10–12]. Autopsy studies have found a number of patients have occult non symptomatic thyroid cancer at the time of death [13], suggesting that a conservative non-operative approach of active surveillance may be appropriate.

In contrast, new studies have shown significant reduction in cancer rated morbidity, and an increase in overall survival for elderly patients who are treated operatively [14,15]. More than 50% of all cancers occur in patients over the age of 65, making age one of, if not the worst risk factor for cancer. It has been shown in the elderly that thyroid cancer is seen to be more aggressive and can lead to significant morbidity even at the micro carcinoma level (T1 <1 cm). Thyroid cancer in the elderly has been shown to be associated with significant economic burden to the health care system [16]. The direct association between observation time and age of patients would warrant consideration of early thyroidectomy

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rather than delayed thyroidectomy for patients who are diagnosed with low risk thyroid cancer. It has been shown that total thyroidectomy for thyroid cancer in the elderly is a safe operation in experienced hands and remains the surgical operation of choice [17].

By performing a systematic review and meta-analysis of the overall mortality rates and recurrence rates of elderly patients following thyroidectomy, the authors of this study attempt to contrast the studies and give a more objective analysis of the viability of a non-operative/observational approach for patients in an elderly age group. Before researchers can entertain the idea of an observational approach to thyroid cancer, the association between age and post-operative morbidity should be taken into account. The present study argues that time, considered from the perspective of patient age, is a high risk factor for increased mortality, recurrence and complication rates compared with patients who are operated on at a younger age.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. A systematic search of the databases MEDLINE (from 1950) and PubMed (from 1946) were used to identify relevant articles. The search used the terms 'Thyroid Cancer' AND 'Thyroidectomy', AND 'elderly', which were searched as text word and as exploded medical subject headings where possible. The reference lists of relevant articles were also searched for appropriate studies. No language restrictions were used in the search, however study selection was limited to English language studies. A search for unpublished literature was not performed.

Study selection

To maintain consistency in results we included studies that met the following inclusion criteria: 1) Studies were required to be retrospective in temporal direction; 2) Post-operative follow up period was stated explicitly or implicitly; 3) English language studies; 4) Patients were greater than or equal to 60 years old at time of diagnosis; 5) Risk was represented in Hazard Ratio or Odds ratio (or as a clear percentage of the control group in relation to complications); 6) Studies included data on overall mortality/survival OR recurrence rates OR rates of post-operative complications.

Data extraction

The data extraction was performed using a standardized data extraction form, collecting information on the publication year, study design, number of cases, number of controls, total sample size, temporal direction, population type, country, case control matching, number of adjusted variables, the Hazard Ratio (HR) (or Odds Ratios were present) or data used to calculate the Hazard Ratio (or Odds Ratio), Confidence Intervals (CIs) or data used to calculate CIs. Adjusted ratios were extracted in preference to non-adjusted ratios, however, where ratios were not provided, unadjusted HRs and CIs were calculated from available data. Where more than one adjusted ratio was reported, we chose the ratio with the highest number of adjusted variables. Where multiple risk estimates were available in the same study, for example due to the use of different comparator groups, they were included as separate risk estimates.

Statistical analysis

Pooled hazard ratios and 95% confidence intervals were calculated for cases of mortality and recurrence including complication rates for elderly patients greater than or equal to the age of 60 years old using a random effects model [19]. We tested heterogeneity with Cochran's *Q* statistic, with $P < 0.10$ indicating heterogeneity, and quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity. I^2 values of 25, 50 and 75% corresponded to low, moderate and high degrees of heterogeneity respectively [20]. We quantified publication bias using the Egger's regression model [21], with the effect of bias assessed using the fail-safe number method. The fail-safe number was the number of studies that we would need to have missed for our observed result to be nullified to statistical non-significance at the $p < 0.05$ level. Publication bias is generally regarded as a concern if the fail-safe number is less than $5n+10$, with n being the number of studies included in the meta-analysis [22]. All analyses were performed with Comprehensive Meta-analysis (version 3.0), Biostat, Englewood, NJ (2014).

Results

Description of the studies

Using out electronic search method 1923 articles were retrieved and an additional 10 articles were retrieved from other sources including the reference lists of other articles. The list was narrowed down to 64 relevant abstracts after care deliberation of the inclusion criteria and exclusion criteria for the review. From this list 15 were selected for the meta-analysis (Fig. 1). To assess the study quality, all studies were examined with respect to a finite number of variables, including numerical description of the eligible participants of the study, independent confirmation of thyroid cancer in patients aged >60 years of age, mortality rates, recurrence rates as well as complication rates.

Results of the pooled analysis

In the present study data was pooled on the risk of mortality, recurrence and complication rates following thyroidectomy in the elderly (patients aged > 60 years old). The risk of mortality was compared to the odds of overall survival. Recurrence rates were further sub differentiated by 3 studies to compare lymph node metastases and distant metastases. Overall complication rates were considered and further sub-classified into permanent hypoparathyroidism, permanent recurrent laryngeal nerve injury, wound infection, post-operative haemorrhage.

Disease free survival and overall survival

A total of 7 studies contained data on 5839 patients in terms of disease free survival in elderly patients compared with younger patients. Table 1 is quantitative summary of the studies that used disease free mortality as a measurable outcome for their patients. A total of 7 studies contained quantitative data pertaining to the overall survival of elderly patients following thyroidectomy for thyroid cancer. The data regarding DFS and OS is mixed. The overall trend is that DFS and OS are reduced in elderly patients A quantitative analysis of the data was attempted however, it was the authors belief that the expression of mortality between studies were too heterogeneous to compare quantitatively using the technique of meta-analysis. Results were expressed in a mixture of Hazard ratios and percentage of survival, as well as differing age groups for comparison. It was not clear how the articles reporting hazard ratios derived their results. A high hazard ratio for DFS and OS would imply that patients are more likely to survive, however, this is contrary to the trends seen in the articles that represented their

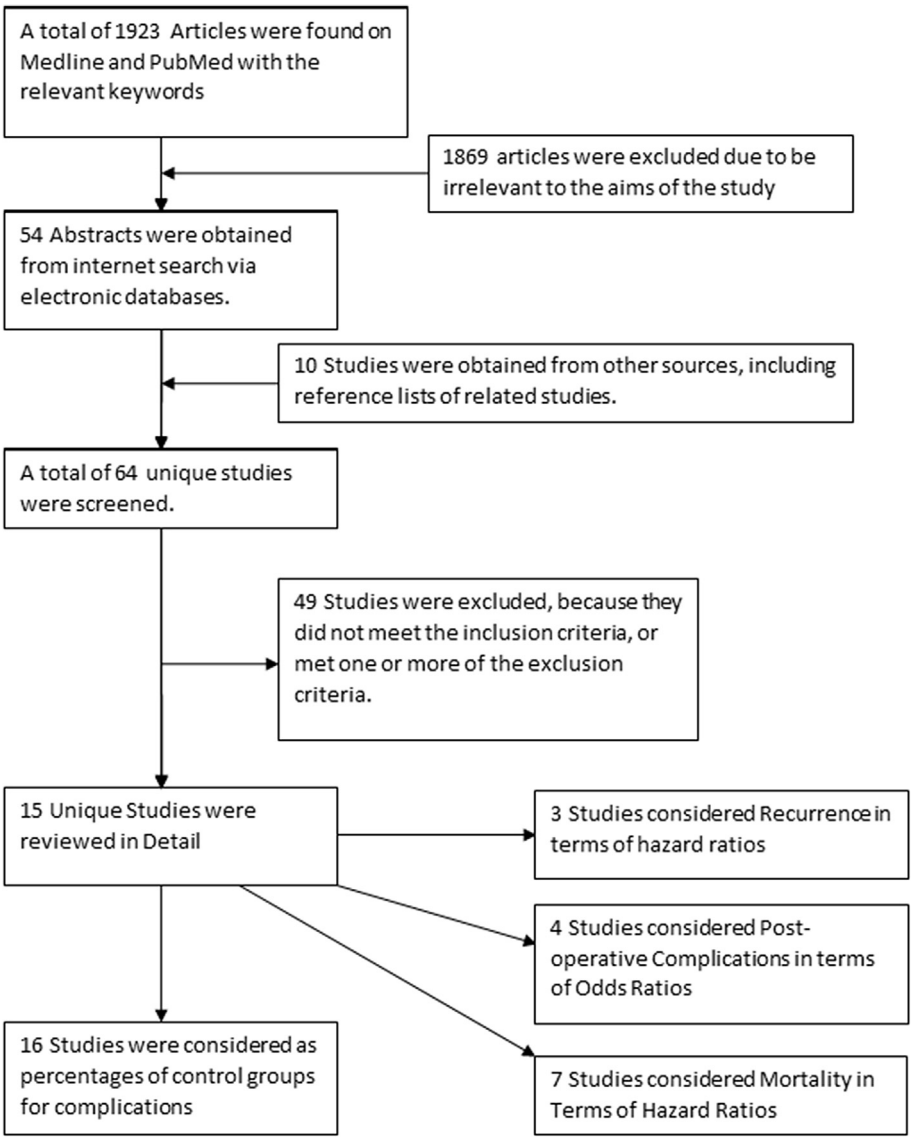

Fig. 1. Flowchart illustrating the process of study selection.

Table 1
Quantitative data on overall survival following total thyroidectomy for thyroid cancer in the elderly.

Author	Publication Year	Country	Temporal Direction	Total Population Size	Age (Minimum)	Median Follow up Period (years)	Disease Free Survival (measured in years)	Overall Survival (measured in years)
Al Qahtani [27]	2016	Saudi Arabia	Retrospective	118	60	5.5	10	10
Calo [17]	2014	Italy	Retrospective	101	65	Nil Follow up Data	Nil Survival Data	Nil Survival Data
Canonico [25]	2014	Italy	Retrospective	200	65	Nil Follow up Data	Nil Survival Data	Nil Survival Data
Chereau [26]	2016	France	Retrospective	450	65	36.4	5	5
Coburn	1995	USA	Retrospective	382	70	30	5 and 10	5 and 10
Falvo [28]	2004	Italy	Retrospective	22	71	3 to 9	Nil Survival Data	9
Garg [29]	2015	India	Retrospective	438	60	5.58	10	Nil Survival Data
Grogan [30]	2012	USA	Retrospective	1322	65	Nil Follow up Data	Nil Survival Data	Nil Survival Data
Grogan [9]	2013	USA	Retrospective	22	60	27	3	Nil Survival Data
Hollenbeack [31]	2013	USA	Retrospective	2833	65	5	10	10
Longheu [14]	2016	Italy	Retrospective	778	65	Nil Follow up Data	Nil Survival Data	Nil Survival Data
Megwalu [24]	2017	USA	Retrospective	2323	65	5	Nil Survival Data	5
Mekel [23]	2009	USA	Retrospective	242	80	Nil Follow up Data	Nil Survival Data	Nil Survival Data
Park [32]	2014	Korea	Retrospective	1867	70	4.25	5	20.16
Toniato [33]	2011	Italy	Retrospective	117	75	7.8	Nil Survival Data	10 and 15
Vini [34]	2003	UK	Retrospective	111	70	9	10	19

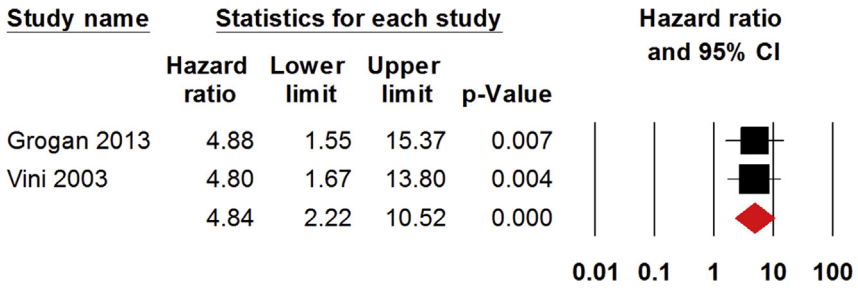

Fig. 2. Recurrence of disease following total thyroidectomy for thyroid cancer in elderly patients.

data as percentages. Four of seven articles reported higher hazard ratios for DFS, whereas only two of seven articles reported higher hazard ratios for overall survival.

Recurrence

A total of 2 articles considered hazard ratios for the recurrence of disease in elderly patients (Fig. 2). Both studies had significantly higher rates of recurrence in patients who are elderly compared with younger. The combined total hazard ratio was HR 4.84 (95% CI = 22.2–10.52) $I^2 = 0.00$ and P = 0.98. A total of 7 articles, containing 7496 patients, had odds ratio or information from which odds ratio could be calculated demonstrating an increased risk of recurrence following total thyroidectomy for thyroid cancer. The odds of recurrence increased 2.13 times for elderly patients (95% CI = 1.21–3.75) $I^2 = 72.11$ and P < 0.001. Eggers Regression P = 0.56 (Fig. 3). Risk of recurrence was further classified into lymph node recurrence and distant metastases in three studies. These studies demonstrated that elderly patients were 2.32 times more likely to develop lymph node recurrences than younger patients (95% CI = 1.26–4.29) $I^2 = 0.00$ P = 0.44. Eggers Regression P = 0.73 (Fig. 4). They also demonstrated that elderly patients were 3.74 times more likely to develop distant metastases (95% CI = 2.43–5.77) $I^2 = 0.00$ P = 0.78. Eggers regression P = 0.98 (Fig. 5).

Complications of total thyroidectomy

A total of 4 studies considered overall complication rates of the elderly following thyroidectomy for thyroid cancer. This included a total of 2626 patients. The total hazard ratio is increased 82% (95% CI = 0.88–3.77) $I^2 = 77.01$ and P = 0.005. Eggers regression value 0.87 (Fig. 6).

A total of 5 studies contained information regarding permanent hypoparathyroidism following total thyroidectomy in the elderly. These contained a total of 3870 patients. With increased risk OR = 2.18 (95% CI = 1.35–3.52) $I^2 = 0.00$ P = 0.55. Eggers regression P = 0.32 (Fig. 7).

A total of 4 studies contained information regarding recurrent laryngeal nerve injury in elderly patients following thyroidectomy for thyroid cancer. These studies included a total of 3092 patients. The increased risk of recurrent laryngeal nerve injury was 35%. (95% CI = 0.55–3.34) $I^2 = 0.00$ and P = 0.99. Eggers Regression P = 0.16 (Fig. 8).

A total of 4 studies contained data on risk of post-operative haemorrhage in elderly patients. This included a total of 2003 patients. The results demonstrated that elderly patients were 3.4 times more likely to have post-operative haemorrhage than younger patients (95% CI = 1.42–8.00) $I^2 = 16.35$ P = 0.31. Eggers Regression P = 0.26 (Fig. 9).

Three studies, a total of 1603 patients, looked at wound infection and revealed an increased risk for the elderly. OR 3.39 (95% CI = 0.91–12.54) $I^2 = 0.00$ and P = 0.67. Eggers regression P = 0.70.

Discussion

Thyroid cancer has good overall prognosis and sees a >90% 5 year survival rate [8]. However, elderly patients who are elderly have the greatest risk of mortality and morbidity in this age group. It has also been shown that this age group costs the health service a significant amount of revenue per annum for what should be considered a relatively rare malignancy [16,36]. Recent studies have

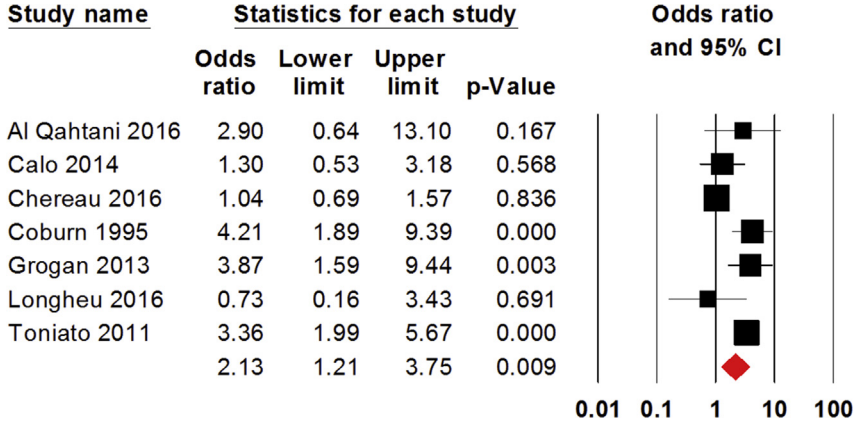

Fig. 3. Recurrence of thyroid cancer in elderly patients following total thyroidectomy for thyroid cancer.

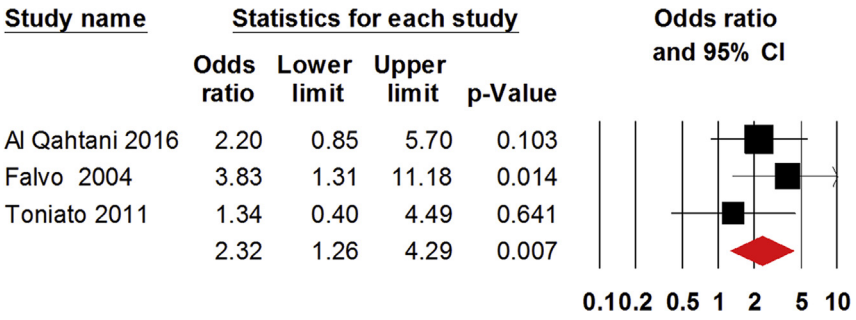

Fig. 4. Lymph node recurrence for elderly patients following total thyroidectomy for thyroid cancer.

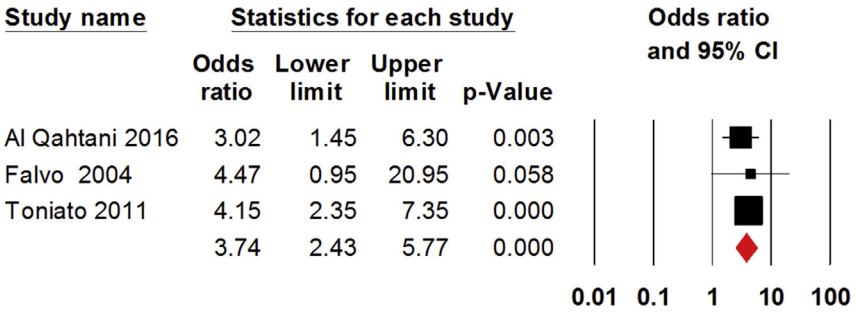

Fig. 5. Recurrence of distant metastases for elderly patients with thyroid cancer undergoing total thyroidectomy.

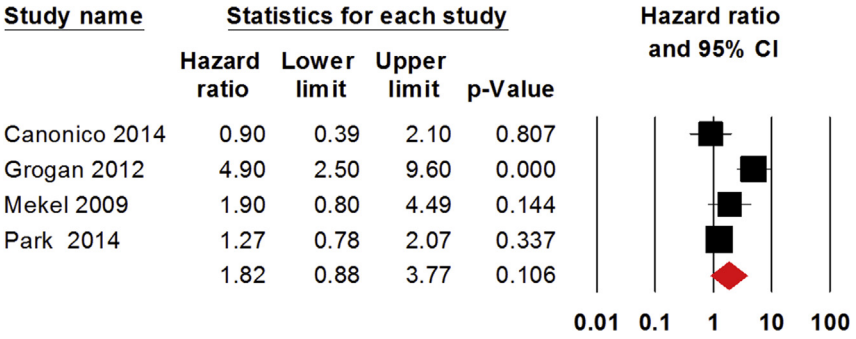

Fig. 6. Complication risk following total thyroidectomy for thyroid cancer in the elderly.

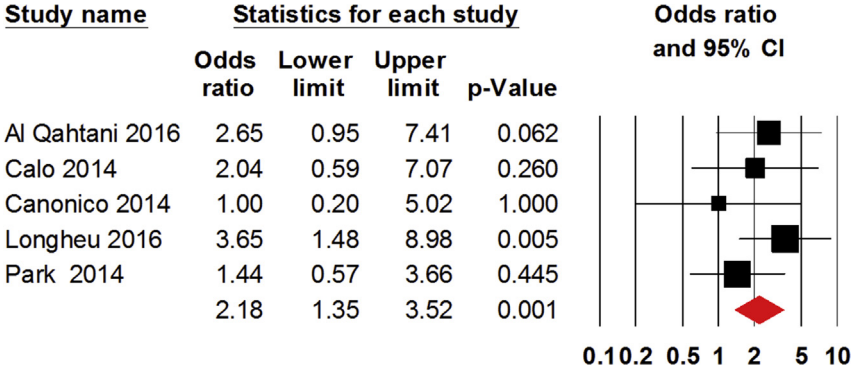

Fig. 7. Risk of recurrent laryngeal nerve injury in elderly patients following thyroidectomy for thyroid cancer.

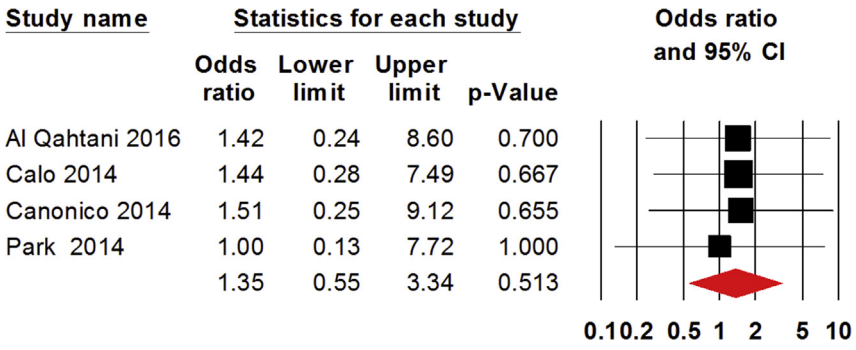

Fig. 8. Risk of post-operative haemorrhage following total thyroidectomy for thyroid cancer in the elderly.

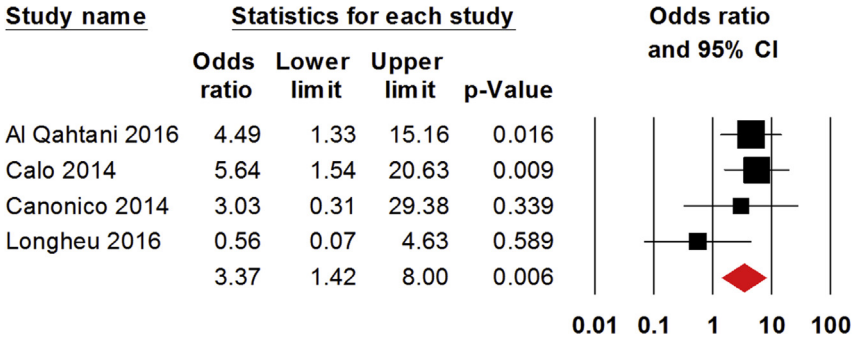

Fig. 9. Risk of wound infection post thyroidectomy for elderly patients with thyroid cancer.

shown that the disease free survival continues to decline with every 5 years above the age of 45 [37]. Thyroid cancer, in particular DTC, is the only cancer which age is considered in the staging criteria (TNM, AMES, DAMES, MACIS) [38,39]. There is little consensus regarding the importance of age as a prognostic factor for thyroid cancer. The present study succeeded in providing quantitative support to the current hypothesis.

This study suggests that elderly patients (>60 years old) with who have thyroidectomy for thyroid cancer have reduced disease free survival and overall survival than patients who are less than 60 years. It is well established that patients who are elderly have poorer outcomes than their younger counterparts. This may be attributed to the general health of the demographic, the existence of multiple co morbidities [35], or delay in presentation resulting in more advanced stage of disease at diagnosis. The present study considered two sets of survival data (due to the availability of data):.Data in the form of percentages of the population, as well as data in terms of hazard ratios. The authors of the current study defined a hazard ratio of >1 for survival data as having a greater chance of survival, than the comparison group. The vast majority articles that reported the data in terms of hazard ratios would thus contradict the trend seen in articles that expressed the raw data in terms of percentages. This may be due to disparities in calculations or the definitions of hazard ratios in this regard.

The present study concluded that patients who are elderly are at greater risk of disease recurrence following operative management. A similar approach was taken where hazard ratios were compared with calculated (or specified) odds ratios. Both sets of analysis confirmed increased risk of recurrence. Recurrence in thyroid cancer can occur at a number of stages. Locoregional recurrence may suggest that there may have been remnant thyroid tissue left behind during the operation. Lymph node recurrence suggests that tumor cells have invaded the lymphatics. Distant metastases suggest that tumor cells have invaded the blood vessels gaining access to circulation. The majority of articles did not distinguish between the different types of recurrence, however a handful of studies considered both lymph node recurrence and distant metastases.

It was also seen that the odds of lymph node metastases and distant metastases were increased significantly in elderly patients following surgery. Despite the distinction only being made in three of the studies, the risk of distant metastases compared with lymph node metastases was significantly higher (OR 3.74 VS 2.32 respectively). This is contrary to what is traditionally understood by the mechanism of metastasis of papillary thyroid carcinoma, where infiltration of the lymphatic vessels is more likely to occur than infiltration of the vasculature. This may be due to exposure of tumor cells during intraoperative bleeding, giving access to the circulation to where once there was none. Further investigation into this field is necessary and a detailed comparison between lymph node and distant metastatic recurrence is required.

The current study considered the safety of elderly patients undergoing thyroidectomy for thyroid cancer by quantitatively considering the risk of complications following surgery. The study found that overall complication rate as well as specific complication rates of permanent hypoparathyroidism, permanent recurrent laryngeal nerve injury, post-operative haemorrhage, and post-operative wound infection were increased. Analysis of the data from this specific population set concludes that patients who are elderly are at increased risk of post-operative complications. There may be a variety of causes for this outcome, and this may be seen in the possibility that elderly patients undergoing thyroidectomy, may already have advanced disease with extensive extra-thyroidal extension, thus making operations more technically difficult. Elderly patients have tissues which are more friable and easily damaged.

Most of the studies included in the current analysis specifically consider patients who were diagnosed with thyroid cancer and operated on after the age of 60. Factors that may explain why such patients were diagnosed later may include increased frequency of late-stage diagnosis in these patients [40]. However it has been shown that older patients are more likely to die of the disease regardless of the stage of thyroid cancer at diagnosis [41]. Another possible explanation is that patients in the more advanced age group are treated less aggressively as a bias of their age. An article by Chereau et al. showed that elderly patients were less likely to undergo operative management for thyroidectomy and even less so for lymph node dissection [26]. The same study also showed that elderly patients were less likely to have radioactive iodine therapy. A specific treatment strategy for elderly patients with PTC is still debated. A number of studies support full operative management for elderly patients with thyroid cancer, including total thyroidectomy and lymph node dissection where appropriate [26].

There has been recent interest in a non-operative approach to low risk thyroid cancer. Such studies advocate active surveillance as the means of monitoring cancers in order to detect any high risk change in characteristics. The present study argues that time, in the form of patient age, is a high risk factor. It suggests that patients in the active surveillance group who undergo malignant transformation above the age of 60, will have significantly increased risk of mortality, recurrence and complication rates compared to if they were operated on at an earlier stage.

The risk of recurrence in patients is mitigated by the use of radioactive iodine and systemic adjuvant therapy. Given the increased risk of recurrence in elderly patients, it is the author's recommendation that such patients are treated more aggressively. This would involve total thyroidectomy and treatment with radioactive iodine and/or systemic therapy. It has been shown that complication rates are reduced in patients who are managed by high volume thyroidectomy surgeons. This includes patients in the elderly age group [42–45].

Limitations

Limitations to the current study include the typical failings of meta-analyses. The current study is able to provide information about the summary effect of mortality, recurrence, and complications in the elderly, however, cannot take into account the treatment variations between individual studies. The authors of the current study attempted to reduce this effect by the consideration and reporting of the heterogeneity in our results. Additionally it was not possible to collect molecular level data on thyroid cancer. The current study used a variety of age groups above the age of 60 years old, as there is no uniformity in the definition of the term 'elderly'. Although this may exaggerate some results, it is not expected to change the summary effect entirely. Part of the meta-analysis method involved assigning weighting to each study, which aimed to mitigate this effect. The current study intentionally did not take into account tumor size, as the evidence has shown that microcarcinomas (tumors <1 cm) also have metastatic potential. The authors are aware of the value of tumor size as a prognostic factor and therefore encourage further research once more data becomes available. Additionally, the data does not take into consideration institution-specific rates, or surgeon specific rates.

The data regarding DFS and OS was not able to be qualitatively compared with the technique of meta-analysis. This was due to the data being too heterogeneous to quantitatively analyze in any meaningful way. For example, many studies used percentages rather than hazard ratios in expressing both DFS and OS. There are variations in the expression of age differences between the studies as well, making the survival modalities of DFS and OS very difficult to compare data sets accurately. Elderly patients will inherently have reduced overall survival. This may be mitigated by the limitation of the parameter to a defined time frame. This however was neither uniformly standardized between studies with some studies using 5 year DFS and others using 10 year DFS. In the case of overall survival, the definitions are less well defined, with a number of studies not explicitly stating how this parameter was calculated. The current review aimed to standardize this by only using articles that had explicitly defined a time frame for OS and DFS.

Future research

Despite not being considered specifically in this current article, there is a suggestion that any operative intervention would improve outcomes inpatients with thyroid cancer and is not limited to total thyroidectomies. Several studies have shown that there is no survival advantage between total thyroidectomy and thyroid lobectomy [46,47]. However, these studies also confirm a reduction in mortality in patients who are treated operatively than patients who are not operated upon.

A sense of awareness is necessary for primary care physicians in order to prevent late detection of disease. Further research considering varying age groups as well as clearer reporting of recurrence types such that they may be analyzed quantitatively in the future. The authors of the current study recommend continued research into this field with further multicenter studies in order to verify the conclusions of the present study. Very old patients should be considered high risk for thyroid disease and should be considered for more prompt surgical as well as systemic management, unless otherwise contraindicated.

Conflicts of interest

The authors declare no conflicts of interest.

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