CLINICAL THYROIDOLOGY

Cancer-specific survival is significantly improved by total thyroidectomy and by a trend for ^{131}I RRA, but not for disease-free recurrence

Doi SA, Engel JM, Onitilo AA. Total thyroidectomy followed by postsurgical remnant ablation may improve cancer specific survival in differentiated thyroid carcinoma. Clin Nucl Med 2010;35:396-9.

SUMMARY

BACKGROUND

Most patients with differentiated thyroid cancer (DTC) have low-risk tumors. As a result, the extent of thyroidectomy that provides optimal outcome is a matter of debate, mainly because there are no prospective randomized studies of the optimal initial surgery and the role of postoperative radioiodine (^{131}I) for thyroid remnant ablation (RRA) in this group of patients with low-risk tumors. The goal of this study was to determine the effect of thyroidectomy followed by postsurgical RRA on the survival of patients with DTC after adjusting for the risk of tumor stage.

METHODS AND PATIENTS

The data for this study are derived from Marshfield Clinic electronic medical records, which provided a cohort of patients with DTC treated from January 1, 1987, through January 31, 2006. Patients with medullary or anaplastic thyroid cancer and cases with missing data were excluded from the study. The following data were obtained on each patient with DTC: age, sex, tumor histology, tumor size, and presence of distant metastases, lymph-node metastases, pathological diagnosis, recurrence and location of recurrence, cause of death ,and length of survival.

Patients were stratified by the extent of surgery into one of two heterogeneous groups to distinguish total or near-total thyroidectomy versus less thyroid resection. One group was designated as “total,” which included total, or near-total thyroidectomy, and the “other“ category included subtotal thyroidectomy or lobectomy with or without isthmusectomy. Patients who had removal of less than a lobe were categorized as having nodulectomy or were classified as thyroidectomy, not otherwise specified, which was included in the category “other.” If a patient initially had lobectomy and then went on to have a complete thyroidectomy, the patient was categorized as having had total thyroidectomy.

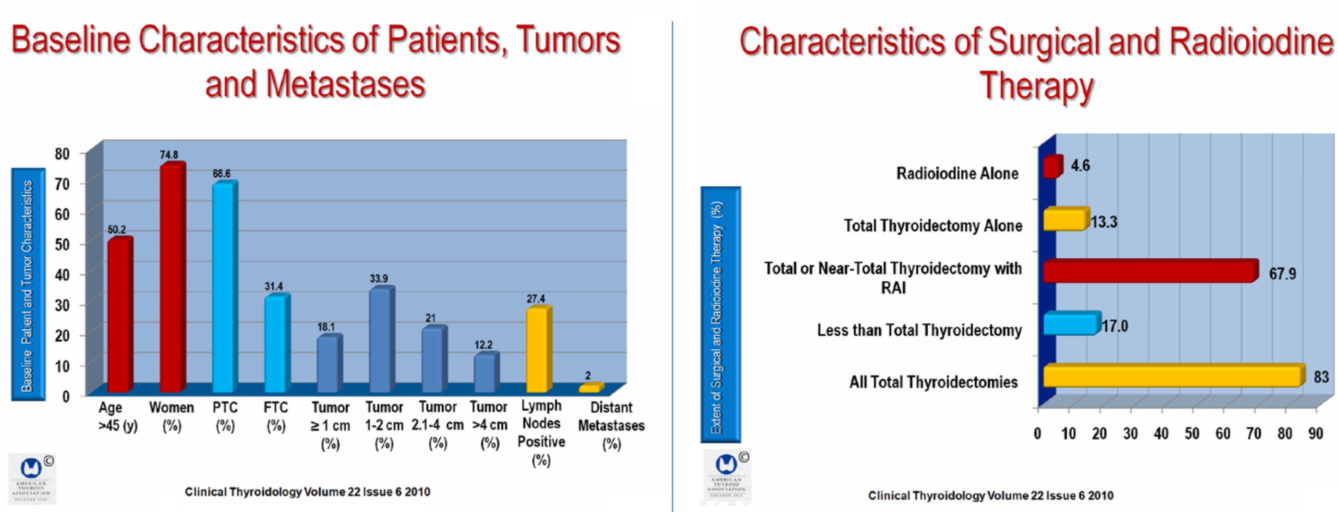
Data on the type of radiation therapy were obtained using the cancer registry database and were verified manually from the Marshfield Clinic electronic medical record. The amount of ^{131}I therapy was determined from the database by manually extracting these data. External beam radiation was used as adjuvant treatment in few cases and was not examined in this analysis.

The Marshfield Clinic risk stratification

The Marshfield quantitative tumor–node–metastasis score was used, which is a unique score that is the sum of the following: histopathology, score 1 = not papillary thyroid carcinoma (PTC), otherwise score 0; age, score 4 was age ≥45 years, otherwise 0; lymph-nodes, score 4 was regional lymph-node metastasis, otherwise score 0; tumor, score 6 was tumor >4 cm in greatest dimension limited to the thyroid or any tumor with extrathyroid extension. The resulting continuous distribution of total risk scores across all patients in the model ranges from 0 to 15 and was used to adjust the Cox proportional-hazards model.

Multivariate analysis

Two treatment variables were dichotomized into the extent of surgery (total thyroidectomy vs. a composite of total thyroidectomy and RRA).



Figures 1A and 1B. 1A, This figure shows the baseline characteristics of patients, primary tumor size, lymph-node metastases and distant metastases. 1B, This figure summarizes the surgical and radioiodine features in the study group (%). RAI = radioactive iodine. The data for these figures are derived from the text and Table 3 of Doi et al.

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RESULTS

Patient and tumor demographics (Figure 1)

The study cohort comprised 614 patients, among whom 459 were women (74.8%) and 155 were men (25.2%). Of this group of 614 patients, 308 (50.2%) were more than 45 years of age. A total of 421 (68.6%) had PTC, and the remaining 193 (31.4%) had follicular thyroid carcinoma. The primary tumor was ≥1 cm in 111 patients (18.1%), 1 to 2 cm in 208 (33.9%), 2.1 to 4 cm in 166 (27%), >4 cm in 75 (12.2%), and of unknown size in 54 (8.8%). Lymph-node metastases were positive in 168 patients (27.4%), negative in 416 (67.8%), and not examined in 30 (4.8%), and metastases were present in 12 (2%) (Figure 1).

Surgical and radioiodine therapy (Figure 2)

Of the 614 patients with DTC, 608 had either total thyroidectomy with bilateral resection, including total or near-total thyroidectomy or lobectomy, or subtotal or unilateral resection, including lobectomy with or without isthmusectomy. Of the 608 patients, 504 (83%) had total thyroidectomy, 104 (17%) had less surgery, and 569 (93.6%) had complete information on tumor size. Treatment was total (bilateral total) or near-total thyroidectomy with RRA in 417 patients (67.9%), total thyroidectomy alone in 82 (13.3%), radioiodine alone in 28 (4.6%), and neither treatment in 59 patients (9.6%) or no information in 28 (4.6%)

Multivariate analysis (Figure 3)

For multivariate analysis, two treatment variables were created: surgical extent dichotomized to total versus other surgery, and a composite of total surgery and RRA, comprising 4 groups: (1) both total surgery and RRA, (2) total surgery only, (3) RRA only, and (4) neither intervention. The outcome was cancer-specific survival, defined as time from diagnosis to a cancer specific-death. The odds for each group was compared with the reference standard of reaching the end point first (i.e., early cancer-specific death after adjusting for the Marshfield quantitative tumor–node–metastasis risk score.

The odds ratio (OR) with 95% confidence interval (95% CI) was an independent variable predicting an adverse outcome of cancer-specific mortality earlier than expected in an individual without effective surgery and RRA. The reference range for expected survival was initial therapy with total thyroidectomy plus RRA (n = 398 patients). Having neither total thyroidectomy nor RRA was associated with a fourfold greater risk of reaching an early end point of cancer-morality (OR, 8.1; 95% CI, 0.8 to 79.9; P = 0.07). RRA without total thyroidectomy was associated with reaching an early end point of cancer-specific mortality (OR, 3.7; 95% CI, 0.9 to 15.4; P = 0.07). Total thyroidectomy without RRA had an OR of 3.7 (95% CI, 0.9 to 15.4; P = 0.07) of reaching an early end point of cancer-specific mortality. Treatment with both total thyroidectomy and RRA had an OR of 2.0 (95% CI, 0.04 to 9.8; of reaching an early end point.

There was a trend for cancer-specific death occurring earlier in patients who did not have RRA. There was no relationship between disease-free survival and either surgical status or RRA.

CONCLUSION

The data in this study supports the routine use of total or near-total thyroidectomy with a trend for ^{131}I RRA for cancer specific-survival but not for tumor recurrence.

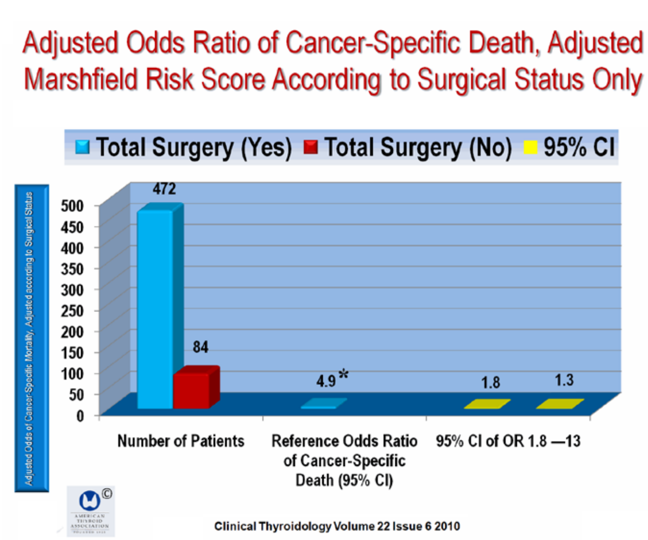

Figure 2. This figure shows the odds ratios of cancer-specific death adjusted for the Marshfield risk score according to surgical status. Total or subtotal thyroidectomy was designated as total surgery, and less surgery comprises subtotal thyroidectomy or lobectomy with or without isthmusectomy. The data for this figure were derived from Table 2 of Doi et al.

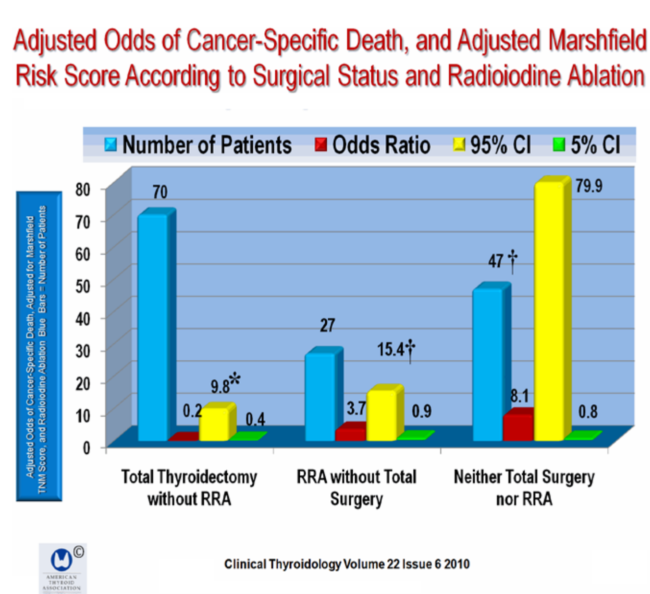

Figure 3. This figure shows the adjusted odds ratios of cancer-specific death, adjusted by Marshfield Risk TNM Score) according to the surgical status, and RRA by multivariable Cox regression analysis.

COMMENTATRY

Of 614 patients with DTC, 504 (83%) had total thyroidectomy and 104 (17%) had less surgery. A total of 24 to 297 mCi (mean, 116) was administered to 394 patients who had total thyroidectomy. Ten-year survival rates were higher for patients who had total thyroidectomy as compared with lobectomy (96% vs. 84%, P<0.001). Ten-year survival for complete versus incomplete surgery for tumor stages 1 and 2 was 99% versus 96%, and for stages 3 and 4 it was 88% versus 52%. Cancer-specific deaths tended to occur earlier in patients not treated with RRA. There was no overall relationship between disease-free survival and RRA or surgery, but in the higher-risk categories, surgery remained significant. As a consequence, the authors advise the routine use of both total and near-total thyroidectomy followed by RRA postoperatively for all risk categories in DTC. Still, although the effect of surgery seems clear, there was only a trend toward improvement with RRA for cancer-specific survival. Still, the study found a lack of surgical and RRA effect on disease-free survival, based on the premises that the patients have low-risk tumors.

Much of this study is predicated on the unique Marshfield quantitative tumor–node–metastasis tumor score, published in 2009 (1), which was formulated on the basis of simplifying the TNM staging system, which requires some edification. The 2009 study (1) was based on the notion that the TNM system can be cumbersome to implement clinically, given the large number of stages within the TNM system. The authors thus decided to quantify each variable in the TNM system to arrive at a simplified quantitative alternative to the TNM system, termed QTNM. The Marshfield electronic record system was used to identify 614 cases of DTC managed from 1987 to 2006 (the same patients in the current study). Cancer-specific survival and disease-free survival were calculated by the Kaplan–Meier method, and a simplified QTNM score was devised with a Cox proportional-hazards model that quantified the TNM system as follows: 4 points each for age >45 years and presence of neck lymph-node metastases, 6 points for a primary tumor >4 cm or extrathyroidal extension, and 1 point for nonpapillary DTC.

A sum of 0 to 5 points was designated as low risk, 6 to 10 points as intermediate risk, and 11 to 15 points as high risk. The authors compared this with the conventional TNM system and two other systems, demonstrating a similar or better discrimination with the QTNM that was maintained when this risk stratification was applied to a unique validation set. The authors concluded that the QTNM system as opposed to the conventional TNM system seems to be a simple and effective method for risk stratification for both recurrence and cancer-specific mortality. Still, in the present study, the stratification of various surgical procedures was relatively wide, raising the question whether this grouping might have produced an ascertainment bias.

It is difficult to evaluate the efficacy of surgical therapy and RRA without directly integrating the multiple features of patient age, tumor size, tumor invasion, lymph-node metastases, and distant metastases to mention a few, and it is hence difficult to translate the QTMN score back to the TNM score, for those who use the TNM score.

Several conclusions in the study by Doi et al. are troublesome. The use of RRA in this group of low-risk patients showed a trend in the improvement of cancer-specific mortality. Although total thyroidectomy has a positive effect on cancer-specific mortality, RRA is of only borderline significance for the end point, although hazard ratios for RRA are indicative of improved cancer-specific survival. Moreover, the study could not verify an effect of disease-free survival. The authors suggest that the potential for recurrent disease is more strongly associated with risk score than with the therapeutic interventions, implying that low-risk patients have better disease-free survival, regardless of the use of therapeutic interventions, but suggest that if these interventions are used, cancer-specific survival is probably related to the initial tumor and is improved even in low-risk patients. As a consequence, the authors advocate total thyroidectomy at initial diagnosis along with RRA, which they opine confers the best possible prognosis for the patient. Yet the authors were unable to run analyses on the low-risk group alone, as there were few outcomes in this group and a stratified analysis was not possible. Lastly, tumor size was unknown in 54 patients (8.8%), suggesting that the tumor staging in this study may have not been fully responsive to tumor size, which has a well-described effect on cancer-specific mortality and disease-free survival.

There are a few robust studies that have found total thyroidectomy to significantly decrease cancer-specific mortality in patients with DTC, including some older studies that find a decrease in mortality and recurrence rates with ^{131}I therapy (2-4). All of these studies have been tightly linked to tumor features, patient age, and histology. Two meta-analyses by Sawka et al. (5,6) failed to find an effect of RRA on thyroid cancer–specific mortality; however, a pooled analysis of 10-year outcomes found that locoregional recurrence was 4% in ^{131}I treated patients and 10% in controls (relative risk, 0.31) and the rate of distant metastases was 2% in ^{131}I treated patients and 4% in controls, and was associated with an absolute decrease in distant metastases in ^{131}I-RRA-treated patients. Still, PTMC fails to show a significant response to ^{131}I RRA, whereas patients with PTMC may be responsive to RRA in tumors invading surrounding tissues or organs, but this occurs rarely.

A relatively recent study by Bilimoria et al. (7) found that 10-year cancer-specific mortality and disease-free recurrence rates were especially related to tumor features and thyroid surgery, especially tumor size and total thyroidectomy, which clearly were found to have a major impact on outcome. For example, the rates of PTC recurrence increased incrementally with tumor sizes ranging from <1 cm (4.6%) to >8 cm, with a recurrence rate of 24.8%. Likewise, the 10-year cancer-specific mortality rates of PTC increase from 2% with tumors <1 cm and incrementally increase to 19% with tumors >8 cm. This study concluded that for patients with primary tumors ≥1 cm, lobectomy was associated with a 15% higher recurrence rate (P = 0.04) and a 31% higher risk of 10-year cancer-specific mortality (P = 0.04). Still, the trend for cancer-specific death occurring earlier in patients who did not have RRA is found in few studies.

— Ernest L. Mazzaferri, MD, MACP

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