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MAIN ARTICLE

Observation versus thyroidectomy for papillary thyroid microcarcinoma in the elderly

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Abstract

Objective: To compare the effectiveness of non-surgical versus surgical therapy in elderly patients with papillary thyroid microcarcinoma.

Methods: The study cohort included 2323 elderly patients (aged 65 years and over) diagnosed with papillary thyroid microcarcinoma between 1988 and 2009, identified in the Surveillance, Epidemiology, and End Results 18 database of the National Cancer Institute.

Results: The five-year overall survival rate was 23 per cent for non-surgical patients compared with 91 per cent for surgical patients ($p < 0.0001$). Unadjusted analysis revealed significantly improved survival in surgical patients compared with non-surgical patients (hazard ratio = 0.06; $p < 0.0001$). Propensity score analysis also revealed significantly improved survival in surgical patients compared with non-surgical patients (hazard ratio = 0.11; $p < 0.0001$).

Conclusion: Thyroidectomy appears to provide a survival benefit for elderly patients with papillary thyroid microcarcinoma. High-quality prospective studies are needed to better evaluate the comparative effectiveness of immediate thyroidectomy versus observation for elderly patients with papillary thyroid microcarcinoma.

Key words: Thyroid Neoplasms; Aged; Thyroidectomy; SEER Program

Introduction

The incidence of thyroid cancer is rising.[1–4] This is mostly attributed to the rapid increase in the incidence of small thyroid cancers, especially papillary microcarcinoma.[2,3,5] This is thought to be associated with overdiagnosis of incidental thyroid cancers as a result of increased use of diagnostic imaging.[3,4,6,7] Thyroid cancer is incidentally identified in a significant proportion of autopsies performed on patients who died of unrelated causes.[8] This suggests that these cancers may be indolent and do not warrant aggressive therapy.

In fact, some authors have suggested that small incidental papillary thyroid cancers should not be treated.[8–12] Several observational studies from Japan have reported success with active surveillance for patients with 'low-risk' papillary thyroid cancers.[9–12] Given the expected indolent course of papillary microcarcinomas, and the relatively lower life expectancy for elderly patients, it appears that this segment of the population may benefit most from non-surgical management. This study aimed to compare the effectiveness of non-surgical versus surgical therapy in elderly patients with papillary thyroid microcarcinoma using a large population-based cancer database.

Materials and methods

Data were extracted from the Surveillance, Epidemiology, and End Results ('SEER') 18 database of the National Cancer Institute, which includes data obtained from 18 population-based registries. Seven registries (Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco (Oakland) and Utah) joined the Surveillance, Epidemiology, and End Results Program in 1973; two registries (Seattle (Puget Sound) and Atlanta) joined in 1974 and 1975, respectively; four registries (Los Angeles, San Jose (Monterey), Rural Georgia and the Alaska Native Tumor Registry) joined in 1992; and five registries (Greater California, Kentucky, Louisiana, New Jersey and Greater Georgia) joined in 2000.[13]

The study cohort included elderly patients (aged 65 years and over) diagnosed with early-stage papillary thyroid carcinoma between 1988 and 2009, with a tumour size of 1 cm or less. The following International Classification of Diseases for Oncology code was used: C73.9 for thyroid gland. Exclusion criteria included regional or distant metastasis, and multiple primaries. Patients in whom surgery was contraindicated were also excluded.

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Two treatment cohorts were established: patients who received surgical therapy (thyroid lobectomy or total thyroidectomy) and patients who received no surgical therapy in the immediate treatment period. The Surveillance, Epidemiology, and End Results registry routinely collects treatment data for four months after diagnosis and, thus, this period is usually used as the timeline for assessing the initial course of therapy.[14]

The Surveillance, Epidemiology, and End Results computer software (SEER*Stat 8.1.5) was utilised to extract data from the database. SAS University Edition software, version 9.4 (SAS Institute, Cary, North Carolina, USA) was used for statistical analysis. Pearson chi-square was employed to evaluate the proportion of patients treated with thyroidectomy. Unadjusted survival analysis was performed using Kaplan–Meier analyses and a Cox proportional hazards regression model. The primary outcome measure was overall cumulative survival. The primary independent variable was the mode of therapy (thyroidectomy *vs* no surgery).

Propensity score analysis was performed to control for allocation bias. Propensity score methods enable one to control for systematic differences in the distribution of measured baseline characteristics of study patients.[15,16] Logistic regression was used to build a model predicting thyroidectomy (*vs* no surgery), including information on patients' age, sex, race, marital status, cancer characteristics (multifocal *vs* unifocal, extrathyroidal extension), and the US state associated with the cancer registry from which patient data were extracted. Interactions between predictor variables were also included in the model. The discrimination of the model was assessed using the c-statistic (goal: c-statistic of at least 0.75–0.90). Once the final model was developed, the overlap in propensity scores was assessed among patients treated with thyroidectomy versus no surgery, to ensure that the distribution of covariates was similar across groups once propensity scores had been adjusted for. The comparative effectiveness of thyroidectomy versus no surgery was assessed by Cox regression using inverse probability weighting (by the inverse of the probability of treatment received). A p value of less than 0.05 was considered statistically significant.

This study was exempt from the Icahn School of Medicine at Mount Sinai Institutional Review Board review because it was conducted using de-identified public data.

Results

From 1988 to 2009, the Surveillance, Epidemiology, and End Results database identified a total of 2323 patients who met the inclusion criteria. The patients' characteristics are displayed in Table I. Patient age ranged from 65 to 97 years. No patient had extrathyroidal extension. Ninety-nine per cent of the patients received surgical therapy.

Kaplan–Meier survival curves are displayed in Figure 1. The five-year overall survival rate was 23 per cent for non-surgical patients compared with 91 per cent for surgical patients ($p < 0.0001$). The results of the Cox regression analysis are shown in Table II. Unadjusted analysis revealed significantly improved survival in surgical patients compared with non-surgical patients (hazard ratio = 0.06; $p < 0.0001$). Propensity score analysis also revealed significantly improved survival in surgical patients compared with non-surgical patients (hazard ratio = 0.11; $p < 0.0001$).

Discussion

The results of this study show that elderly patients with papillary thyroid microcarcinoma who were initially treated with thyroidectomy had improved survival compared with non-surgical patients. Over the past several decades, there has been a rapid increase in the incidence of small thyroid cancers.[2,3,5] Less aggressive management of papillary thyroid microcarcinoma is becoming more acceptable. Several studies have shown that total thyroidectomy does not offer any survival advantage over thyroid lobectomy. Lin and Bhattacharyya examined the effect of extent of thyroidectomy on survival in 7818 patients with papillary microcarcinoma, using the Surveillance, Epidemiology, and End Results database.[17] They found no difference in overall survival between patients treated with total thyroidectomy, near-total or subtotal thyroidectomy, or lobectomy. Similarly, Wang *et al.* found no difference in disease-specific survival between patients undergoing total thyroidectomy and thyroid lobectomy.[18] However, patients who did not undergo any surgery had worse disease-specific survival.

Some authors have suggested that papillary thyroid microcarcinomas should not be treated. Ito *et al.* evaluated the effectiveness of observation without surgical intervention for patients with papillary microcarcinoma.[10] They offered observation or surgical therapy to 732 patients diagnosed with papillary microcarcinoma between 1993 and 2001. A total of 162 patients chose observation. Although there was an increase in the mean tumour size over four years, 70 per cent of tumours did not increase in size. Fifty-six patients subsequently underwent surgical treatment either because of an increase in nodule size or patient preference. Of the 626 total patients who underwent surgical therapy, 50.5 per cent had nodal metastasis, and 42.8 per cent had multifocal disease. The five-year recurrence rate in the surgical group was 5 per cent. No patients died of disease in the surgical group; however, no survival outcomes were reported for the observation group.

A follow-up study by the same research group, which included patients from the previous cohorts, reported on 340 patients treated with observation and 1855 patients treated with immediate surgical therapy.[11] An increase in tumour size was noted in 15.9 per cent of the observation cohort at the 10-year follow up. There was no difference in the rate of new nodal metastasis between the surgical and observation groups. Two mortalities were noted in the surgical

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TABLE I
PATIENTS' CHARACTERISTICS

Variable	Overall*	Thyroidectomy†	No surgery‡	p
Multifocal disease (n (%))	2129 (91.7)	2115 (91.6)	14 (93.3)	0.73
Extrathyroidal invasion (n (%))	0 (0)	0 (0)	0 (0)	N/A
Females (n (%))	1846 (79.5)	1836 (79.6)	10 (66.7)	0.21
Mean age (years)	71.4	71.4	73.3	0.35
Race (n (%))				<0.0001
– Black	137 (5.9)	136 (5.9)	1 (6.7)	
– Other	207 (8.9)	204 (8.8)	3 (20)	

*n = 2323; †n = 2308; ‡n = 15. N/A = not applicable

group. Again, in contrast to our study, there was no comparison of survival outcomes between the two groups. A total of 109 patients from the observation cohort eventually underwent surgical therapy for several reasons, including tumour growth, patient preference and unknown reasons.

A second follow-up study evaluated the effect of age on progression of disease.[12] The authors used three parameters to measure disease progression: increase in tumour size, new lymph node metastasis and progression to clinical disease (defined as tumour size of 12 mm or greater). They found that young age was an independent predictor of disease progression in the observation cohort. Given the low rate of disease progression (especially in the elderly), and the relatively lower life expectancy for elderly patients, it would be expected that surgical therapy should not provide a significant survival advantage over observation. In

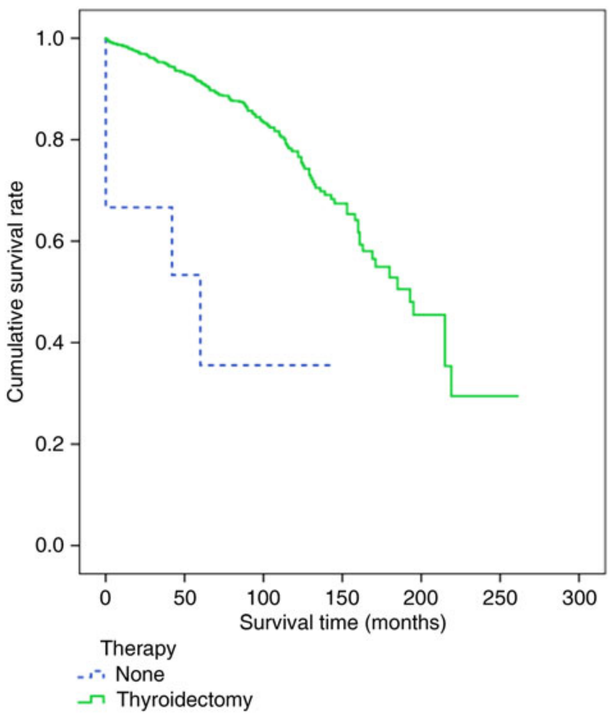

FIG. 1
Overall survival for patients based on therapy. Patients who received thyroidectomy had better disease-specific survival than patients who did not receive thyroidectomy ($p < 0.0001$).

contrast, the results of this current study show that thyroidectomy provides a survival advantage in elderly patients with papillary microcarcinoma.

One potential explanation for the higher mortality rate in the observation group is that those patients may have been selected for observation because of more advanced age, and co-morbidities that made them poor candidates for surgery. This potential source of bias was minimised by including age as a covariate in the propensity score analysis, although there was no significant difference in age between the two cohorts. In addition, patients in whom surgery was contraindicated were excluded from the analysis. Unfortunately, the Surveillance, Epidemiology, and End Results database does not include information on co-morbidity, which is a potential confounder. Overall cumulative survival was chosen as the outcome measure in this study, instead of disease-specific survival, because of the high competing risk of death from other causes in the elderly.[19] As the overall risk of mortality is high in elderly patients, many patients would die of other causes and be censored before having the opportunity to experience the event of interest (cancer-specific death in this case). Consequently, an estimate of the disease-specific survival in this population would be biased.

The main strength of this study lies in the quality of data in the Surveillance, Epidemiology, and End Results database. Utilising this database allows the analysis of a large and diverse population, with outstanding quality control. The catchment areas used in the database were selected for their ability to maintain a high-quality cancer reporting system and for demographic characteristics that are representative of the US population as a whole. In this study, patients with regional and distant metastasis were excluded because these patients usually require radioactive iodine therapy, which would necessitate total thyroidectomy.

This study has several limitations. The Surveillance, Epidemiology, and End Results database does not provide information on tumour size for cases diagnosed prior to 1988. Consequently, these cases were excluded from the analysis. The database also does not include information on disease recurrence. This study is further limited by the retrospective nature of the analysis. However, allocation bias was controlled for

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TABLE II
IMPACT OF THYROIDECTOMY ON OVERALL SURVIVAL

Type of analysis	Co-efficient (SE)	Wald chi-square	Hazard ratio	95% CI	*p*
Unadjusted analysis	−2.81 (0.39)	52.47	0.06	0.03–0.13	<0.0001
Propensity score analysis	−2.23 (0.10)	472.87	0.11	0.09–0.13	<0.0001

SE = standard error; CI = confidence interval

using propensity score analysis with inverse probability weighting. Propensity score methods allow one to control for systematic differences in the distribution of measured baseline characteristics of study patients.[15,16] Furthermore, propensity score analysis using inverse probability weighting allows effective control of allocation bias, without sacrificing statistical power.

- **Some observational studies indicate that small incidental papillary thyroid cancers should not be treated**
- **Given the expected indolent course of papillary microcarcinomas, elderly patients may benefit from non-surgical management**
- **Non-surgical versus surgical therapy was evaluated in elderly papillary thyroid microcarcinoma patients using a large population-based cancer database**
- **Surgical patients had significantly improved survival compared with non-surgical patients**

In conclusion, several studies suggest that papillary thyroid microcarcinoma can be safely treated with observation, especially in elderly patients. However, the findings of this current study suggest that thyroidectomy provides a survival benefit for elderly patients with papillary thyroid microcarcinoma. High-quality prospective studies with comparisons of survival outcomes are needed to better evaluate the comparative effectiveness of immediate thyroidectomy versus observation for elderly patients with papillary thyroid microcarcinoma. This is an important area of research; given the relatively lower life expectancy for elderly patients, this segment of the population may benefit from non-surgical management, if surgical therapy does not provide any significant benefit over observation.

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