Elderly patients with differentiated thyroid cancer not treated with total thyroidectomy and radioiodine have higher mortality rates than elderly patients treated more aggressively

Park HS, Roman SA, Sosa JA.Treatment patterns of aging Americans with differentiated thyroid cancer.Cancer 2009.

SUMMARY

BACKGROUND

The incidence of differentiated thyroid cancer (DTC) increases with age and is more aggressive in patients ≥45 years, a group that is more likely to have biologically aggressive tumors and a poor outcome as compared with that of younger patients. This is of considerable importance as elderly individuals comprise a steadily increasing segment of the US population. Park et al. emphasize that in 2000, Americans ≥65 years of age constituted slightly more than 12% of the population, which is projected to increase to 20% by 2050. This group requires careful study, as there are more than 30,000 new cases of thyroid cancer diagnosed annually in the United States.

PATIENTS AND METHODS

The National Cancer Institutes' Surveillance, Epidemiology, and End Results (SEER) program was used to identify patients with papillary, follicular and Hürthle cell thyroid cancer. This retrospective cohort study identified all patients who had histologically confirmed differentiated thyroid cancer. Excluded from study were patients <45 years of age who were missing data regarding surgery, tumor stage, and diagnoses established by autopsy or only or by death certificate, and patients with tumors < 1 cm.

Included in this study were patient demographics, primary tumor site, histology, tumor stage at diagnosis, and the first course of treatment, including surgery and radiation therapy. Independent demographic variables included age at diagnosis, sex, race/ethnicity, including white, black Asian/Pacific Islander, Other, and Hispanic origin, and the year of diagnosis, from 1988 to 1991, 1992 to 1995, 1996 to 1999, and 2000 to 2003. Clinical variables studied included the number of primary tumors, and surgical therapy described as none, lobectomy/isthmusectomy, or total/near-total thyroidectomy. Data for lymph-node dissection were available only from 1998 through 2002. It was assumed that radioactive isotopes were ^{131}I for all patients with thyroid cancer. Other study variables were disease stage at the time of diagnosis, tumor size, and extension/thyroid capsular invasion and lymph-node metastases. The 6th edition of the American Joint Commission on Cancer (TNM) classification was used to stage the tumors in this study.

RESULTS

The study data (Figure 1)

The study initially focused on 43,657 adults who had a diagnosis of DTC in 1988 through 2003. Of this group, 24,055 (55%) were >45 years of age, and 11,394 (47%) had tumors ≥1 cm. Complete surgical data were available on 10,896 patients (96%), and staging data were available on 9377 patients (83%), including information on tumor size, tumor extension, lymph-node metastases and TNM data. Thus a total of 8899 patients had complete surgery and staging data; 2271 patients (26%) were age 65 to 79 years and 444 (5%) were ≥80 years of age. (Figure 1). Analyses were performed on three age groups: 45 to 64, 65 to 79, and ≥80 years of age.

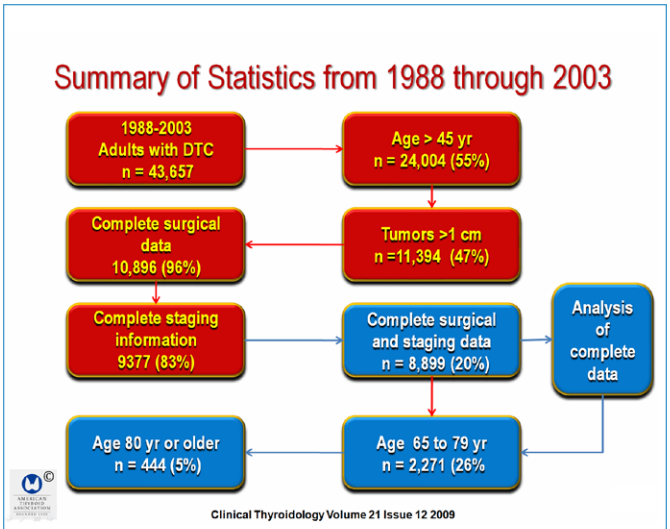

Figure 1. This figure shows the progression of SEER data from 24,044 patients with DTC who had tumors >10 mm and complete surgical and staging information, 2271 of whom were 65 to 79 years.

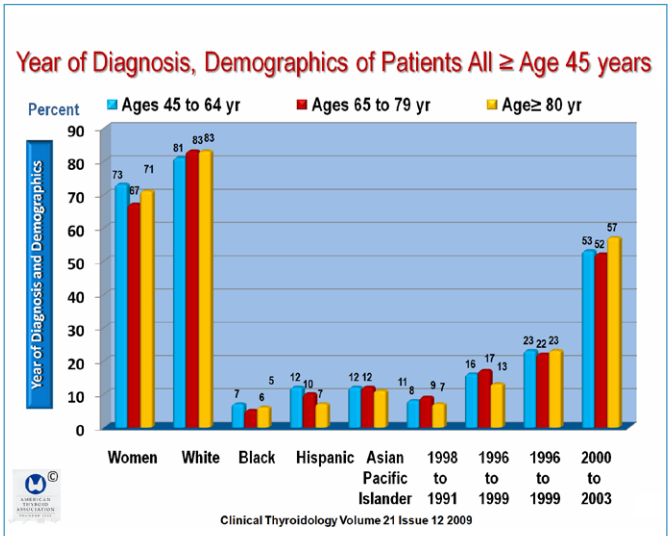

Figure 2. This figure shows the key patient and tumor demographics in this study; 71 % of the patients were women, 81% were white, 89% were non-Hispanic and 70% were married. The figure shows the differences in three age groups: 45 to 64, 65 to 79, and ≥80 years of age. The data for the all figures are derived from Tables 1 to 4 of Park et al. The differences in among the three age are significantly different (P<0.001 for women vs. and among the ethnic groups and race).

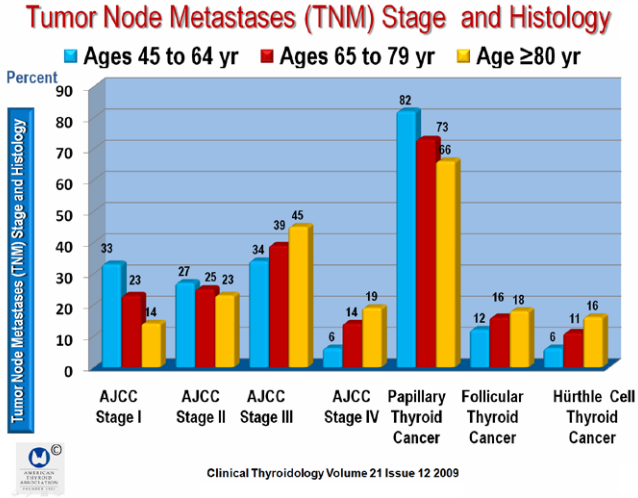

Figure 3. This figure shows the TNM stages (P<0.01) the tumor histology among the age groups (P <0.01) for both histology and TNM stages, comparing the difference in three age groups.

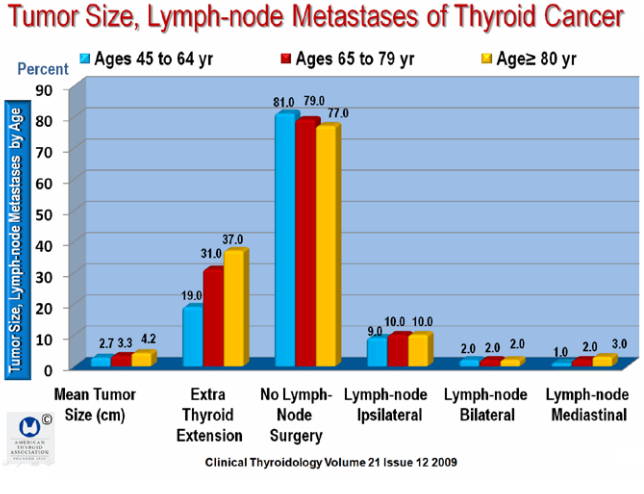

Figure 4. This figure shows tumor size, the location of lymph-node metastases, and the degree of extrathyroid tumor extension in the three age groups (P<0.001 for all three variables).

Patient sex, race and ethnicity (Figure2)

From 1988 to 2003, for all study patients combined, the cohort comprised 71% women; however, with age this changed to 73%, 67% and 71% for the three age groups, respectively. (Figure 2) Also, the ethnicity and race for all patients was 81% white, 6% black, 12% Asian/Pacific Islanders, 11% Hispanic, and 1% Others; however, this changed to 81% 83% and 83% for the three age groups, respectively, during the years shown in Figure 2.

Tumor features (Figures 3 and 4)

Tumor stage increased significantly with increasing age. For all patients combined, 30% of the tumors were stage I, but the rate decreased with advancing age to 33%, 23% and 14% in the three age groups, respectively. For all patients combined, 26% were stage II, but this changed to 27%, 25% and 23% in the three age groups. For all patients combined, 9% of tumors were stage IV; but this also changed with advancing age to 6%, 14% and 19% in patients in the three age groups (P<0.001). (Figure 3)

The rates of papillary thyroid cancer became less frequent with advancing age and other types of thyroid cancer became more common. For all patients combined, the tumor histology was papillary thyroid cancer in 79%, but this changed to 82%, 73%, and 66% of the three patient age groups, respectively. (Figure 3) Tumor size increased with age. Mean tumor size±SD was 3±2.2 cm for all patients combined, but was 2.7±1.9, 3.3±2.1cm and 4.2±5.1 cm for patients in the three age groups, respectively (P< 0.001). (Figure 4) Tumor extension beyond the thyroid capsule was found in 23% of all patients combined, but occurred in 19%, 31%, and 37% in the three age groups. (Figure 4)

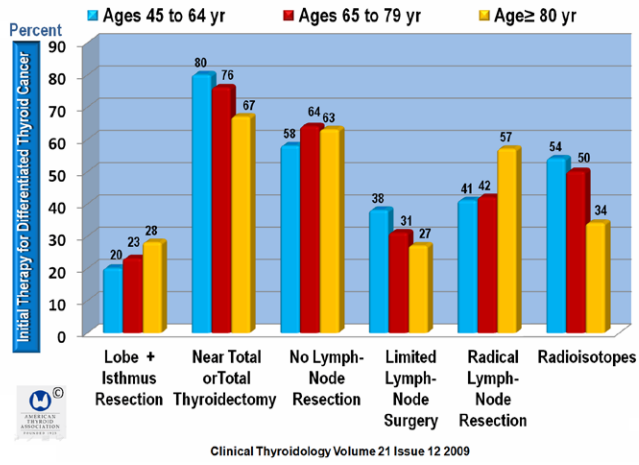

Figure 5. This figure shows the initial surgical and ^{131}I therapy in the three age groups P< 0.001) comparing the differences among age groups in both variables.

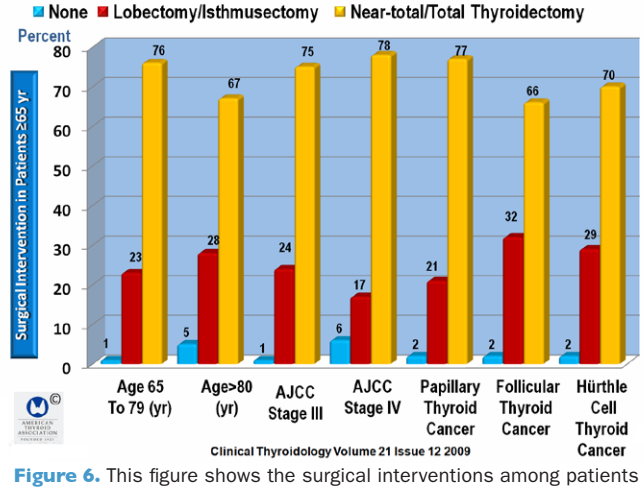

Figure 6. This figure shows the surgical interventions among patients ≥ 65 years of age and the tumor histology in this group, the TNM tumor stage and histology P<0.001) comparing differences among age in all variables.

Initial surgical findings in the primary tumor site (Figures 5 and 6)

In all patients combined, no lymph-node metastases were found in 80% of the patients, but this declined to 82%, 79%, and 77%, in the three age groups; and the rate of ipsilateral cervical lymph-node metastases was 9% for all patients, which changed to 9%, 10% and 10% in the three age groups. The same trend with advancing age was found in bilateral/contralateral/midcervical, mediastinal, and regional metastases (Figure 5)

The surgical intervention among elderly patients ≥ 65 years of age are shown in Figure 6, In all patients combined, no thyroidectomy was performed in 1% (87 patients); and this remained at 1%, 1% and 5% in the three age groups, respectively. (Figure 5) Thyroidectomy in all patients combined, was lobectomy/isthmusectomy in 21%, and this remained approximately the same at 20%, 23% and 28% in the three age groups, respectively. In all patients combined, near-total or total thyroidectomy was performed in 78% of all patients combined; but this changed to 80%, 76% and 67%, in the three groups, respectively. (Figure 5) Among the 87 patients who did not have surgery, it was contraindicated in 15%, was not recommended in 37%, and was refused by the patient or guardian in 24%, and the reason was unknown in 30%. (Figure 5)

No lymphadenectomy was performed in 60% of all patients combined, and in 58%, 64% and 63% of the three age groups, respectively (Figure 5). Limited lymphadenectomy was performed in 36% of all patients combined, and in 38%, 31% and 27% of the three age groups. (Figure 5) Limited lymph-node surgery was done in 36% of all patients combined, and in 38%, 31% and 27%, in the three age groups, respectively.

Initial radioiodine therapy for the primary tumor site (Figure7)

Adjuvant Radioisotope therapy (^{131}I) was administered to 52% of all patients combined, and to 54%, 50%, and 34% of all three age groups, respectively (Figure 5). Of elderly patients 65 to 79 years of age, (50%) received ^{131}I and (50%) did not; of patients ≥80 years of age 34% received ^{131}I and 66% did not. Of patients with ipsilateral cervical lymph-node metastases, 57% received ^{131}I and 43% did not. Of patients with bilateral/contralateral/midcervical lymph-node metastases, 61% received ^{131}I and 31% did not, and of patients with mediastinal lymph node metastases, 56% received ^{131}I and 44% did not, and of patients with distant metastases 50% received ^{131}I and 50% did not. (Figure 7)

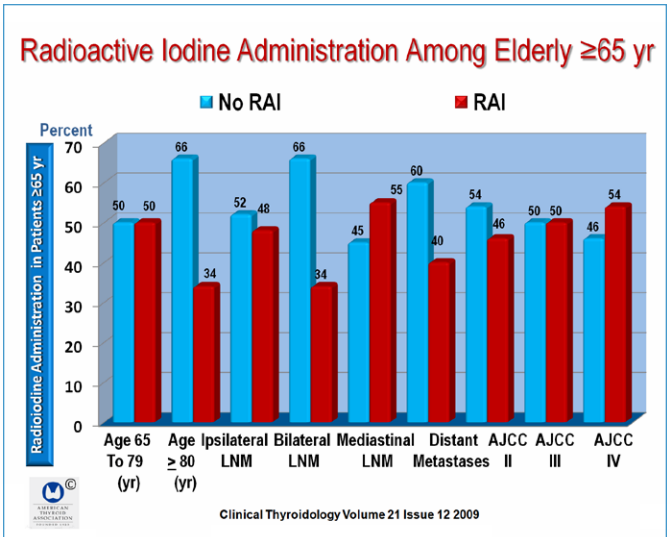

Figure 7. This figure shows the difference in ^{131}I therapy according to patient age, tumor stage and tumor histology. P< 0.001) comparing the differences in variables among the three age groups. LNM = Lymph-Node Metastases.

Second primary tumors

One primary malignancy was found in 83% of all patients combined, but was found in 86%, 75% and 75% in the three age groups, respectively; two primary malignancies were found in 15% of all patients combined, but were found in 12%, 20% and 19% in the three age groups, respectively; three or more primary malignancies were found in 3% of all patients combined, but >3were found in 2%, 5% and 6% of the three age groups.

Bivariate Analysis

Patients ≥65 years who had total or near-total thyroidectomy were more likely to have advanced tumor stage (P<0.05) and nonpapillary histology (P<0.001), and those who were treated with ^{131}I were more likely to have advanced-stage disease (P<0.001)

Multivariate Analysis (Figure 8)

Three variables associated with not undergoing total thyroidectomy were (1) ages 69 to 79 years, odds ratio (OR) 1.27, P<0.001; (2) age≥ 80 years, OR, 2.32, P< 0.001; and (3) stage IV disease OR, 1.35, P<0.05.

The four variables associated with not being treated with^{131}I were (1) ages 65 to 79 years OR, 1.16, P<0.01; (2) age≥80

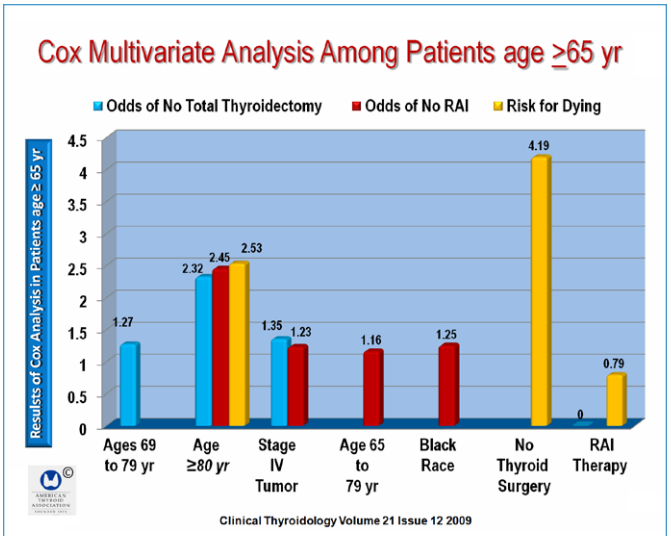

Figure 8. This figure shows the results of a Cox proportional hazards regression module, that found age at the time of diagnosis was a strong predictor of survival; patients aged ≥80 years had a 2.53-fold greater risk for dying than that of patients of ages 65 to 79 years. Not undergoing surgery was associated with a 4.19-fold greater risk for dying as compared with patients undergoing surgery. Stage III and IV disease also was associated with decreased survival (P<0.01 for both no surgery and disease stage). Radioiodine therapy significantly reduced the risk for dying. (OR 0.79)

years, OR, 2.45, P<0.001,(3) stage IV disease, OR, 1.23, P<0.05; and (4) black race, OR, 1.25, p<0.05)

A Cox proportional hazards regression module found age at the time of diagnosis was a strong predictor of survival; patients aged ≥80 years had a 2.53-fold greater risk for dying than that of patients of ages 65 to 79 years. Not undergoing surgery was associated with a 4.19-fold greater risk for dying as compared with patients undergoing surgery. Stage III was associated with and IV disease also was associated with decreased survival (P<0.01 for both no surgery and disease stage). (Figure 8)

CONCLUSION

Elderly patients with differentiated thyroid cancer often fail to receive total thyroidectomy and radioiodine therapy and have higher mortality as compared with patients treated more aggressively.

COMMENTARY

This important study shows that elderly Americans ≥65 years of age with differentiated thyroid cancer larger than 1 cm receive, as a population, less aggressive treatment with total or near-total thyroidectomy and radioiodine therapy as compared with younger patients. This trend is even more evident among patients age 80 years or older and has persisted throughout the 16-year study period encompassed by the Park study. Although the number of patients treated with total or near-total thyroidectomy and radioiodine was increased in older patients with stage IV tumors, older age was still associated with a lower likelihood of being treated with total or near-total thyroidectomy and radioiodine. Yet the elderly population had tumors that were larger, more invasive and more often metastatic than those in younger patients. This all underscores the aggressive tumor behavior in older patients that requires optimal therapy.

The 2009 American Thyroid Association (ATA) management guidelines for differentiated thyroid cancer (1) recommends that patients with thyroid cancer >1cm should be treated with total or near-total thyroidectomy unless there are contraindications to this surgery. This A recommendation is supported by a number of studies, including a study by Bilimoria et al. (2) of over 50,000 patients with papillary thyroid cancer that found on multivariate analysis that total thyroidectomy significantly improved recurrence and survival rates for tumors >1.0 cm. Even patients with 1 to 2 cm tumors were found to have a 24% higher risk of recurrence and a 49% higher risk of thyroid cancer mortality with lobectomy as compared with total or near-total thyroidectomy (P< 0.04 and p<0.04, respectively). Other large studies also have found that recurrence and mortality rates in low-risk patients are significantly reduced by total or near total thyroidectomy (3;4). Despite these findings, the Park study found that older patients are often treated with less than total thyroidectomy without radioiodine therapy for reasons that remain elusive.

In another study by Bilimoria et al. (5) that examined the use of total thyroidectomy in over 90,00 patients, found that the its use increased from approximately 71% in 1985 to 90% in 2003 (P< .0001). Patients were less likely to have total thyroidectomy if they were black, older than 45 years, had Medicare, had lower household incomes, or had less education (P< .0001). Patients treated at high-volume or academic centers were more likely to receive total thyroidectomy than were patients treated at low-volume or community hospitals (P <0.0001). The disparities in access to care and the use of total thyroidectomy were thus related to several factors, including the patient, the tumor, and the hospital.

Park et al. found that among 87 patients who did not undergo surgery, the procedure was contraindicated in 15%, was not recommended in 37%, was refused by the patient or guardian in 24%, and the reason was unknown in 30%. This small sample does not provide a full understanding of this problem. Even less data were available to know why elderly patients failed to receive radioiodine.

Recommendation 32 of the ATA guidelines advises RAI for remnant ablation for all patients with known distant metastases, gross extrathyroidal extension of the tumor regardless of tumor size, or primary tumor size >4 cm, even in the absence of other higher risk features, and is recommended for selected patients with 1 to 4cm thyroid cancers confined to the thyroid with documented lymph-node metastases or other higher risk features. Radioiodine ablation is recommended when the combination of age, tumor size, lymph-node status, and individual histology predicts an intermediate to high risk of recurrence or death from thyroid cancer. This is a C Recommendation (expert opinion). Most elderly patients meet the criteria for radioiodine remnant ablation. The conundrum remains as to why elderly patients in the Park study were not treated with surgery and radioiodine. One possible reason for the omission of radioiodine therapy is that large thyroid cancer databases are derived from hospitalized patients that often miss therapies such as radioiodine provided in an outpatient setting (6).

Comorbidities contribute to poor outcomes in the elderly. For example, a population-based observational study from the Netherlands (7) found that hypertension was the most frequent comorbidity with thyroid cancer (18%), followed by other serious conditions such as cardiovascular diseases (6%) and diabetes mellitus (6%). The prevalence of hypertension was twice as high as expected in all age groups, yet comorbidity was not independently associated with overall survival up to 5 years, which might be insufficient follow-up to fully evaluate the effect of comorbidity.

The observations from the Netherlands are similar to those in a recent study by Masuyama et al. (8) that compared the clinical characteristics of thyroid cancers in 85 elderly patients ≥75 years of age with those of 37 patients <30 years of age. Elderly patients with papillary thyroid carcinoma had a significantly worse cumulative 5-year survival rate with papillary

thyroid cancer than that of young patients (92% vs. 100%, P = 0.03). The cumulative 2-year survival with high-risk tumors was significantly lower in elderly patients treated surgically compared with those who were not so treated (80% vs. 100%, P = 0.02). Furthermore, the quality of life was severely impaired in 67% and 6% of the patients treated with and without surgical therapy, respectively. This study demonstrated that surgery for thyroid cancer increases the survival rate and promotes the quality of life in elderly patients if they are well enough to undergo surgery.

A study of octogenarians by Mekel et al (9) found that the two independent risk factors predicting postoperative complications in patients undergoing thyroid surgery were male sex and a high American Society of Anesthesiologists risk score. Of importance, advanced age by itself was not an independent factor predicting postoperative complications; instead it was comorbidities that predicted complications. This is similar to the Park study in which elderly patients who did not have surgery did not report higher rates of contraindications to surgery. Moreover, there was no significant difference among age groups with regard to the contraindication rates cited as the primary reason for not undergoing surgery.

Park et al. clearly demonstrated that many elderly patients with DTC received less aggressive surgery and RAI therapy, despite having more advanced disease, and had improved survival with aggressive therapy. This study, along with others, suggests a careful preoperative evaluation and consultation with the patient should be performed before recommending limited therapy for elderly patients with thyroid cancer.

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