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Selective Use of Radioactive Iodine in Intermediate-Risk Papillary Thyroid Cancer

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Objective: To describe the outcomes with the selective use of radioactive iodine (RAI) in patients who are at intermediate risk of death from papillary thyroid cancer, focusing on 2 subgroups: patients older than 45 years with low-risk tumors and patients younger than 45 years with high-risk tumors.

Design: Retrospective case review.

Setting: Tertiary referral US cancer center.

Patients: The study incluced 532 consecutive patients who were surgically treated between 1986 and 2005.

Interventions: All patients underwent total thyroidectomy; 307 also received RAI.

Main Outcome Measures: Disease-specific survival (DSS) and recurrence-free survival (RFS).

Results: Of 344 patients older than 45 years with low-risk tumors, 148 (43%) received RAI and 196 (57%) were selected not to receive RAI. The patients who were treated without RAI were more likely to be female and have pT1N0 disease. The 5-year DSS and RFS were 100% and 98%, respectively. The presence of nodal metastases predicted poorer 5-year RFS within this group (99% vs 91%; $P=.004$). Of 188 patients younger than 45 years with high-risk tumors, 159 (85%) received RAI, and only 29 (15%) were selected not to receive RAI. The 5-year DSS and RFS for these patients were 100% and 95%, respectively. The presence of nodal metastases predicted poorer 5-year RFS within this group (100% vs 86%; $P=.02$).

Conclusion: Our study shows that the subgroup of patients who are older than 45 years with tumors that are smaller than 4 cm in greatest dimension and confined to the thyroid gland and who do not have nodal metastases can safely be treated without RAI.

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THE AMERICAN THYROID ASSOCIATION (ATA) guidelines endorse the selective use of postoperative radioactive iodine (RAI) in all patients with well-differentiated thyroid cancer (WDTC) greater than 1 cm in greatest dimension and go on to recommend the routine use of RAI in patients with advanced local disease (pT3 or pT4) irrespective of age.[1] Despite these recommendations, the guidelines highlight the conflicting data particularly in relation to patients with less aggressive local disease. Based on clinical and histopathologic features, all WDTC cases can be classified into low-, intermediate-, and high-risk groups for death based on the Memorial Sloan-Kettering Cancer Center (MSKCC), New York, New York, previously published risk stratification system GAMES (**Table 1**).[2] In this system, patients younger than 45 years who present with papillary carcinomas smaller than 4 cm in greatest dimension and confined to the thyroid gland (intraglandular), without evidence of distant metastatic disease, are considered at low risk of death. Patients older than 45 years with extrathyroid extension (ETE), aggressive histopathologic features, disease larger than 4 cm in greatest dimension, or distant metastatic disease are at higher risk. Young patients with, or older patients without, aggressive histopathologic features form an intermediate-risk group.[3] This intermediate-risk group formed the patient cohort on which our study was based.

The head and neck service at MSKCC has long used a selective approach to the use of RAI in these patients who are considered to be at intermediate risk of death from WDTC. Our hypothesis is that older patients with low-risk tumors can safely

Table 1. GAMES Risk Stratification

Risk Level	Patient Factor	Tumor Factor
Low	Age <45 y	Papillary carcinoma, M0, no ETE, size <4 cm
High	Age >45 y	Follicular/Hürthle cell carcinoma, M1, ETE, size >4 cm
Low	Low-risk patient	Low-risk tumor
Intermediate	Low-risk patient	High-risk tumor
	High-risk patient	Low-risk tumor
High	High-risk patient	High-risk tumor

Abbreviation: ETE, extrathyroid extension.

be treated without the need for RAI. The objectives of this study were to evaluate and compare outcomes in these intermediate-risk patients stratified by the use of RAI by examining a contemporary data set of intermediate-risk patients with papillary thyroid cancer (PTC) treated with total thyroidectomy at MSKCC between 1986 and 2005.

METHODS

After approval by the institutional review board, 532 consecutive patients with PTC who were classified as being at intermediate risk (according to the GAMES system) and who had undergone a total thyroidectomy between 1986 and 2005 were identified from our institutional database of 1810 patients treated for WDTC at MSKCC. Patients who underwent initial treatment elsewhere, those whose tumors were considered unresectable at the time of referral or surgery, those who were treated with less than total thyroidectomy, and those presenting with evidence of distant metastasis were excluded. Data collected included patient demographics and surgical details, including the presence of gross ETE. Histopathologic details recorded included histologic type of tumor, primary tumor size, presence of ETE, and presence of metastatic lymph nodes. Postoperative treatment details recorded included the use of RAI. Ninety-seven percent of our cohort received RAI in our institution, and 3% were treated outside following the recommendations from MSKCC. In the cohort of patients from 1986 to 2005, ultrasonography was not routinely used for preoperative assessment of the central and lateral compartment lymph nodes. Assessment of the lateral neck nodes was based on the results of the preoperative clinical examination, and if the nodes were enlarged, ultrasonography was performed. Evaluation of the central compartment for all patients was carried out by intraoperative examination and palpation of the lymph nodes at the time of thyroidectomy. If no suspicious nodes were present in the central compartment, then no elective central compartment neck dissection was performed. If suspicious nodes were noted, then a central compartment neck dissection was carried out. Frozen section of the lymph nodes was generously used. Postoperative thyroid-stimulating hormone suppression is practiced for all patients, aiming for a level of between 0.1 and 0.5 mIU/L.

The risk of recurrence in our intermediate-risk patients (according to the GAMES system) was determined using the recent ATA guidelines.[1] Patients with fully excised disease without any of the following features—ETE, aggressive histologic features, vascular invasion, or regional or distant metastases—are at low risk of recurrence. Patients with macroscopic ETE, distant metastases, or incomplete tumor resection are at high risk of recurrence. All other patients represent an intermediate-risk group. All patients within our group were also retrospectively classified using this system.

Outcomes data included local, regional, and distant recurrence as well as details of death. Local and regional recurrences were determined by clinical examination supplemented with imaging and fine-needle aspiration if recurrence was suspected. Initially, all surgical patients were followed up by the attending surgeon in MSKCC, with input from the endocrinologists and nuclear medicine physicians as required. As the volume of surgical practice has increased, routine follow-up of many patients has passed to the endocrinology service at MSKCC. Most patients are now followed up by endocrinologists at MSKCC, all of whom are specialized in the management of thyroid cancer. A minority of patients were followed up by local endocrinologists.

During the study period from 1986 to 2000, serum thyroglobulin levels were not routinely used to detect recurrence. Similarly, annual ultrasonography was not uniformly used as a tool for detection of recurrent disease during most of the study period. Both ultrasonography and thyroglobulin measurement have become routine in the follow-up of patients with PTC within our institution; however, the presence of local or regional recurrence after treatment was based on cytologic or histopathologic confirmation of disease. Local recurrence was defined as recurrent disease located in the surgically treated thyroid bed and confirmed by cytologic sampling or histologic analysis after further surgery. Regional recurrence was defined as recurrent disease found in cervical lymph nodes, again confirmed by cytologic sampling or histopathologic features after subsequent surgical resection. Distant recurrence was determined by imaging studies, including radioiodine uptake scans, computed tomography, and positron emission tomography, or cytologic and histopathologic evidence when available. Biochemical recurrence alone was not coded as recurrence within this data set.

Disease-specific outcomes were calculated using the date of the last follow-up visit with the treating surgeon or endocrinologist at MSKCC. Details of death were determined from death certificates and hospital records when available. All patients who had evidence of active structural disease at the time of last follow-up and died during follow-up were considered to have died of disease. The median follow-up for the entire patient cohort was 60 months (range, 1-282 months). Outcomes data were therefore calculated at 5 years. Statistical analysis was carried out using SPSS software (SPSS Inc). Variables were compared within groups using the Pearson χ^2 test. Survival outcomes were analyzed using the Kaplan-Meier method. Univariate analysis was carried out by the log-rank test. $P < .05$ was considered significant.

RESULTS

INTERMEDIATE-RISK PATIENTS OLDER THAN 45 YEARS WITH LOW-RISK TUMORS

There were 344 patients older than 45 years with low-risk tumors. Within this group, 196 patients (57%) did not receive RAI. The descriptive statistics of this group are shown in **Table 2**. These patients were more likely to be female, to have pT1 disease, and to be free of nodal metastases. Using the ATA risk of recurrence system, retrospective analysis shows that the vast majority of patients who were selected not to have RAI (91%) were at low risk of recurrence.

Table 2. Descriptive Statistics of Intermediate-Risk Patients Older Than 45 Years With Low-Risk Tumors Stratified by the Use of Radioactive Iodine (RAI) or No Use of RAI

Variable	No. (%)			*P* Value
	Patients (N = 344)	No RAI (n = 196)	RAI (n = 148)	
Sex				<.001
Female	265 (77)	166 (85)	99 (67)	
Male	79 (23)	30 (15)	49 (33)	
pT stage				<.001
T1	273 (79)	176 (90)	97 (66)	
T2	71 (21)	20 (10)	51 (34)	
Microcarcinoma, cm				<.001
<1	152 (44)	118 (60)	34 (23)	
>1	192 (56)	78 (40)	114 (77)	
pN stage				<.001
N0	283 (82)	183 (93)	100 (67)	
N1	61 (18)	13 (7)	48 (33)	
ATA risk				<.001
Low	277 (80)	179 (91)	98 (66)	
Intermediate	66 (19)	17 (9)	49 (33)	
High	1 (1)	0	1 (1)	

Abbreviation: ATA, American Thyroid Association.

Table 3. Factors Predictive of Recurrence-Free Survival (RFS) in Patients Older Than 45 Years With Low-Risk Tumors

Variable	Patients, No. (%) (N = 344)	5-Year RFS, %	Univariate *P* Value
Sex			.38
Female	265 (77)	97	
Male	79 (23)	97	
pT stage			.95
T1	273 (79)	97	
T2	71 (21)	98	
Microcarcinoma, cm			.41
<1	152 (44)	97	
>1	192 (56)	97	
pN stage			.004
N0	283 (82)	99	
N1	61 (18)	91	
ATA risk			<.001
Low	277 (80)	99	
Intermediate	66 (19)	94	
High	1 (1)	100	
RAI			.23
No	196 (57)	98	
Yes	148 (43)	96	

Abbreviations: ATA, American Thyroid Association; RAI, radioactive iodine.

With a median follow-up of 51 months, the 5-year DSS and RFS were 100% and 97%, respectively. The 5-year RFS was 96% vs 98% for the RAI group vs the no RAI group ($P = .28$). Two non-RAI patients developed recurrence (both regional), whereas 6 patients who received RAI developed recurrence (1 locoregional, 1 regional, 2 regional and distant, and 2 isolated distant recurrences). Analysis of factors predictive of recurrence identified positive nodal status as significant (**Table 3**) (5-year RFS, 99% for N1 vs 91% for N0 [$P = .004$]). Stratifying by primary tumor size, no significant difference in DSS or RFS was found between the RAI group and the no RAI group (5-year DSS for <1 cm, 100.0% vs 97.2% [$P = .55$]; 1-2 cm, 97.1% vs 100.0% [$P = .31$]; and 2-4 cm, 100% vs 100% [$P > .99$] for the RAI group vs the no RAI group, respectively).

INTERMEDIATE-RISK PATIENTS YOUNGER THAN 45 YEARS WITH HIGH-RISK TUMORS

One hundred eighty-eight intermediate-risk patients were younger than 45 years and had pT3 or pT4 disease. The descriptive statistics of this subgroup are shown in **Table 4**. As expected, the vast majority of patients were treated with RAI. Only 29 patients (15%) were treated without postoperative RAI.

With a median follow-up of 54 months, the 5-year DSS and RFS in this group were 100% and 89%, respectively. The 5-year RFS was 88% vs 95% for the RAI group vs the no RAI group. There was 1 distant recurrence in the group selected not to receive RAI. In the group treated with RAI, there were 18 recurrences (1 locoregional and distant, 10 isolated regional recurrences, 4 regional and distant, and 3 isolated distant recurrences). Analysis of RFS confirmed nodal status as the only significant predictor of poor outcome within this group (5-year RFS, 100% for N0 vs 86% for N^+ [$P = .02$]). Administration of RAI was not found to predict outcome (**Table 5**).

Further analysis of the records of the 29 patients who were treated without RAI was performed to determine the reason for this selection. In 3 patients, the decision was based on negative postoperative RAI scan results. Two patients chose not to receive RAI. A further 2 patients had advanced-stage synchronous malignant neoplasms, which influenced treatment. One patient was pregnant. Of the remaining 21 patients, 5 had pT3 disease without evidence of ETE, and 8 had pT3 disease with microscopic ETE. Both of these groups were considered to be at low risk for recurrence. Four patients had N1 disease,

Table 4. Descriptive Statistics of Intermediate-Risk Patients Younger Than 45 Years With High-Risk Tumors Stratified by the Use of Radioactive Iodine (RAI) or No Use of RAI

Variable	No. (%)			*P* Value
	Patients (N = 188)	No RAI (n = 29)	RAI (n = 159)	
Sex				.96
Female	124 (66)	19 (65)	105 (66)	
Male	64 (34)	10 (35)	54 (34)	
pT stage				.50
T3	161 (86)	26 (90)	135 (85)	
T4	27 (14)	3 (10)	24 (15)	
Microcarcinoma, cm				.53
<1	19 (10)	2 (7)	17 (11)	
>1	169 (90)	27 (93)	142 (89)	
ETE				.03
None	21 (11)	7 (24)	14 (9)	
Microscopic	115 (61)	13 (45)	102 (64)	
Macroscopic	52 (28)	9 (31)	43 (27)	
pN stage				.01
N0	49 (26)	13 (45)	36 (23)	
N1	139 (74)	16 (55)	123 (77)	
ATA risk				.22
Low	13 (7)	4 (14)	9 (6)	
Intermediate	123 (65)	16 (55)	107 (67)	
High	52 (28)	9 (31)	43 (27)	

Abbreviations: ATA, American Thyroid Association; ETE, extrathyroid extension.

Table 5. Factors Predictive of Recurrence-Free Survival (RFS) in Patients Younger Than 45 Years With High-Risk Tumors

Variable	Patients, No. (N = 188)	5-Year RFS (19 Events), %	Univariate *P* Value
Sex			.92
Female	124	89.3	
Male	64	87.3	
pT stage			.56
T3	161	89.8	
T4	27	81.7	
Microcarcinoma, cm			.15
<1	19	100	
>1	169	87.6	
ETE			.97
None	21	87.5	
Microscopic	115	90.3	
Macroscopic	52	85.1	
pN stage			.02
N0	49	100	
N1	139	85.5	
ATA risk			.52
Low	13	100	
Intermediate	123	88.8	
High	52	85.1	
RAI			.26
Yes	159	87.9	
No	29	94.7	

Abbreviations: ATA, American Thyroid Association; ETE, extrathyroid extension; RAI, radioactive iodine.

which was low volume (<5 nodes positive and <1 cm maximum size). In the remaining 5 patients, no cause could be found for the decision not to give RAI (**Figure**).

COMMENT

The role of RAI in the treatment of patients with PTC has changed over the decades. This change in treatment is because of the recognition that RAI has associated complications[4-11] and has been reported to increase the risk of second cancers.[12-15] Also, there is controversy over its efficacy in some patients. Despite this, an increasing proportion of patients now receive RAI, and there is significant variation in those rates across the United States.[16]

A variety of risk stratification systems are available for clinicians; however, for approximately 30 years in our institution, treatment decisions have been based on the GAMES classification. For this reason, we selected the intermediate-risk GAMES patients as the focus of our study. Current guidelines agree that for the lowest-risk patients, with small primary lesions limited to the thyroid gland, RAI does not confer any survival or recurrence advantage, whereas for larger, more aggressive high-risk tumors, RAI is beneficial.[1,17,18] The role of RAI in patients deemed at intermediate risk of death (according to the GAMES system) is less clear. In this group, there is conflicting or inadequate evidence, which is likely to contribute to the heterogeneous use of RAI in the United States and which is why we chose this patient group as the focus for this study.

After surgical therapy, a decision regarding whether to proceed with RAI ablation must be made among the surgeon, the endocrinologist, and the patient. International guidelines recommend RAI for all tumors that are over 1 cm in greatest dimension, that are associated with ETE, or that have metastatic disease.[1,17,18] Given the known high rates of occult nodal metastasis to the central[19] and lateral aspects of the neck,[20] clinicians may therefore con-

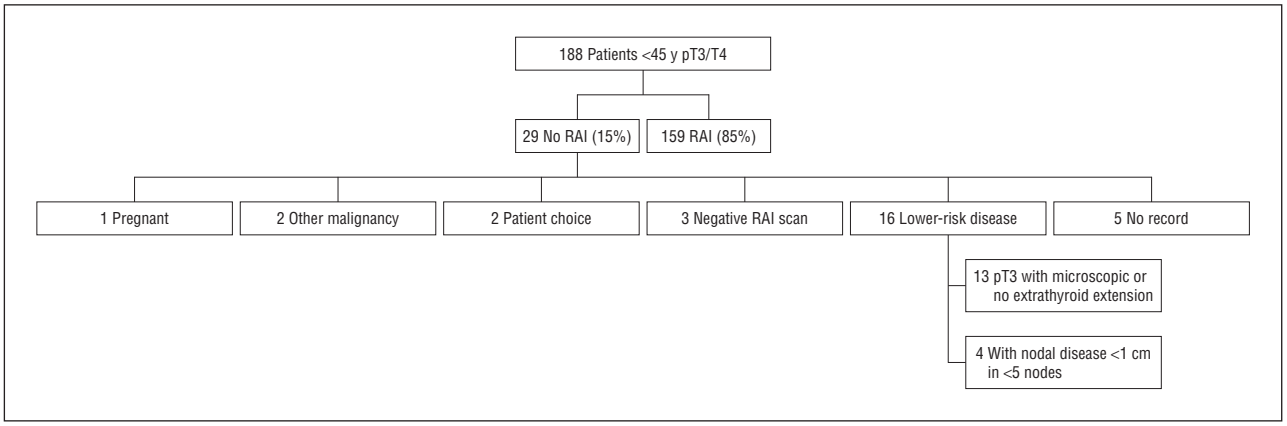

Figure. Flowchart showing the reasons 29 patients younger than 45 years with pT3/T4 disease did not receive radioactive iodine (RAI).

sider the use of RAI in almost all patients who are believed to be at intermediate risk. Indeed, in units that select only thyroid nodules that are larger than 1 cm to target for fine-needle aspiration, all patients diagnosed are potential candidates for RAI.

Although the adverse effects of RAI are of reduced severity in comparison to those of external beam radiotherapy to the head and neck, they are potentially long lasting and significant to the patients affected. A number of groups have shown that iodine uptake outside thyroid tissue results in substantial salivary and lacrimal dysfunction.[4,6] A recent report on the effect of RAI after total thyroidectomy suggested increased rates of dysphagia in patients who received RAI.[4] These late adverse effects have been reported to have a negative impact on quality-of-life scores for patients who receive high doses of RAI.[8] Perhaps more important is the reported increased risk of second primary malignant neoplasms developing in patients who are treated with high-dose RAI, with groups reporting increased rates of salivary and hematological malignant neoplasms after RAI therapy.[12,15] This improved understanding of the long-term effects of RAI means that a balance between the risks and benefits of RAI must be made in treating individual patients.

Because of these factors, and the limited data on the efficacy of RAI in low- and intermediate-risk GAMES patients, we have become more selective in the use of RAI over the last 25 years in our institution. We have practiced a selective approach to therapy, treating patients on a case-by-case basis. It is the results of this approach in relation to RAI that we report in this article. We present data on the 2 intermediate subgroups: low-risk patients with high-risk tumors and high-risk patients with low-risk tumors.

There were 344 patients older than 45 years with low-risk tumors (pT1/T2) (Table 2). One hundred ninety-six patients (57%) in this group were selected not to receive RAI. These patients were more likely to be female and have smaller primary disease and no evidence of regional metastases. This select group of patients had excellent 5-year DSS and RFS outcomes (100% and 98%, respectively [Table 3]), showing that our selection was justified. Only 7 of these older patients (3%) with evidence of nodal disease were selected for treatment without RAI, as previous work from our institution has shown that survival in older patients is negatively affected by the presence of nodal disease.[21]

In contrast, the subgroup of patients younger than 45 years with high-risk tumors (pT3/T4) received RAI in most cases (84%). Only 29 of these patients (16%) did not receive RAI (Table 4) for reasons including pregnancy, synchronous aggressive malignant neoplasms, and patient choice. Most patients in this group who did not receive RAI had low-risk local or regional disease. The 5-year DSS and RFS of these patients were 100% and 95%, respectively (Table 5). Therefore, using very careful selection, even a small number of young patients with high-risk tumors can be treated without RAI. However, it must be emphasized that this selection requires a multidisciplinary team of surgeons and endocrinologists with a large experience.

Like all retrospective studies, our data have limitations. There is obvious selection bias, by both physician and patient, in the decision to use RAI. During the period studied, the use of RAI, both locally and nationally, evolved toward more patients being treated; however, our patients were all treated within a single tertiary referral cancer center with a fairly uniform approach to surgery, histopathologic reporting, postoperative treatment, and follow-up, which cannot be said for studies that are based mainly on the records of national databases. The median follow-up within this cohort was approximately 5 years, which limits the conclusions that can be drawn from survival data, as deaths may occur beyond this time. For this reason, recurrence data were also included as a surrogate end point. Follow-up protocols during the period studied were based on the results of clinical examination, without the routine use of thyroglobulin measurement or annual ultrasonography. Therefore, most recurrences were palpable structural disease rather than sonographically identified small-volume, or "biochemical," recurrence. Our aim was not to assess the efficacy of RAI; therefore, we cannot draw conclusions on its overall effects. However, our data can be used to identify patients who can be safely treated without RAI. These patients are older than 45 years with T1 and T2 tumors and without any adverse histologic features or pathologically positive neck disease. All other intermediate-risk patients should be treated with adjuvant RAI with the exception of a few highly selected young patients with lim-

ited neck disease in both the number and the size of affected nodes.

In conclusion, as the adverse effects of RAI and the long-term impact on quality of life have been recognized, clinicians must now appropriately select patients for adjuvant therapy. Those cases judged to be at intermediate risk of death after surgical therapy can expect excellent long-term outcomes. Our study shows that the subgroup of patients who are older than 45 years with tumors smaller than 4 cm that are confined to the thyroid gland or with limited ETE and with negative neck disease can safely be treated without RAI.

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