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CLINICAL REVIEW 170

A Systematic Review and Metaanalysis of the Effectiveness of Radioactive Iodine Remnant Ablation for Well-Differentiated Thyroid Cancer

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Radioactive iodine remnant ablation destroys residual thyroid tissue after surgical resection of papillary or follicular thyroid cancer. We systematically reviewed 1543 English references to determine whether remnant ablation decreases the risk of thyroid cancer-related death or recurrence after bilateral thyroidectomy for papillary or follicular thyroid cancer. In 13 cohort studies in which the analysis of thyroid cancer-related outcomes was statistically adjusted to a variable degree for prognostic factors or cointerventions, rates of recurrences of thyroid cancer-related outcomes were significantly decreased in the following: one of seven studies examining thyroid cancer-related mortality, three of six studies examining any tumor recurrence, three of three studies examining locoregional recurrence, and two of three studies examining distant metastases. Thyroid hormone suppressive therapy was not adjusted for in the majority of these analyses. In 18 cohort studies not adjusted for prognostic factors or interventions, the benefit of radioactive iodine ablation in decreasing the thyroid cancer-related mortality and any recurrence at 10 yr was inconsistent among centers. However, pooled analyses were suggestive of a statistically significant treatment effect of ablation for the following 10-yr outcomes: locoregional recurrence (relative risk of 0.31, 95% confidence interval, 0.2, 0.49) and distant metastases (absolute decrease in risk 3%, 95% confidence interval, risk decreases 1–4%). In conclusion, radioactive iodine ablation may be beneficial in decreasing recurrence of well-differentiated thyroid cancer; however, results are inconsistent among centers for some outcomes, and the incremental benefit of remnant ablation in low-risk patients treated with bilateral thyroidectomy and thyroid hormone suppressive therapy is unclear. (*J Clin Endocrinol Metab* 89: 3668–3676, 2004)

THYROID CANCER IS the most common endocrine malignancy (1–3). The most frequent histologic subtype of thyroid carcinoma is papillary (accounting for 80.2% of cases), followed by follicular carcinoma (11.4% of cases), which are commonly collectively referred to as well-differentiated thyroid cancer (3). Currently in the United States, 64.8% of patients with papillary carcinoma and 54.5% of patients with follicular carcinoma are treated with total or near-total thyroidectomy (3). According to an American national cancer database, approximately 38% of such patients also receive postoperative radioactive iodine (RAI)-131 ablation or therapy, although this estimate may be low due to lack of physician registration of this intervention (4). RAI ablation (or remnant ablation) refers to the destruction of residual macroscopically normal thyroid tissue after complete gross surgical resection of cancer. The theoretical goals of RAI ablation are to destroy any residual microscopic thyroid carcinoma and facilitate follow-up and early detection of recurrent or metastatic disease by measurement of serum thyroglobulin or RAI scanning (thereby enabling earlier treatment of recurrent disease). Recommendations for remnant ablation are variable between specialty organizations (5–9).

Our aim was to systematically review the literature to determine whether radioactive iodine remnant ablation decreases the risk of thyroid cancer-related death or recurrence in adults who have had grossly complete resection of papillary or follicular thyroid carcinoma.

Abbreviations: CI, Confidence interval; RAI, radioactive iodine; RD, risk difference; RR, relative risk.

This review will serve as the basis of the practice guideline on radioactive iodine ablation for well-differentiated thyroid cancer being developed by the Radiopharmaceutical Guidelines Groups of the Program in Evidence-Based Care, Cancer Care Ontario.

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Patients and Methods

Selection of relevant studies for review

A committee consisting of an endocrinologist, radiation oncologist, epidemiologist, methodologist, and nuclear medicine physician formulated eligibility criteria for the inclusion of studies before commencing the search strategy. Studies were eligible for inclusion if they were

randomized controlled trials or cohort studies of adult patients who had: 1) well-differentiated thyroid cancer (defined as papillary, follicular, or follicular variant of papillary); 2) surgical treatment involving bilateral resection (*i.e.* surgery that was more extensive than ipsilateral lobectomy and isthmectomy); 3) RAI ablation given within 1 yr after the operation; 4) a median or mean follow-up period of at least 5 yr; and 5) listing of the outcome(s) of cancer-related deaths, any cancer recurrence, local regional recurrence in the thyroid bed, or regional lymph nodes, or distant metastases (all at 10 yr for data unadjusted for prognostic factors or interventions). When studies of overlapping groups of patients were identified (*i.e.* updates of previously published cohort studies), only the report with the largest number of patients was included unless additional reports provided nonoverlapping information (such as reports of different outcomes).

Search strategy

Two investigators independently searched each of the electronic databases, including: Medline (1966–September 2002), Pre-Medline, Cochrane Database for Systematic Reviews, American College of Physicians Journal Club (September 1991–October 2002), Database of Abstracts and Reviews, The Controlled Clinical Trials Database, Cancerlit (1975–2002); Proceedings of the American Society of Clinical Oncology (1997–2002), Proceedings of the American Society for Therapeutic Radiology and Oncology (1997–2002), and Embase (1988 to August 2002). The search was restricted to English-language publications involving adults 19 yr of age and older and included the following terms: papillary thyroid carcinoma, follicular thyroid carcinoma, RAI, iodine radio isotopes, thyroid neoplasms, and iodine-131. In addition to these electronic searches, the tables of contents of online versions of: Thyroid (January 2001 through January 2002), Journal of Clinical Endocrinology & Metabolism (October 1996 through October 2002), Clinical Endocrinology (January 1998 through November 2002), and the Journal of Nuclear Medicine (January 1996 through November 2002) were included. Experts in endocrinology and nuclear medicine were also contacted to obtain further references. Other sources for publications included "related articles" that were identified through PubMed as well as articles cited in guidelines from the British Thyroid Association, The Northern Cancer Network, The National Comprehensive Cancer Network, the American Association of Clinical Endocrinologists, and the American Thyroid Association.

All of the retrieved abstracts and titles were independently reviewed by two different investigators to determine eligibility and relevance. Disagreements were resolved by consensus; both reviewers agreed completely on the studies deemed relevant for abstraction (10–60) and those that were finally included in the review (after exclusion of overlapping studies).

Data abstraction

One investigator abstracted the data. If numbers of events were not explicitly stated in studies, primary authors were contacted to obtain primary patient data, or data were extrapolated from graphs (by measurement of proportions on survival curves and multiplication by the initial sample size) or tabulated proportions of events (multiplied by number of patients initially in the study). If detailed information on completeness of resection of gross disease was absent in studies, we abstracted data from subgroup analyses comprised mainly of low-risk patients (as defined by the individual author or the standard staging system) because low-risk patients would typically have complete surgical resection of gross tumor. The definitions of low-risk staging (if not provided by individual authors within the included papers) were defined based on a previously published review (61). If "completely resected" or "low risk" were not specified by original authors, summaries of multivariable analyses were still summarized, if stage of disease was adjusted for within the statistical models.

Statistics

Data adjusted for prognostic factors or cointerventions was tabulated as presented in the primary studies, and pooling was not performed because variables adjusted for in individual models differed between studies. A statistically significant result was defined by $P < 0.05$ for multivariable analyses. For unadjusted data (consisting of crude data, without statistical adjustment for prognostic factors or cointerventions), pooled analyses were performed for the 10-yr outcomes of thyroid cancer-specific mortality, any recurrence, local recurrence (in the neck or upper mediastinum), and distant metastases, respectively. Studies were categorized according to thyroid cancer histology (papillary or follicular, with follicular variant of papillary cancer included in the papillary subset). Studies in which separate analyses were not performed for patients with papillary or follicular cancer were grouped in a category "papillary and follicular." A χ^2 analysis was performed to assess for heterogeneity of treatment effect for each outcome and if present ($P < 0.10$), then a pooled estimate of treatment effect was not presented. A sample funnel plot was created for the outcome of any thyroid cancer recurrence at 10 yr to assess for publication bias. A random effects model was used to estimate pooled treatment effects, if statistically significant heterogeneity of treatment effect was not noted The relative risk (RR) with 95% confidence interval (CI) was used to estimate treatment effect for any recurrence and locoregional recurrence but a risk difference (RD) was calculated for evaluation of cause-specific mortality and distant metastases, given infrequent event rates for the latter outcomes. A risk difference was defined by the event rate in the nonablated group minus the event rate in the ablated group. This is the decrease in absolute event rate attributed to the intervention. Review Manager Version 4.1 for Windows (Cochrane Collaboration, Oxford, UK) was used for all analyses.

Results

Results of the search and assessment of methodologic quality

The detailed searches yielded no randomized controlled trials. In total 1504 abstracts and titles were obtained through electronic searches, and of these 228, full-text papers were deemed relevant and retrieved. Another 39 full-text articles identified through hand searches were also retrieved. Thus, 267 unique full-text papers were independently reviewed by the two investigators; 51 of these were deemed relevant by both and were examined in detail (10–60) (Fig. 1). Following this review, 23 studies met the inclusion/exclusion criteria for this review. Thirteen of these studies performed a multivariable analysis (10, 12, 14, 19, 23–25, 29, 35, 42, 55, 57, 60), and 18 studies reported unadjusted data (10–12, 14, 15, 18, 20, 23, 24, 28, 38, 41, 43, 46, 55, 57, 59, 60).

Both reviewers agreed that the adjudicators of outcomes were not blinded to the therapy received in any of the studies. A funnel plot for the outcome of any thyroid cancer-related occurrence did not suggest any publication bias.

Summary of analyses statistically adjusted for prognostic factors and/or cointerventions

Adjusted analyses: thyroid cancer-related mortality. A summary of adjusted analyses examining the outcome of thyroid-cancer related mortality for patients with papillary and follicular thyroid carcinoma is shown in Table 1 (adjusted for prognostic factors and/or cointerventions). One study reported a statistically significant benefit of RAI ablation in decreasing thyroid cancer-related mortality ($P < 0.05$) (10). Six other studies (12, 23, 24, 35, 42, 60) examining 135-2282 patients, with overall cause-specific mortality rates ranging from 1.3 to 15% at 10 yr, did not report a mortality advantage for ablated patients, after adjustment for prognostic factors and cointerventions. RAI therapy was not a significant variable in univariate analysis, so this was not entered in a multivariable model in another study (35).

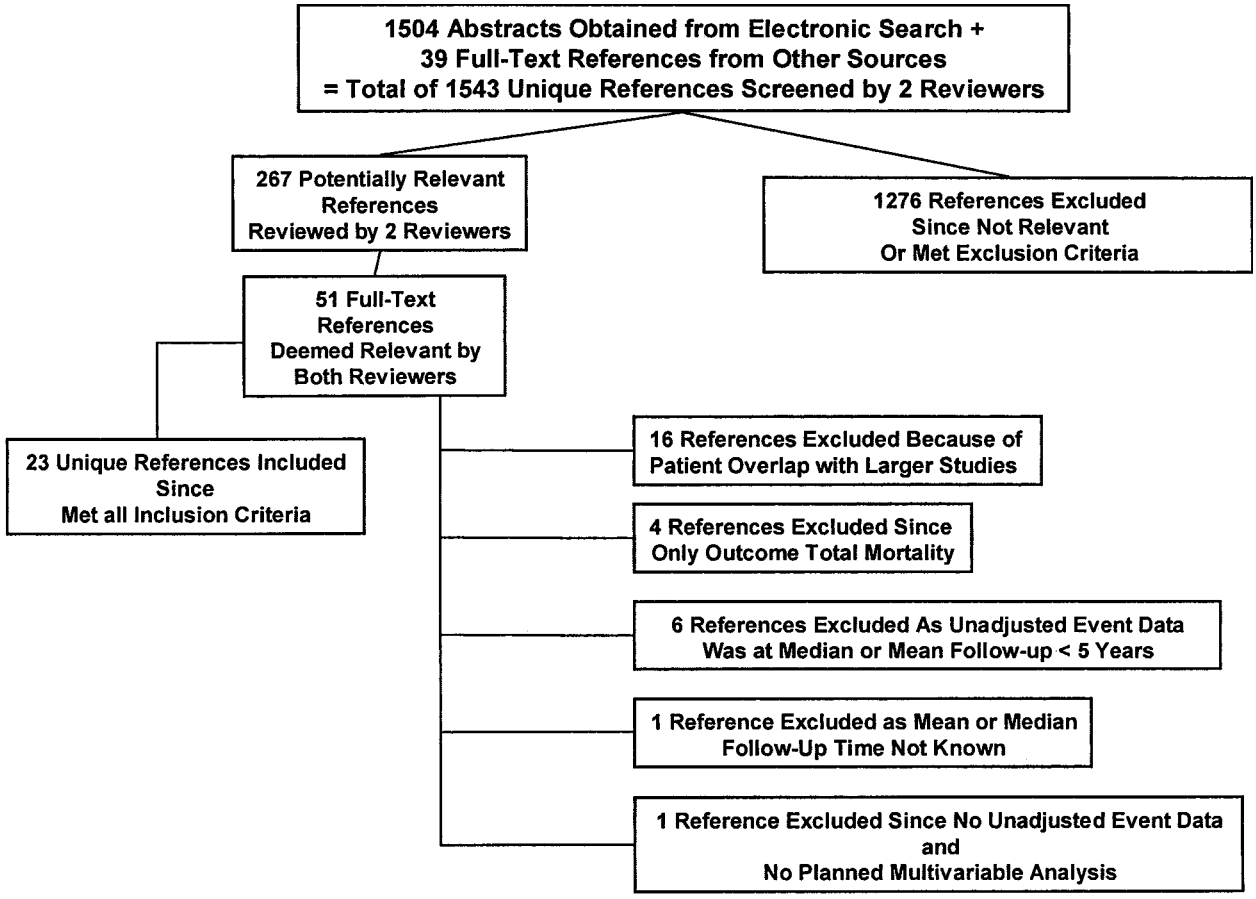

FIG. 1. Process of exclusion of studies.

Adjusted analyses: any tumor recurrence. Postoperative RAI therapy decreased the adjusted risk of any recurrence in the two largest studies (1501 and 1599 patients, respectively) (10, 57) as well as a smaller study (187 patients) (24) (Table 1). All three positive studies had recurrence rates of over 20% with median follow-up periods ranging from 10.6 to 16.6 yr. However, a positive treatment effect of RAI was not noted in three smaller studies (including 177, 273, and 229 patients, respectively) (25, 29, 55). Of note, the lowest event rate (3.9%, median follow-up 7.3 yr) was seen in a study of patients with tumors 1 cm or less in diameter (38% of whom had multifocal disease and 43% of whom had lymph node metastases), and ablation was not effective in decreasing recurrence in that study (55).

Adjusted analyses: locoregional recurrence. Postoperative RAI ablation decreased the adjusted risk of locoregional recurrence in three studies of 135, 587, and 382 patients with papillary or follicular thyroid cancer, with relative risks (95% CI) of 0.05 (0.005, 0.51) in follicular patients (60), 0.29 (0.17, 0.51) in papillary patients (12), and 0.4 (0.2, 0.7) in papillary and follicular patients (23).

Adjusted analyses: distant metastases. Postoperative RAI therapy decreased the adjusted risk of distant metastatic recurrence in patients with papillary or follicular thyroid cancer in the largest study (n = 1510). In individuals with distant metastases at the time of diagnosis, the hazard ratio was 0.6 (95% CI 0.5, 0.8, $P = 0.002$) (10). In a study of 587 patients with papillary carcinoma, RAI ablation reduced the adjusted risk of distant metastases (adjusted RR 0.2, 95% CI 0.07, 0.64, $P = 0.006$) (12). However, the same investigators did not detect a reduced risk of distant metastatic recurrence in 135 patients with follicular thyroid cancer (median follow-up 10.8 yr) (60).

Multivariable analyses: adjustment for thyroid hormone suppressive therapy. After adjustment for postoperative thyroid hormone suppressive therapy, RAI ablation was observed to reduce the risk of thyroid cancer-related mortality of borderline statistical significance in one study (multivariable odds ratio in nonablated patients 1.54, 95% CI 1.01, 2.35, $P = 0.05$) (42), but no benefit was observed for the outcome of any recurrence in another study (29). Thyroid hormone suppressive therapy was not adjusted for in any of the studies examining the outcomes of locoregional recurrence nor distant metastases.

Analyses statistically unadjusted for prognostic variables or cointerventions

Effect of RAI ablation on 10-yr thyroid cancer-related mortality and recurrences in unadjusted analyses. Characteristics of patients in the studies included in the review of unadjusted outcomes of thyroid cancer and mortality and recurrence are shown in Table 2. The dose of RAI administered was not reported in several studies (11, 14, 18, 20) and ranged from 28 to 200 mCi in the rest of the included studies. The use of

TABLE 1A. Summary of adjusted analyses of thyroid cancer-related deaths

Study	n	Histology	Median follow-up (yr)	Event rate (%)	Independent variables in the model	Effectiveness of radioiodine ablation for thyroid cancer-related mortality[a]
Ohio State (10)	1510[b]	P, F	16.6	N/A	Age, gender, surgical extent, tumor characteristics, time to treatment	RR = 0.5 (95% CI, 0.4–0.7); $P < 0.0001$
UCSF (24)[c]	187	P, F, H	10.6	7	Surgical extent, external radiotherapy, immunotherapy, chemotherapy	NS
Hong Kong (F) (60)[d]	135	F	10.8	1.9	Age, gender, surgical extent, tumor characteristics	NS
Hong Kong (P) (12)[d]	587	P	9.2	1.3	Age, gender, surgical extent, tumor characteristics	NS
Toronto (23)	382	P, F	10.8	7 (P); 15 (F)	Age, surgical extent, tumor characteristics, external radiotherapy	NS
Illinois Registry (42)	2282	P, F	6.5	N/A	Age, gender, tumor characteristics, race, postoperative thyroid hormone	NS

P, Papillary; F, follicular; H, Hurthle cell; N/A, not available; NS, not significant.
[a] Excluded patients with distant metastases at presentation from analysis.
[b] Information obtained from author.
[c] Includes only patients with primary tumors larger than 1 cm.
[d] Excluded patients with distant metastases, no gross or microscopic residual disease after thyroid surgery.

TABLE 1B. Summary of individual multivariable analyses of any thyroid cancer-related tumor recurrence

Study	n	Histology	Median follow-up (yr)	Event rate (%)	Independent variables in the model	Effectiveness of radioiodine ablation for any recurrence[a]
Ohio State (10)	1510[b]	P, F	16.6	23.5	Age, surgical extent, tumor characteristics,	RR = 0.8 (95% CI, 0.7–0.97), $P = 0.016$
Gunderson/Lutheran (25)	177	P, F, H	7.2	13 (P) 8 (F) 7 (H)	Age, gender, surgical extent, tumor characteristics,	NS
Gustave-Roussy (55)	273	P, F	7.3	3.9	Gender, surgical extent, tumor characteristics external radiation, mode of diagnosis	NS
UCSF (24)[c]	187	P, F, H	10.6	20.5	Surgical extent, external radiotherapy, immunotherapy, chemotherapy	RR = 0.48 (95% CI 0.32, 0.67), $P = 0.0001$[d]
MD Anderson (57)	1599	P, F, H	11	23	Age, gender, surgical extent, tumor characteristics, external radiotherapy	$P < 0.001$
Mexico (29)	229	P, F	5	15	Age, gender, surgical extent, tumor characteristics, benign thyroid disease, thyroid hormone suppression	NS

P, Papillary; F, follicular; H, Hurthle cell; NS, not significant. Note: Liverpool study (35) of 249 patients with papillary and follicular thyroid cancer patients not shown in above table as RAI was not entered in the multivariable model, because it was not found to be a statistically significant variable in univariate analysis.
[a] Excluded patients with distant metastases at presentation from analysis.
[b] Information obtained from authors.
[c] Primary tumor at least 1 cm in diameter.
[d] Calculated as the inverse of the reported RR for individuals who did not receive radioiodine (*i.e.* 2.1; 95% CI, 1.5–3.1, $P = 0.0001$).

thyroid hormone suppressive therapy was not clearly reported in the majority of studies (10, 11, 14, 20, 28, 38, 57, 59). The mean or median follow-up period was longer than 10 yr in eight of the 20 analyses shown in Table 2 (10, 11, 15, 18, 23, 24, 43, 57).

Unadjusted analysis: 10-yr thyroid cancer-related mortality. Ten-year unadjusted thyroid cancer-related mortality for well-differentiated thyroid cancer ranged from 0 to 23.1% for RAI-treated patients and from 0 to 25.3% in patients not treated with RAI (Table 2). Significant statistical heterogeneity ($P < 0.10$) of treatment effect (difference between studies) was present, and pooling was not performed for the analyses of thyroid cancer-related mortality in the combination of papillary or follicular histologies as well as the papillary subgroup alone. Of note, the cause-specific 10-yr mortality rates were very low in the papillary and papillary/follicular subgroups, 1.7 (45 of 2627) and 3.4% (107 of 3157), respectively. In contrast, in the follicular subgroup, there was no statistically significant heterogeneity ($\chi^2 = 4.97$, degrees of freedom [*df*] = 5, $P = 0.42$), and the event rates were 10% in the radioiodine-treated patients (27 of 274) and 10% (41 of 406) in the nonablated patients. There was no significant treatment effect of RAI on patients with follicular histology (RD 2%, −2 to 7%, $P = 0.4$, z = 0.92).

TABLE 2. Characteristics of patients included in unadjusted metaanalyses and unadjusted 10-yr thyroid cancer-related mortality

Study (Ref.)	No. of patients	10-yr thyroid cancer-related deaths	Histology	Stage of disease prior to surgery
Canada (P) 1988 (59)	RAI: 108[a]	5 (4.6%)[a]	P	N/A
	No RAI: 497[a]	26 (5.2%)[a]		
Florence, Italy 1985 (46)	RAI: 72	2 (2.8%)	P	Size ≤1 cm in 14.5%, stage not compared
	No RAI: 103	8 (7.8%)		Size ≤1 cm in 18.3%, stage not compared
Hong Kong (P) 2002 (12)	RAI: 444	2 (0.5%)	P	Patients with distant metastases or residual locoregional disease excluded
	No RAI: 143	2 (1.4%)		
Mayo 2002 (11)	RAI: 498[b]	0 (0%)[b]	P	All MACIS <6
	No RAI: 665[b]	0 (0%)[b]		
U Chicago 1990 (43)	RAI: 106[a]	N/A	P	Patients with intrathyroidal disease with or without positive cervical lymph nodes
	No RAI: 111[a]	N/A		
Zurich (P) 2001 (14)	RAI: 43	0 (0%)	P	Only TNM stage I and II included in this analysis
	No RAI: 54	0 (0%)		
France 1998 (55)	RAI: 117	0 (0%)	P, F	All ≤1 cm in diameter, with or without lymph node metastases, 38% multifocal, patients with distant metastases excluded
	No RAI: 156	0 (0%)		
MD Anderson 1992 (57)	RAI: 446	N/A	P, F, H	N/A
	No RAI: 863	N/A		
Mt Sinai, U of T 1991 (41)	RAI: 63	N/A	P, F	N/A
	No RAI: 7	N/A		
New Mexico 1998 (20)	RAI: 401	7 (1.7%)	88% P; 12% F	52.1% had disease not extending past thyroid capsule, the rest regional disease, no distant metastases
	No RAI: 674	12 (1.8%)	83% P, 17% F	76.9% had disease not extending past thyroid capsule, the rest regional disease, no distant metastases
Ohio State 2001 (10)	RAI: 230	1 (0.4%)[b]	70% P; 30% F or H[b]	Mean TNM (AJC) stage = 1.43 (0.59 is SD),[b] tumors >1.5 cm in diameter
	T4 only: 789	17 (2.2%)[b]	83% P, 17% F or H[b]	Mean TNM (AJC) stage = 1.37 (0.59 is SD),[b] tumors >1.5 cm in diameter
Taipei, Taiwan 1996 (28)	RAI: 231	22 (9.5%)	P, F	N/A
	No RAI: 67	17 (25.3%)		
U of Toronto, Princess Margaret 1998 (23)	RAI: 121	Overlap with Canadian study	P, F	UICC stage: I = 87 patients, II = 34 patients
	No RAI: 99			UICC stage: I = 81 patients, II = 18 patients
UCSF 1997 (24)	RAI: 305[b]	24 (7.9%)	P, F, H	Tumors ≥1 cm in diameter, otherwise no comparison of stage
	No RAI: 187[b]	7 (3.7%)		
BC Canada 1992 (38)	RAI: 17	3 (17.6%)[a]	F	No extrathyroidal extension nor distant metastases
	No RAI: 46	7 (15.2%)[a]		
Canada (F) 1988 (59)	RAI: 91[a]	21 (23.1%)[a]	F, H	N/A
	No RAI: 212[a]	31 (14.6%)[a]		
Cleveland 2001 (15)	RAI: 6[b]	1 (16.6%)[b]	F	All intrathyroidal
	No RAI: 55[a]	2 (3.6%)[b]		
Hong Kong (F) 2002 (60)	RAI: 123[b]	2 (1.6%)	F	RAI not compared to non-RAI. No distant metastases.
	No RAI: 12[b]	0 (0%)		
Lahey Clinic 1998 (18)	RAI: 20	0 (0%)	F, H	N/A
	No RAI: 72	0 (0%)		
Zurich (F) 2001 (14)	RAI: 17	0 (0%)	F	N/A
	No RAI: 9	1 (11.1%)		

N/A, Not available; P, papillary; F, follicular; H, Hurthle cell.
[a] Extrapolated from survival curve or calculated from information in paper.
[b] Information obtained from author.

Pooled analysis: any thyroid cancer-related recurrence. Upon pooling 10-yr data for any recurrence for 4996 patients, marked statistical heterogeneity ($P < 0.10$) was again observed when histologic subgroups were combined as well as within the subgroup of studies combining papillary and follicular, so results were not pooled. Statistical heterogeneity was not noted in the respective subgroups of papillary and follicular patients (when categorized in the primary studies separately), and the pooled estimate suggested that there was no significant benefit of radioiodine ablation on any recurrence in either of these subgroups ($P = 0.9$ in both subgroups, respectively) (Fig. 2). The pooled 10-yr "any" recurrence rates in the studies of papillary patients were: 73 of 719 (10%) in ablated patients and 81 of 933 (9%) in non-

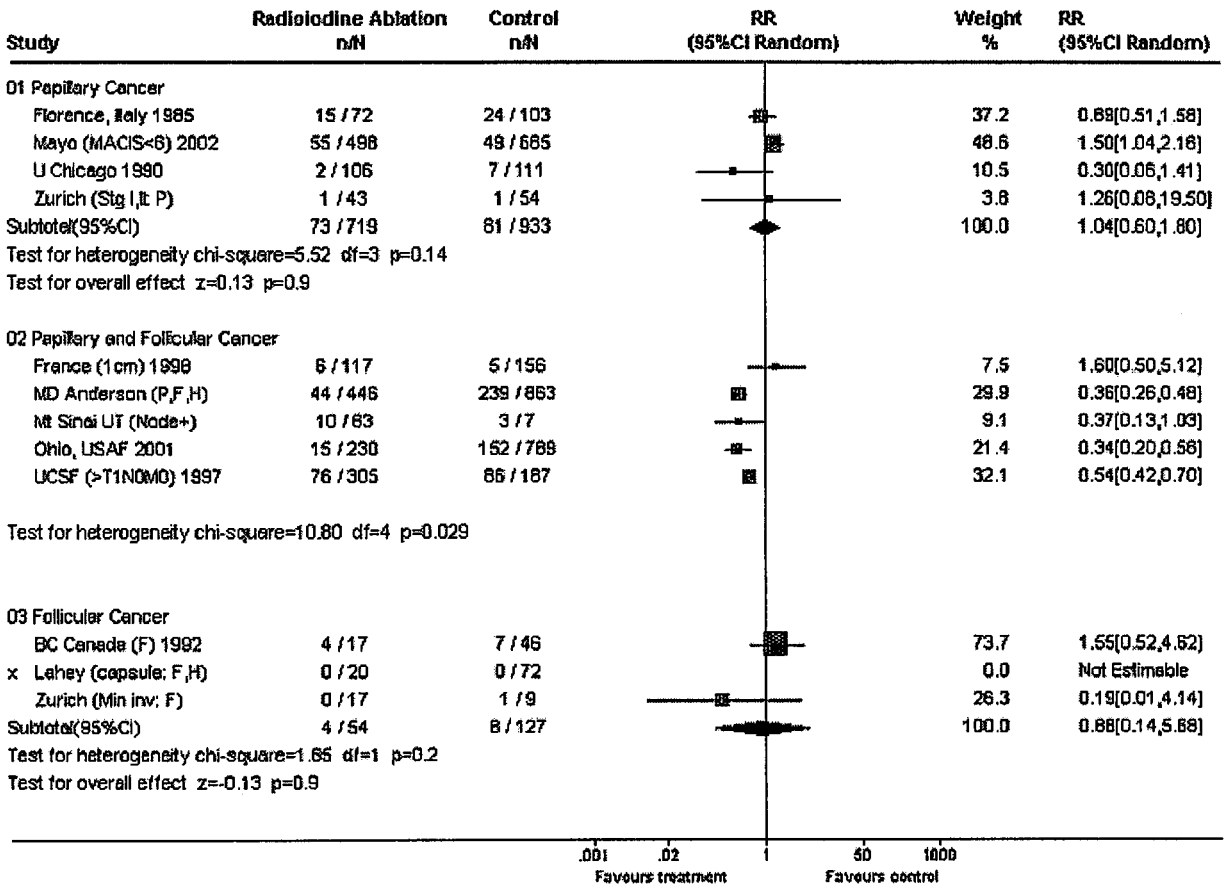

FIG. 2. Random effects pooled estimate of RR of any thyroid cancer recurrence in patients treated with radioiodine and compared with those not treated with radioiodine according to histologic subtype analyzed in each publication. n, Number of events; N, size of population studied; P, papillary; F, follicular; H, Hurthle cell; Min inv, minimally invasive; capsule, only capsular invasion; MACIS<6, MACIS score less than 6; Stg I,II, stage I or II; 1cm, tumor less than 1 cm in diameter; >T1NOMO, stage worse than T1NOMO; node+, including cervical lymphadenopathy.

ablated patients (RR = 1.04, 95% CI = 0.60–1.80). The pooled 10-yr "any" recurrence rates in the studies of follicular patients were: four of 54 (7%) in the radioiodine-treated patients and eight of 127 (6%) in the nonradioiodine-treated patients (RR = 0.88, 95% CI = 0.14–5.68).

Pooled analyses: locoregional recurrence, distant metastases. Further pooled analyses were performed examining the effect of radioiodine on 10-yr locoregional recurrence (Fig. 3) and distant metastases (Fig. 4) (test of heterogeneity not significant). For the outcome of locoregional recurrence in patients of all histologies combined, the event rate in the radioiodine-treated patients was 32 of 768 (4%) and in nonradioiodine-treated patients, it was 40 of 389 (10%), such that the pooled relative risk of locoregional recurrence was 0.31 (95% CI = 0.20, 0.49) in ablated patients (Fig. 3). For the outcome of distant metastases in patients of all histologies combined, the rate of distant metastases was 15 of 877 (2%) in ablated patients, compared with 41 of 1079 (4%) in nonablated patients; the pooled risk of distant metastases was decreased by 3% with ablation (95% CI = decrease of 1 to 4%) (Fig. 4).

Discussion

A systematic review of the English literature revealed that in 13 cohort studies in which thyroid cancer-related outcomes were adjusted to a variable degree for prognostic factors or cointerventions, thyroid cancer-related outcomes appeared to be decreased in the following: one of seven studies examining thyroid cancer-related mortality, three of six studies examining any tumor recurrence, three of three studies examining locoregional recurrence, and two of three studies examining distant metastases. Thyroid hormone suppressive therapy was not adjusted for in the majority of the multivariable models. Furthermore, in 18 cohort studies not adjusted for prognostic factors or interventions, the benefit of RAI ablation in decreasing the thyroid cancer-related mortality and any recurrence was inconsistent among centers. Moreover, a pooled analysis suggested that ablation may decrease locoregional recurrence in papillary and follicular patients (RR 0.31, 95% confidence interval 0.2, 0.49). A pooled analysis also suggested that distant metastases at 10 yr were statistically significantly decreased in patients with well-differentiated thyroid cancer with remnant ablation (3% decrease in risk, with 95% CI of 1 to 4% decrease in risk), noting that the absolute risk of distant metastases at 10 yr in nonablated patients was relatively low at 4%.

The adjusted and unadjusted data summarized were subject to many limitations. The multivariable analyses were limited by inclusion of high-risk patients within some mod-

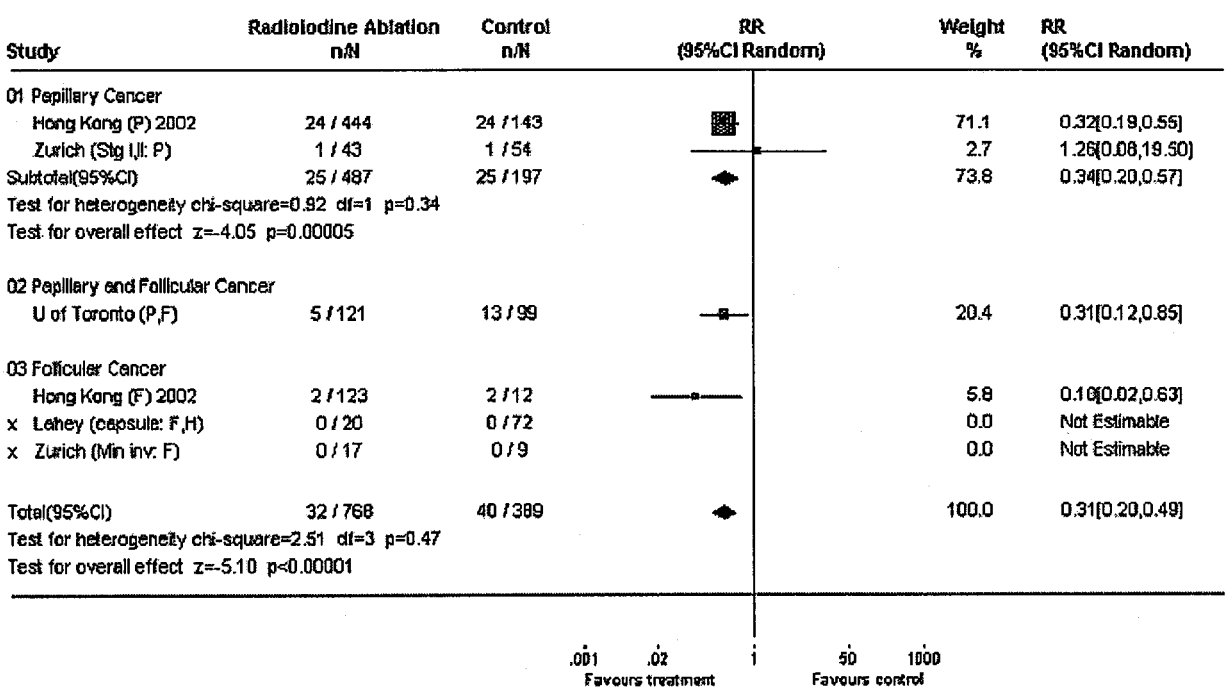

FIG. 3. Random effects pooled estimate of RR reduction of RAI ablation on development of locoregional recurrence at 10 yr. n, Number of events; N, size of population studied; P, papillary; F, follicular; H, Hurthle cell; Stg I,II, stage I or II; Min inv, minimally invasive; capsule, only capsular invasion.

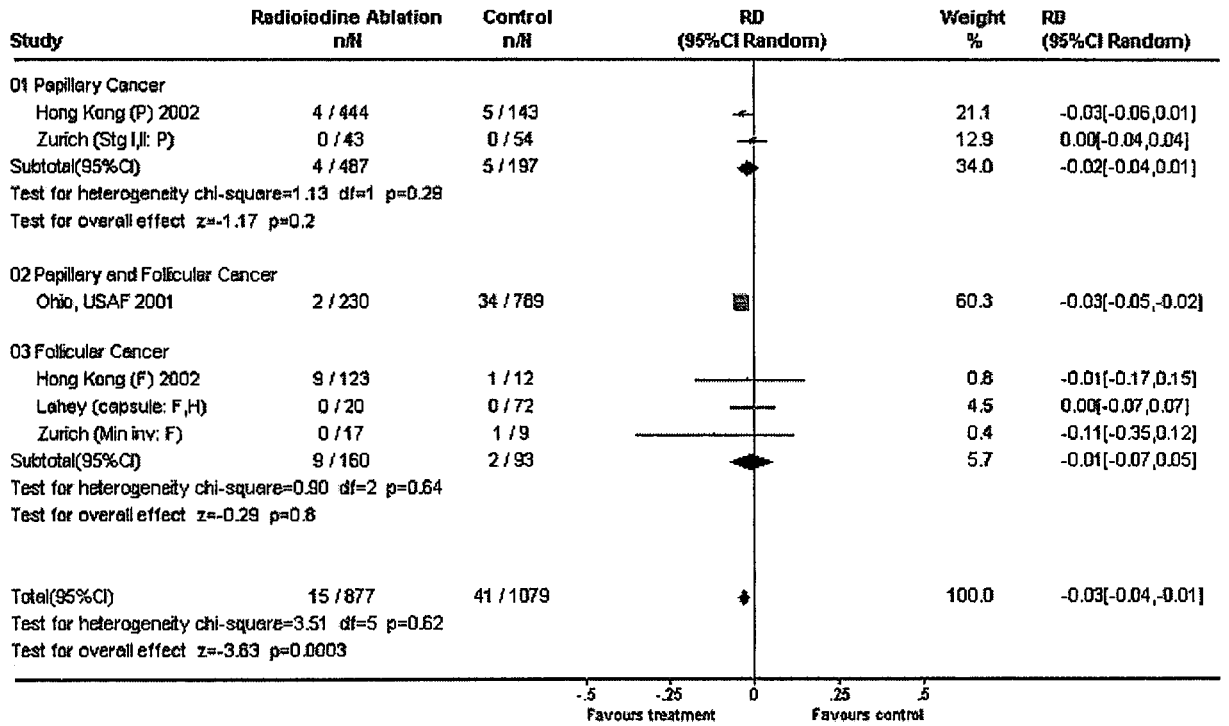

FIG. 4. Random effects model examining the RD of RAI ablation on development of distant metastases at 10 yr. n, Number of events; N, size of population studied; P, papillary; F, follicular; H, Hurthle cell; Stg I,II, stage I or II; Min inv, minimally invasive; capsule, only capsular invasion; node+, including cervical lymphadenopathy.

els, the lack of adjustment for the cointervention of thyroid hormone suppressive therapy, and underpowering of studies due to small sample sizes or event rates. Furthermore, registry data may have been limited by incomplete registration of interventions and outcomes. Moreover, ascertainment bias (of recurrence) may have resulted in underestimation of treatment effect of RAI ablation, particularly if ablated patients were followed up more frequently (such as with radioiodine whole-body scans) than ablated patients. Pooled unadjusted treatment effects in observational cohort studies

appeared inconsistent among centers for the outcomes of thyroid cancer-related mortality and any recurrence, suggesting the populations or interventions studied may not have been comparable. Furthermore, in many studies there was lack of complete 10-yr data due to loss to follow-up or inclusion of patients less than 10 yr after their initial diagnosis. Our review was also limited by the fact that primary patient data were not available for all studies so that some data had to be extrapolated from graphs or tables, possibly resulting in some error, particularly in pooled analyses. Given the methodologic limitations of the pooled observational data, such analyses may be regarded as exploratory. An optimal dose of RAI for ablation cannot be recommended based on the reviewed data because a variety of fixed doses were used in different clinical centers, and some centers did not report doses used.

Thus, the effectiveness of RAI ablation decreasing recurrence and possibly mortality in low-risk patients with well-differentiated thyroid carcinoma, although suspected, cannot be definitively verified by summarizing the current body of observational patient data. Only a long-term randomized controlled trial may definitively resolve this issue. The feasibility of a randomized controlled trial examining potential benefit of adjuvant radioiodine ablation in thyroid cancer has been frequently debated; the sample size required to determine whether a mortality benefit exists with this intervention may not be feasible, particularly given the rarity of thyroid cancer-related mortality in low-risk papillary patients (62). However, a randomized controlled trial incorporating a carefully stratified randomization strategy, with the outcome of recurrence may be feasible (63). In the meantime, the decision for RAI ablation must be individualized, based on the risk profile of the patient, as well as patient and physician preference, while balancing the risks and benefits of such therapy.

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References

1. Health Canada. Health Statistics Division of Statistics Canada. Population and Public Health Branch. Cancer Surveillance. Available at: http://cythera.ic.gc.ca/dsol/cancer/index_e.html. Accessed December 2002
2. **Wartofsky L, rhTSH-Stimulated Thyroglobulin Study Group** 2002 Techniques in thyroidology: management of low-risk well-differentiated thyroid cancer based only on thyroglobulin measurement after recombinant human thyrotropin. Thyroid 12:583–589
3. **Edwards BK, Howe HL, Ries LA, Thun MJ, Rosenberg HM, Yancik R, Wingo PA, Jemal A, Feigal EG** 2002 Annual report to the nation on the status of cancer, 1973–1999, featuring implications of age and aging on the U.S. cancer burden. Cancer 94:2766–2792
4. **Hundahl SA, Fleming ID, Fremgen AM, Menck HR** 1998 A national cancer data base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985–1995. Cancer 83:2638–2648
5. **British Thyroid Association, Royal College of Physicians** 2002 Guidelines for the management of thyroid cancer in adults. 6.1
6. **Regional Thyroid Cancer Group** 2000 Northern Cancer Network guidelines for management of thyroid cancer. Clin Oncol 12:373–391
7. **National Comprehensive Cancer Network** 2003 Practice guidelines in oncology: thyroid carcinoma. V. 1.2003; MS11
8. **American Association of Clinical Endocrinologists/American College of Endocrinology, American Association of Endocrine Surgeons** 2001 AACE/AAES medical/surgical guidelines for clinical practice: management of thyroid carcinoma. Endocr Pract 7:203–220
9. **Singer PA, Cooper DS, Daniels GH, Ladenson PW, Greenspan FS, Levy EG, Braverman LE, Clark OH, McDougall IR, Ain KV, Dorfman SG** 1996 Treatment guidelines for patients with thyroid nodules and well-differentiated thyroid cancer. Arch Intern Med 156:2165–2172
10. **Mazzaferri EL, Kloos RT** 2001 Clinical review 128: current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 86:1447–1463
11. **Hay ID, McConahey WM, Goellner JR** 2002 Managing patients with papillary thyroid carcinoma: insights gained from the Mayo Clinic's experience of treating 2,512 consecutive patients during 1940 through 2000. Trans Am Clin Climatol Assoc 113:241–260
12. **Chow SM, Law SC, Mendenhall WM, Au SK, Chan PT, Leung TW, Tong CC, Wong IS, Lau WH** 2002 Papillary thyroid carcinoma: prognostic factors and the role of radioiodine and external radiotherapy. Int J Radiat Oncol Biol Phys 52:784–795
13. **Chow SM, Law SC, Au SK, Chan PT, Leung TW, Chan PT, Wong IS, Mendenhall WM, Lau WH** 2002 Differentiated thyroid carcinoma: comparison between papillary and follicular carcinoma in a single institute. Head Neck 24:670–677
14. **Gemsenjager E, Heitz PU, Seifert B, Martina B, Schweizer I** 2001 Differentiated thyroid carcinoma. Follow-up of 264 patients from one institution for up to 25 years. Swiss Med Wkly 131:157–163
15. **Saadi H, Kleidermacher P, Esselstyn Jr C** 2001 Conservative management of patients with intrathyroidal well-differentiated follicular thyroid carcinoma. Surgery 130:30–35
16. **Zidan J, Kassem S, Kuten A** 2000 Follicular carcinoma of the thyroid gland: prognostic factors, treatment, and survival. Am J Clin Oncol 23:1–5
17. **Hay ID, Bergstralh EJ, Grant CS, McIver B, Thompson GB, van Heerden JA, Goellner JR** 1999 Impact of primary surgery on outcome in 300 patients with pathologic tumor-node-metastasis stage III papillary thyroid carcinoma treated at one institution from 1940 through 1989. Surgery 126:1173–1181
18. **Sanders LE, Silverman M** 1998 Follicular and Hurthle cell carcinoma: predicting outcome and directing therapy. Surgery 124:967–974
19. **Cooper DS, Specker B, Ho M, Sperling M, Ladenson PW, Ross DS, Ain KB, Bigos ST, Brierley JD, Haugen BR, Klein I, Robbins J, Sherman SI, Taylor T, Maxon 3rd HR** 1998 Thyrotropin suppression and disease progression in patients with differentiated thyroid cancer: results from the National Thyroid Cancer Treatment Cooperative Registry. Thyroid 8:737–744
20. **Morris DM, Boyle PJ, Stidley CA, Altobelli KK, Parnell T, Key C** 1998 Localized well-differentiated thyroid carcinoma: survival analysis of prognostic factors and ^{131}I therapy. Ann Surg Oncol 5:329–337
21. **Sanders LE, Cady B** 1998 Differentiated thyroid cancer: reexamination of risk groups and outcome of treatment. Arch Surg 133:419–425
22. **Wenig BM, Thompson LD, Adair CF, Shmookler B, Heffess CS** 1998 Thyroid papillary carcinoma of columnar cell type: a clinicopathologic study of 16 cases. Cancer 82:740–753
23. **Tsang RW, Brierley JD, Simpson WJ, Panzarella T, Gospodarowicz MK, Sutcliffe SB** 1998 The effects of surgery, radioiodine, and external radiation therapy on the clinical outcome of patients with differentiated thyroid carcinoma. Cancer 82:375–388
24. **Loh KC, Greenspan FS, Gee L, Miller TR, Yeo PP** 1997 Pathological tumor-node-metastasis (pTNM) staging for papillary and follicular thyroid carcinomas: a retrospective analysis of 700 patients. J Clin Endocrinol Metab 82:3553–3562
25. **Martins RG, Caplan RH, Lambert PJ, Rooney B, Kisken WA** 1997 Management of thyroid cancer of follicular cell origin: Gundersen/Lutheran Medical Center, 1969–1995. J Am Coll Surg 185:388–397
26. **Gemsenjager E, Heitz PU, Martina B** 1997 Selective treatment of differentiated thyroid carcinoma. World J Surg 21:546–551
27. **Mazzaferri EL** 1997 Thyroid remnant ^{131}I ablation for papillary and follicular thyroid carcinoma. Thyroid 7:265–271
28. **Tseng LM, Lee CH, Wang HC, Shyr YM, Chiu JH, Wu CW, Lui WY, P'eng FK** 1996 The surgical treatment and prognostic factors of well-differentiated

thyroid cancers in Chinese patients: a 20-year experience. Chin Med J (Taipei) 58:121–131
29. **Herrera MF, Lopez-Graniel CM, Saldana J, Gamboa-Dominguez A, Richaud-Patin Y, Vargas-Vorackova F, Angeles-Angeles A, Llorente L, Castillo C, Perez B, Rivera R, Gonzalez O, Rull J** 1996 Papillary thyroid carcinoma in Mexican patients: clinical aspects and prognostic factors. World J Surg 20: 94–99
30. **DeGroot LJ, Kaplan EL, Shukla MS, Salti G, Straus FH** 1995 Morbidity and mortality in follicular thyroid cancer. J Clin Endocrinol Metab 80:2946–2953
31. **Sanders LE, Rossi RL** 1995 Occult well differentiated thyroid carcinoma presenting as cervical node disease. World J Surg 19:642–646
32. **Staunton MD** 1994 Thyroid cancer: a multivariate analysis on influence of treatment on long-term survival. Eur J Surg Oncol 20:613–621
33. **Mazzaferri EL, Jhiang SM** 1994 Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 97:418–428
34. **DeGroot LJ, Kaplan EL, Straus FH, Shukla MS** 1994 Does the method of management of papillary thyroid carcinoma make a difference in outcome? World J Surg 18:123–130
35. **Balan KK, Raouf AH, Critchley M** 1994 Outcome of 249 patients attending a nuclear medicine department with well differentiated thyroid cancer: a 23 year review. Br J Radiol 67:283–291
36. **Krausz Y, Uziely B, Karger H, Isacson R, Catane R, Glaser B** 1993 Recurrence-associated mortality in patients with differentiated thyroid carcinoma. J Surg Oncol Suppl 52:164–168
37. **Hay ID, Grant CS, van Heerden JA, Goellner JR, Ebersold JR, Bergstralh EJ** 1992 Papillary thyroid microcarcinoma: a study of 535 cases observed in a 50-year period. Surgery 112:1139–1146
38. **Davis NL, Gordon M, Germann E, McGregor GI, Robins RE** 1992 Efficacy of ^{131}I ablation following thyroidectomy in patients with invasive follicular thyroid cancer. Am J Surg 163:472–475
39. **Chonkich GD, Petti Jr GH** 1992 Treatment of thyroid carcinoma. Laryngoscope 102:486–491
40. **Sothy K, Mafauzy M, Mohamad WB, Mustaffa BE** 1991 Carcinoma of thyroid—clinical presentation and outcome. Med J Malaysia 46:212–217
41. **McHenry CR, Rosen IB, Walfish PG** 1991 Prospective management of nodal metastases in differentiated thyroid cancer. Am J Surg 162:353–356
42. **Cunningham MP, Duda RB, Recant W, Chmiel JS, Sylvester JA, Fremgen A** 1990 Survival discriminants for differentiated thyroid cancer. Am J Surg 160: 344–347
43. **DeGroot LJ, Kaplan EL, McCormick M, Straus FH** 1990 Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab 71:414–424
44. **Shaw JH, Dodds P** 1990 Carcinoma of the thyroid gland in Auckland, New Zealand. Surg Gynecol Obstet 171:27–32
45. **Mazzaferri EL** 1987 Papillary thyroid carcinoma: factors influencing prognosis and current therapy. Semin Oncol 14:315–332
46. **Carcangiu ML, Zampi G, Pupi A, Castagnoli A, Rosai J** 1985 Papillary carcinoma of the thyroid. A clinicopathologic study of 241 cases treated at the University of Florence, Italy. Cancer 55:805–828
47. **Samaan NA, Maheshwari YK, Nader S, Hill Jr CS, Schultz PN, Haynie TP, Hickey RC, Clark RL, Goepfert H, Ibanez ML, Litton CE** 1983 Impact of therapy for differentiated carcinoma of the thyroid: an analysis of 706 cases. J Clin Endocrinol Metab 56:1131–1138
48. **Wanebo HJ, Andrews W, Kaiser DL** 1983 Thyroid cancer: some basic considerations. CA Cancer J Clin 33:87–97
49. **Wanebo HJ, Andrews W, Kaiser DL** 1981 Thyroid cancer: some basic considerations. Am J Surg 142:474–479
50. **Mazzaferri EL, Young RL** 1981 Papillary thyroid carcinoma: a 10 year follow-up report of the impact of therapy in 576 patients. Am J Med 70:511–518
51. **Young RL, Mazzaferri EL, Rahe AJ, Dorfman SG** 1980 Pure follicular thyroid carcinoma: impact of therapy in 214 patients. J Nucl Med 21:733–737
52. **Mazzaferri EL, Young RL, Oertel JE, Kemmerer WT, Page CP** 1977 Papillary thyroid carcinoma: the impact of therapy in 576 patients. Medicine (Baltimore) 56:171–196
53. **Varma VM, Beierwaltes WH, Nofal MM, Nishiyama RH, Copp JE** 1970 Treatment of thyroid cancer. Death rates after surgery and after surgery followed by sodium iodide I-131. JAMA 214:1437–1442
54. **Hay ID, Thompson GB, Grant CS, Bergstralh EJ, Dvorak CE, Gorman CA, Maurer MS, McIver B, Mullan BP, Oberg AL, Powell CC, Van Heerden JA, Goellner JR** 2002 Papillary thyroid carcinoma managed at the Mayo Clinic during six decades (1940–1999): temporal trends in initial therapy and long-term outcome in 2444 consecutively treated patients. World J Surg 26:879–885
55. **Baudin E, Travagli JP, Ropers J, Mancusi F, Bruno-Bossio G, Caillou B, Cailleux A, Lumbroso JD, Parmentier C, Schlumberger M** 1998 Microcarcinoma of the thyroid gland the Gustave-Roussy Institute experience. Cancer 83:553–559
56. **Kuijpens JL, Hansen B, Hamming JF, Ribot JG, Haak H, Coebergh J-WW** 1998 Trends in treatment and long-term survival of thyroid cancer in southeastern Netherlands, 1960–1992. Eur J Cancer 34:1235–1241
57. **Samaan NA, Schultz PN, Hickey RC, Goepfert H, Haynie TP, Johnston DA, Ordonez NG** 1992 The results of various modalities of treatment of well differentiated thyroid carcinoma: a retrospective review of 1599 patients. J Clin Endocrinol Metab 75:714–720
58. **Obaldo JM, Silvestre dela Cruz T, Bidana AFM, Bandong-Reyes E, Cruz RM** 1989 Post-surgical iodine-131 therapy in differentiated thyroid cancer. Philip J Intern Med 27:301–308
59. **Simpson WJ, Panzarella T, Carruthers JS, Gospodarowicz MK, Sutcliffe SB** 1988 Papillary and follicular thyroid cancer: impact of treatment in 1578 patients. Int J Radiat Oncol Biol Phys 14:1063–1075
60. **Chow SM, Law SC, Mendenhall WM, Au SK, Yau S, Yuen KT, Law CC, Lau WH** 2002 Follicular thyroid carcinoma: prognostic factors and the role of radioiodine. Cancer 95:488–498
61. **Brierley JD, Panzarella T, Tsang RW, Gospodarowicz MK, O'Sullivan B** 1997 A comparison of different staging systems and predictability of patient outcome: thyroid carcinoma as an example. Cancer 79:2414–2423
62. **Wong JB, Kaplan MM, Meyer KB, Pauker SG** 1990 Ablative radioactive iodine therapy for apparently localized thyroid carcinoma: a decision analytic perspective. Endocrinol Metab Clin North Am 19:741–760
63. **Dragoiescu C, Hoekstra OS, Kuik DJ, Lips P, Plaizier MABD, Rodrigus PTR, Huijsmans DAKCJM, Ribot JC, Kuijpens J, Coebergh JWW, Teule CJJ** 2003 Feasibility of a randomized trial on adjuvant radio-iodine therapy in differentiated thyroid cancer. Clin Endocrinol (Oxf) 58:451–455

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