Influence of Initial Treatment on the Survival and Recurrence in Patients With Differentiated Thyroid Microcarcinoma

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Jasna Mihailovic, MD, PhD,† Ljubomir Stefanovic, MD, PhD,* and Ranka Stankovic, PhD‡*

Purpose: Differentiated thyroid microcarcinoma (DTM) has a good prognosis and survival, but recurrent disease may appear during follow-up. The aim of this study was to evaluate the influence of initial treatment including surgery and radioactive iodine (^{131}I) on the survival and recurrence in patients with DTM.

Methods: Between January 1979 and December 2006, 130 patients with DTM were retrospectively evaluated, with a median follow-up of 10 years. Total/near-total thyroidectomy was performed in 121 (93.1%) of 130 patients, followed with ^{131}I ablation in 71 (54.6%) of 130 patients.

Results: The probability of disease-specific survival was 97.7% ± 1.3% after 5 and 10 years; the probability of disease-specific survival was 95.9% ± 2.2% after 15, 20, 25, and 28 years after the initial treatment and was significantly influenced by recurrence, clinical stage, and patients' age ($P = 0.0001$, $P = 0.0005$, and $P = 0.02$, respectively). Sex, histopathological type of the tumor, metastases at presentation, initial treatment, performance of radioactive therapy, and risk categories had no influence on survival ($P = 0.8$, $P = 0.6$, $P = 0.1$, $P = 0.4$, $P = 0.5$, and $P = 0.1$, respectively). The overall recurrence rate was 10.8%, (6.9% in lymph nodes, 1.5% in thyroid bed, and 2.3% at distant sites), with a median appearance time of 30 months. Recurrences were significantly influenced by regional metastases at presentation, radioiodine ablation, and initial treatment ($P = 0.0002$, $P = 0.005$, and $P = 0.003$, respectively); there was no relationship based on age, sex, histological type of the tumor, and tumor multifocality.

Conclusions: To perform more accurate surveillance for recurrence, total/near-total thyroidectomy followed by radioiodine ablation may be the optimal initial treatment for patients with DTM.

Key Words: thyroid gland, microcarcinoma, recurrence, survival, surgery, radioiodine ablation

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Microcarcinoma of the thyroid gland is also called *occult* or *small thyroid carcinoma*. It is a term used to describe differentiated thyroid carcinoma (DTC) measuring 1 cm or less. The frequency of occult papillary carcinoma varies among published studies from 3.5% to 39.5% of all patients undergoing thyroidectomy.[1–4]

From 1988 to 2002, there was an increase of 49% in the number of thyroid cancers identified as microcarcinomas. This astonishing high increase in incidence is likely due to advances in thyroid diagnostics including ultrasound and fine-needle aspiration biopsy.[5] There is, however, also a high prevalence of incidental papillary thyroid microcarcinoma (PTM) in postmortem studies and in pathological resection specimens. Significant but unexplained geographic differences of PTM incidence rates in autopsy series are also observed as follows: 1% in Brazil,[6] 13% in Hong Kong,[3] and 35.6% in Finland.[7]

Differentiated thyroid microcarcinoma (DTM) is usually indolent in nature, with mortality as low as 0.15%,[8] with a range from 0.2% to 1% mortality incidence.[3,9–12] Nevertheless, some patients develop recurrent disease: in 4.0% to 13.4% of patients, metastases appear in lymph nodes,[3,8,13–16] whereas the frequency of distant metastases ranges from 0.2% to 1.5%.[3,8,9,12,16–18]

At present, it is not possible to define the single best initial treatment for all patients. Although several guidelines suggest optimal management for microcarcinoma of the thyroid gland, debates continue regarding the best initial treatment. In low-risk patients with unifocal intrathyroidal microcarcinomas without evidence of nodal or distant metastases, both the American Thyroid Association (ATA) Guideline and the European Consensus Guideline recommend lobectomy alone as a sufficient treatment.[19,20] The guidelines of the German Society of Nuclear Medicine suggest that radioiodine (RAI) ablation is not necessary after limited surgical resection in patients with PTM.[21] The British Thyroid Association is in agreement with previous guidelines suggesting that microcarcinomas of the thyroid gland can be adequately treated by lobectomy alone followed by L-thyroxine therapy.[22] Ito et al[18] conclude that hemithyroidectomy with elective lymph node dissection without RAI therapy is an adequate surgical treatment owing to a 1% risk of recurrence among patients with solitary PTM without lymph node or distal metastases.

Multifocality is common in occult carcinoma and is associated with an increased rate of recurrence.[8] The extent of thyroid gland resection is still controversial for incidental multifocal papillary microcarcinomas. These tumors are not identified preoperatively but are recognized only after the final histopathological result after unilateral lobectomy. According to the previously mentioned guidelines, completion thyroidectomy should be offered to those patients.[18,22] Radioactive iodine, as adjuvant therapy after total or near-total thyroidectomy (TT/NTT), is recommended only in high-risk patients presenting with nodal or distant metastases because their risk of relapse and cancer-specific mortality is higher than in low-risk patients.[23,24]

The aim of this study was to retrospectively evaluate influence of surgery and RAI therapy as an initial treatment, on the recurrence and survival of patients with DTM.

PATIENTS AND METHODS

Patients

A retrospective review of patients with DTM presenting at the Oncology Institute of Vojvodina from January 1979 to December 2006 was performed. During this period, a total of 1040 patients with DTC were treated. In this study, we evaluated 130 (12.5%) patients classified as microcarcinoma.

All relevant clinical information including diagnosis at presentation, histological reports from the initial surgery (size, type of the tumor), and cause of death were extracted from medical records. Study end points included date of last follow-up and date of death.

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From the *Department of Nuclear Medicine, Oncology Institute of Vojvodina, Sremska Kamenica & University of Novi Sad, Technical Faculty "Mihajlo Pupin", Zrenjanin; †Department of Nuclear Medicine, Oncology Institute of Vojvodina, Sremska Kamenica-retired; and ‡Faculty of Mining and Geology, University of Belgrade, Belgrade, Serbia.

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Dr Stefanovic is deceased.

Reprints: Department of Nuclear Medicine, Oncology Institute of Vojvodina, Institutski put 4,Sremska Kamenica 21204, Serbia; University of Novi Sad, Serbia,Technical Faculty "Mihajlo Pupin", Djure Djakovica bb, Zrenjanin 23000, Serbia. E-mail: jasnans@eunet.rs.

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Patients who underwent RAI therapy but were lost to follow-up were excluded from this study.

Patients were selected and staged according to the Union for International Cancer Control (IUCC) 7th edition of TNM classification.[25] Patients' categorization into risk groups was made according to the pathologist's reports and the 2006 European consensus guideline.[20]

Treatment

Surgery

The Oncology Institute is a referral hospital for diagnosis, treatment, and follow-up of DTC in the region. Primary surgery was performed in several hospitals throughout the country using a variety of surgical protocols. There was no uniform protocol among the institutions for the extent of surgery and of node sampling. Those patients who underwent initial treatment in our institution were treated according to the protocol of diagnostics, treatment, and control of malignant thyroid tumors.[26] This protocol suggests that all DTC patients including DTM should be treated with total thyroidectomy followed by RAI ablation. Patients who did not undergo postsurgical treatment with RAI received replacement or suppressive L-thyroxine therapy and were referred only for postsurgical ^{131}I whole-body scan (^{131}I-WBS) and follow-up.

Radioiodine Therapy

Because there was no consensus throughout the country, initial treatment of patients differed among hospitals. Some patients were advised to receive RAI ablation and others were not. Our institution was the only facility in the country treating DTC with radioactive iodine (^{131}I) until 2006; 3.7-GBq (100 mCi) ^{131}I was used for ablation in patients without nodal and distal metastases (N0M0), whereas 5.55-GBq (150 mCi) ^{131}I was used in patients with regional and distal metastases (N1M0/N1M1). Radioiodine therapy was administered additionally if a patient did not achieve successful ablation or in case of persistent disease (patients with persistently detectable thyroglobulin [Tg] levels on L-thyroxine treatment) or recurrence detection on imaging. Posttherapy ^{131}I-WBS was performed 72 to 96 hours after the RAI treatment in all patients.

Follow-up

The median follow-up of our patients was 10 years and ranged from 8 months to 25 years. Patients were monitored every 3 months during the first year, at 6-month intervals during the next 5 years, and annually thereafter. Routine follow-up included physical examination of the patient's neck, laboratory tests, ultrasound study of the neck (only in those who underwent partial thyroidectomy), and ^{131}I-WBS. Diagnostic WBS was performed 1 year after the RAI ablation using the activity of 111-MBq (3 mCi) ^{131}I. Successful ablation was confirmed in the absence of pathological uptake of ^{131}I and if Tg level was less than 1 ng/mL.

In patients with confirmed recurrent disease (confirmation was done by ^{131}I-WBS, increased Tg serum level, or fine-needle aspiration with cytology), secondary treatment was performed. This treatment included additional surgery, tumor removal and/or lymphadenectomy, and neck dissection if necessary. If pathological WBS uptake was still present after the second surgical treatment, patient underwent additional RAI therapy with ^{131}I (between 5.55 and 7.4 GBq).

Laboratory Analyses

Analyses included routine measurements of Tg, Tg antibodies, free triiodothyronine, and thyroid-stimulating hormone. From 2006, we changed laboratory technique and switched from radioimmunoassay to electrochemiluminescence immunoassay (Roche Diagnostics GmbH Mannheim, Germany) (normal Tg levels was considered as <5 μg/L and <1.00 ng/mL, respectively).

Statistical Analysis

The χ^2 test was used to analyze variables. The Kaplan-Meier method and log-rank test were used to calculate time-dependent variables using statistical software SPSS version 8 (SPSS Inc, Chicago, IL). A value of $P < 0.05$ was considered to be significant.

RESULTS

A summary of the patients' characteristics including demographic and histological data as well as mode of initial treatment is outlined in Table 1. We analyzed 130 patients with DTM: 108 (83.1%) were female and 22 (16.9%) were male patients (female-to-male ratio, 5.9:1) aged from 10 to 80 years (mean age, 44 years). Among the studied group, only 5.4% of patients had follicular thyroid cancer; the remainder was classified as papillary carcinoma. Total thyroidectomy was performed in 50 patents, combined with neck dissection in 12 of them. At the time of diagnosis, approximately 13% of patients were managed with less than TT (8 patients underwent NTT, whereas partial thyroidectomy was performed in 9 patients: lobectomy was performed in 6, isthmectomy was performed in 1, and nodulectomy was performed in 2). Surgery followed by RAI ablation was performed initially in 63 patients, combined with neck dissection in 23 of them.

Patients were classified according to the UICC 7th TNM classification and staging system. However, 9 patients submitted to surgical procedures less than TT/NTT were not staged. There were 88 patients (72.7%) with unifocal tumor (T1a) and 33 patients (27.3%) with multifocal spread of the tumor (T1b). Classification of patients according to the presence or absence of regional/distal metastases are

TABLE 1. Patients' Data at Presentation

Patients' Data and Initial Treatment	n	%
Demographic and histological characteristics		
Sex		
Women	108	83.1
Men	22	16.9
Total	130	100.0
Age group		
<45	69	53.1
>45	61	56.9
Total	130	100.0
Histology		
Papillary	123	94.6
Follicular	7	5.4
Total	130	100.0
The mode of initial treatment		
Surgical treatment		
TT	50	38.5
NTT	8	6.2
PT	9	6.9
Total	67	51.6
Surgical treatment + RAI		
TT + RAI	63	48.4
Total no. treated patients	130	100.0

EBRT, external beam radio therapy; PT, partial thyroidectomy.

TABLE 2. Patients' TNM Classification and Staging

Initial N + M Classification			Revised N + M Classification at the End of Follow-up Period		
Group	n	%	Group	n	%
N0M0	76	62.8	N0M0	75	62.0
N1M0	43	35.5	N1M0	41	33.9
N1M1	2	1.7	N1M1	5	4.1
Total	121	100.0	Total	121	100.0
Initial TNM staging			Revised TNM Staging at the End of Follow-up Period		
Stage	n	%	Stage	n	%
I	106	87.6	I	104	86.0
II	1	0.8	II	2	1.6
III	10	8.3	III	10	8.3
IVa	3	2.5	IVa	2	1.6
IVc	1	0.8	IVc	3	2.5
Total	121	100.0	Total	121	100.0

Patients' categorization was done according to the UICC 7th TNM classification.[25]

shown at Table 2. At presentation, approximately one third of the patients (36%) had regional lymph nodes (N1M0), whereas 1.7% of the patients had distant metastases combined with regional metastases (N1M1). During the course of disease, TNM classification and staging were revised owing to the alteration in the course of disease. Thus, one patient who was initially free of metastases (N0M0) developed regional metastases and upstaged into N1M0, whereas another 3 patients who presented initially with regional metastases (N1M0) developed distal metastases and upstaged into N1M1. Distal metastases involved the lungs in all 5 patients.

Different initial treatment, recurrences, and different outcome of patients are shown at Figure 1. During the follow-up, some of patients received additional treatment owing to persistent or recurrent disease, including surgical removal of tumor tissue, neck dissection alone, or combined with RAI therapy, whereas external beam radio therapy was performed in 2 patients. The type of recommended treatment was ordered according to the medical board consisted of several different specialists (nuclear medicine physician, oncologist, specialist for radiotherapy, and surgeon). At the last follow-up, 121 patients (93.1%) were alive, and 9 patients (6.9%) had died. Among living patients, 126 (96.9%) achieved remission of disease (complete remission, 122 patients [93.8%]; partial remission, 4 patients). Among them, 5 of 126 patients died of other causes. Disease-related deaths occurred in 4 patients (owing to progression of recurrences in regional lymph nodes in 2, progression of recurrences in thyroid bed in 1, progression of recurrences in thyroid bed associated with recurrences in regional lymph nodes in 1, and progression of regional lymph node recurrences associated with recurrences of distal sites in 1).

The probability of disease-specific survival (DSS) was 99.2% ± 0.8% 1 year after initial treatment, 97.7% ± 1.3% after 5 and 10 years, and 95.9% ± 2.2% after 15, 20, 25, and 28 years (Fig. 2A). Kaplan-Meier analyses demonstrated that DSS was significantly influenced by recurrence ($P = 0.0001$), clinical stage ($P = 0.0005$), and patients' age ($P = 0.02$) (Fig. 2B–D, respectively). However, other prognostic factors such as sex, histopathological tumor type, metastases at presentation, type of the initial treatment, RAI therapy, and risk categories showed no influence on survival ($P = 0.8$, $P = 0.6$, $P = 0.1$, $P = 0.4$, $P = 0.5$, and $P = 0.1$, respectively).

During the course of disease, 14 patients (10.8%) who achieved remission after initial treatment, developed local recurrence—in lymph nodes in 9 patients (6.9%) and in thyroid bed (local recurrence) in 2 patients (1.5%), whereas recurrence at distant site appeared in 3 patients (2.3%)—isolated in 1 patient, associated with lymph node recurrence in another patient, and combined with local recurrence in a third patient. The median appearance time of recurrence was 30 months (range, 8 months to 8 years). The median follow-up of patients who developed recurrences was approximately 7 years (range, 4 months to 23 years). The probability of appearance of recurrences is shown in Figure 3A. It was significantly influenced by lymph node metastases at the time of presentation ($P = 0.0002$) (Fig. 3B), by application of RAI ($P = 0.005$) (Fig. 3C) and by initial treatment ($P = 0.003$) (Fig. 3D). However, there was no significant difference associated with the following prognostic factors: multifocality of the tumor, histological type of the tumor, age, and sex ($P = 0.1$, $P = 0.3$, $P = 0.8$, and $P = 0.6$, respectively).

DISCUSSION

Differentiated microcarcinoma was detected in 12.5% of all thyroid cancer patients seen in our institution for evaluation. According to many authors, the overall survival for PTM is excellent.[23,24] Our analysis of 130 patients with DTM confirms the

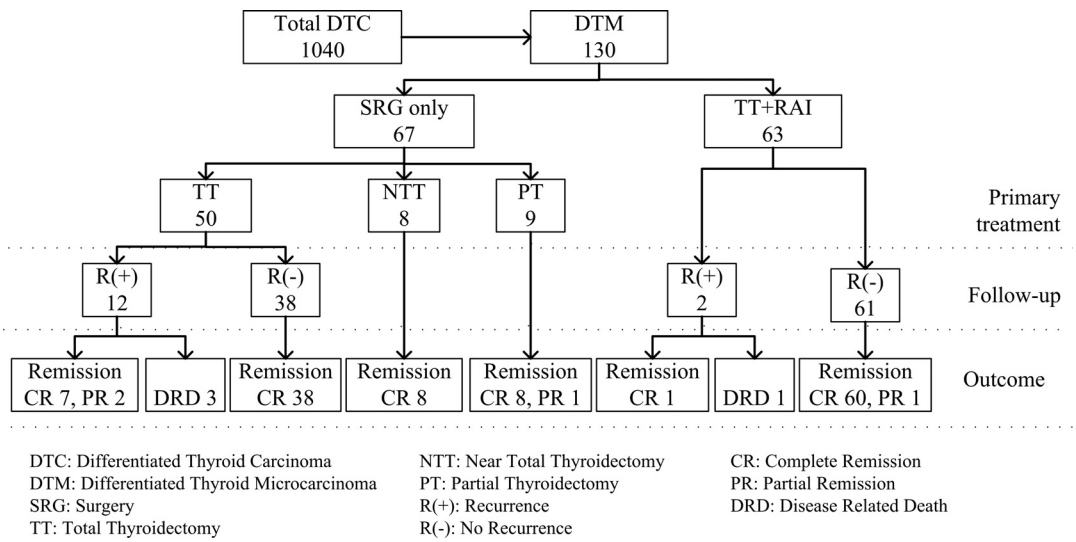

FIGURE 1. Type of initial treatment, follow-up, and outcome of patients.

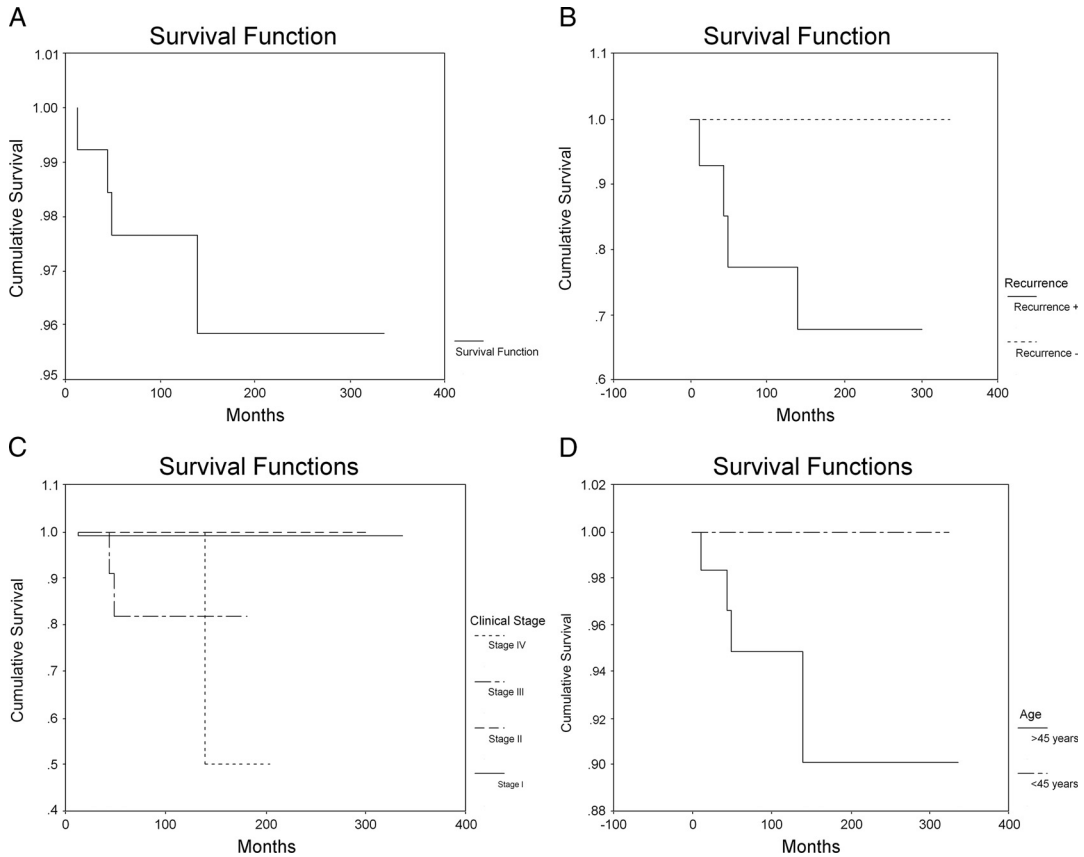

FIGURE 2. **A**, Probability of DSS. **B**, Influence of recurrence on DSS; - - - patients without recurrence, patients with recurrence ___. **C**, Influence of clinical stage on DSS. ____ patients staged I; _ _ _patients staged II; __ _ patients staged III; - - - - - patients staged IV. **D**, Influence of patients' age on DSS; ___ _ patients younger than 45 years; ____ patients older than 45 years.

excellent long-term survival of patients with this finding and is consistent with published reports. Disease-specific survival was approximately 98% after 5 and 10 years, and 96% after 15, 20, 25, and 28 years from the initial treatment. The disease-specific mortality rate is 3% in our study. This is somewhat higher than those of other reports with a wide range from 0.04%[18] to 0.4%.[15] Several authors do not report disease-related deaths in their studies.[1,2,13,14,17,27–29] Whether this reflects differences in access to medical diagnosis, surgical practice, or simply statistical sampling is not possible to determine.

Consistent with the larger studies of Hay et al[16] (900 patients) and Ito et al[28] (732 patients), our study showed that among several prognostic factors, recurrence, clinical stage, and patients' age had a statistically significant influence on DSS ($P = 0.0001$, $P = 0.0005$, and $P = 0.02$, respectively). Sex, histopathological type of the tumor, metastases at presentation, type of the initial treatment, performance of radioactive therapy, and risk categories had no influence on survival ($P = 0.8$, $P = 0.6$, $P = 0.1$, $P = 0.4$, $P = 0.5$, and $P = 0.1$, respectively).

Multiple foci of microcarcinoma are often found on histopathological examination. In general, there has been reasonable consistency between our findings and those published by others (Table 3). Among all thyroid carcinomas, multifocal papillary microcarcinoma has been reported to have a frequency of 0.5%.[1] In the cohort of papillary microcarcinomas only, the frequency of tumor multifocality varies from 15% to 38%.[1,2,8,27] Baudin et al[13] detected multifocality as the most effective predictor of local relapse, correlating with the initial presence of nodal metastases. Consistent with these findings, Pelizzo et al,[17] Pellegriti et al,[27] and Ito et al[28] found a similar prevalence of multifocal tumor foci and lymph node metastases (12.1% and 13.4%, 31.8% and 30.1%, and 42.8% and 47.9%, respectively). Ito et al reported more than 40% of patients who presented with lymph node metastases and multiple tumor foci.[2] Our data are consistent with the reports of a similar frequency of tumor multifocality (25%) and lymph node metastases at presentation (34.6%). Nevertheless, others suggest that multiple tumor foci are not indicative of tumor aggressiveness. Thus, Roti et al[2] reported multifocal disease in 32% of cases, whereas lymph node metastases were present in only 13.2%; however, in 1992, Hay et al reported that recurrences were influenced by the presence of metastatic lymph nodes as well as the extent of initial surgery.[15]

Distant metastases at presentation were observed in 1.5% of patients in our study; others have reported distal metastases in 2.0% to 2.7%.[2,3] According to some reports, multifocality is associated with increased rates of recurrent diseases if patients undergo less than NTT.[8] In contrast, our univariate analysis showed that there was no influence of tumor multifocality on the probability of recurrences ($P = 0.1$).

Reported lymph node recurrence rates ranged in other studies from 1.7% to 6.7%.[2–4,8,13] The overall recurrence rate in our study was 10.8%, with the median follow-up of 7 years. The probability of recurrences during the first year was 5.4% and 9.3% during the 5 years after the initial treatment. A possible explanation of the high recurrence rate may be that our study population had their primary surgery at hospitals throughout the country performed with a variety

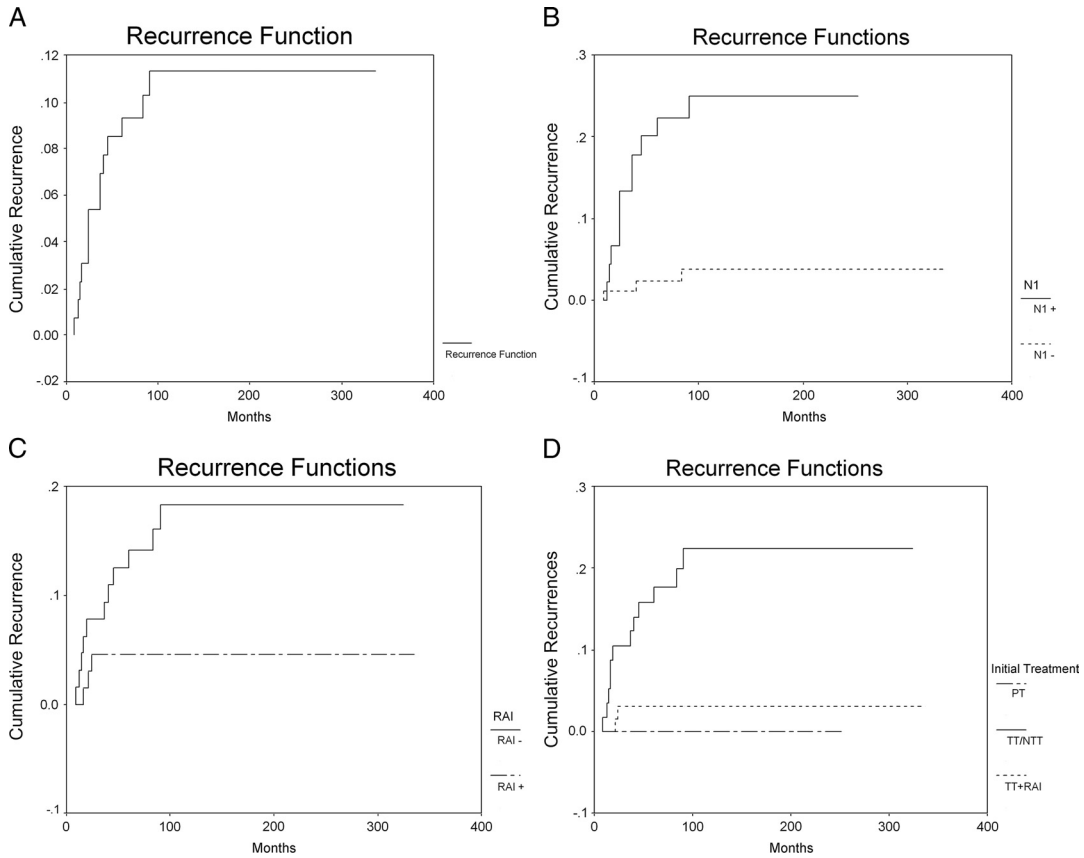

FIGURE 3. **A**, Probability of recurrence. **B**, Influence of initial N1 on probability of recurrence; ___ patients with nodal metastases (N1+); ----patients without nodal metastases (N–). **C**, Influence of RAI on probability of recurrence; — – patients who received RAI ablation (RAI+); ___ patients who did not receive RAI ablation (RAI–). **D**, Influence of initial treatment on probability of recurrence; ---- patients who underwent total thyroidectomy and RAI ablation (TT + RAI); __ _ patients who underwent partial thyroidectomy (PT); ___ patient who underwent TT/NTT.

of surgical protocols and surgical experience. Consequently, the skill of the diverse surgeons, especially those in small community facilities with limited number of total thyroidectomies annually resulted in less complete nodal dissections compared with the more experienced thyroid surgeons at a large academic center.

Regardless of the location, there remains today a variety of opinions about appropriate surgical practice involving sampling of lymph nodes at surgery. Not surprisingly, there is still controversy as to whether the presence of lymph node metastases at presentation represents a risk factor for recurrent disease. Several authors report a similar frequency recurrence rate and nodal metastases at presentation,[4,14] whereas others detected increased[3,27] or low recurrence rates.[13,15] It is not possible to determine in a retrospective study whether these differences are a consequence of variable surgical technique or true differences in different populations. Wada et al[29] reported a high prevalence of 64% for lymph node metastases at presentation and a paradoxically low recurrence rate of only 0.5%. Similarly, Ito et al[28] detected 47.9% of lymph node metastases at presentation in contrast to low recurrence rate after a follow-up of 5 and 8 years (2.6% and 5%, respectively). More recently, Hay et al[16] also reported higher recurrence rates in node-positive patients ($P < 0.001$). In agreement with the data of Hay et al, our data indicated that the probability of recurrence was significantly influenced by regional lymph node metastases at the time of presentation ($P = 0.0002$). We also detected that recurrence rate was significantly influenced by RAI and the type of initial treatment ($P = 0.005$ and $P = 0.003$, respectively). At the same time, there was no relationship based on age, sex, histological type of the tumor, and tumor multifocality.

The treatment of the thyroid microcarcinoma still remains controversial. We, like other, have reviewed the literature to determine the best approach to treating thyroid microcarcinoma.[30] Near-total thyroidectomy is preferred in DTC by many clinicians over partial thyroidectomy because of the following: (*a*) potential multicentricity in papillary cancer, (*b*) frequent nodal disease, (*c*) highly invasive nature of follicular carcinoma (when follicular carcinoma is detected), and (*d*) difficulty in ablation of large thyroid remnant by ^{131}I.[31] However, in patients with thyroid microcarcinoma, who represent a low-risk group, lobectomy or subtotal thyroidectomy is recommended as a sufficient surgical treatment,[19–22] whereas others state that total removal of the thyroid gland is essential.[18] In an early study, Hay et al[15] found a higher recurrence rate in patients who underwent hemithyroidectomy and presented initially with lymph node metastases. However, these authors published contradicting results with respect to their earlier study and reported no difference in recurrence rate regardless of the extent of initial surgery (unilateral lobectomy vs total thyroidectomy).[16] Most recently, Ogilvie et al[32] stated that total thyroidectomy should be considered as the initial surgical operation for thyroid tumors 6 to 10 mm in which preoperative fine-needle aspiration biopsy is diagnostic or suspicious for well DTC. They showed that 61% of patients with tumors of 6 to 10 mm had 1 or more adverse pathologic factor (multifocality, extrathyroidal extension,

TABLE 3. Review of Author's Data

Author	Reference No.	n	MF, %	N1, %	M1, %	R, %	DSR, %	Mortality, %
Dietlin et al	[1]	142 PTM	15.5	ND	ND	ND	0	0
Roti et al	[2]	243 PTM	32.1	13.2	1.6	1.7*	0	0
Chow et al	[3]	203	31	24.6	1	13.3† 4.9* 6.9‡	1.5	1
Kucuk et al	[4]	120 PTM	15	6	0	7‡	0	0
Ross et al	[8]	710	38	28	ND	2.6*	0.2	0.15
Yamashita et al	[9]	1743	ND	11.6	ND	1.8†	0.2	0.2
Noguchi et al	[12]	867	ND	9	0	1.4† 0.6*	0.2	0.2
Baudin et al	[13]	281	40	43	2.8	3.9† 2.5*	0.36	0
Giordano et al	[14]	97	18	8	ND	9† 4*	1	0
Hay et al	[15]	535	20	32.1	0.4	5†	0.4	0.4
Hay et al	[16]	900 PTM	23	30	0.3	8† 4*	0.2	0.3
Pelizzo et al	[17]	149 PTM	12.1	13.4	ND	2‡	0.4	0
Ito et al	[18]	1620 PTM ≤1 cm	37	57	ND	1.6*	0.2	0.04
Pellegriti et al	[27]	299 PTM	31.8	30.1	2.7	5.7	0.7	0
Ito et al	[28]	732 PTM	42.8	47.9	0	2.6† 1.9* 1.1‡	0	0
Wada et al	[29]	259	25.1	69.5	0	2.3†	ND	0
Our study	—	130	25	34.6	1.5	10.8† 6.9* 1.5‡	2.3	3

DSR, distant site of recurrence; M1, distant metastasis at presentation; MF, tumor multifocality; N1, lymph node metastasis at presentation; ND, no data; R, recurrence rate.
*Recurrence in lymph node
†Overall recurrence rate.
‡Local recurrence (recurrence in thyroid bed).

lymphovascular invasion, and central node metastases). According to their data, almost two thirds of tumors 6 to 10 mm and one third of tumors 5 mm or less would not meet ATA criteria for thyroid lobectomy.

In addition to these controversies with respect to initial surgical treatment of microcarcinoma, the issue of adjuvant RAI therapy is also the matter of debate. In Germany, standard treatment for multifocal PTM should be thyroidectomy combined with systematic lymph node dissection of the cervico-central compartment,[33] or subtotal thyroidectomy followed by ^{131}I therapy without completion thyroidectomy and neck dissection in case of incidental multifocal PTM.[1] The recent ATA guidelines recommend postoperative RAI therapy for all patients with stage III and IV disease, as well as stage II patients older than 45 years. This guideline also states that RAI ablation is indicated in selected patients with stage I disease, especially if there is evidence of multifocal disease, nodal metastases, extrathyroidal or vascular invasion, and/or more aggressive histologies such as tall cell or diffuse sclerosing tumor types.[19] The complexity of decision making in determining the optimal course of therapy is well summarized in a recent review: a physician "must make a patient specific decision in the setting of RAI ablation based upon his/her experience and review of the details in each case and continue to review the evidence on this subject as it becomes available."[34]

In low-risk patients, data have shown no significant benefit of RAI therapy on mortality or survival.[16,35,36] However, there are mixed reports on this aspect of therapy. After a literature review, Sacks et al[35] concluded that more studies evaluating the effect of RAI therapy indicated no improvement on survival or mortality, even in high-quality studies adjusted for stage/risk or other variables. Sawka et al[37] reported that RAI ablation reduced a risk of distant metastatic recurrence ($P = 0.005$). Our results indicate that patients who received RAI had significantly lower probability of recurrence than those who did not ($P = 0.005$).

Kucuk et al[4] evaluated 120 papillary microcarcinoma patients treated with TT/NTT and RAI. They reported a recurrence rate of 7% in thyroid bed, without distant site recurrence or disease-related mortality. These authors advocated that PTM should be treated in a same way as papillary thyroid carcinoma (PTC) suggesting thyroidectomy followed by RAI ablation as a possible option for PTM treatment.

Our study has some limitations. It was done retrospectively on a small number of patients with a relatively long follow-up. In patients who did not have TT/NTT but only the incidental finding of microcarcinoma, there seems to be no need to do more than careful observation. Patients in whom positive lymph nodes or extrathyroidal tumor extension were demonstrated after TT should receive RAI. Although it is not likely that a randomized trial can be performed, an appropriate design of such a trial should define the criteria for the surgical approach to be used as well as a staging/risk system for patient classification and to include a precise histological classification because various histopathological findings may have diverse impact on long-term outcome.

CONCLUSIONS

There is currently no consensus regarding the optimal treatment for patients with microcarcinoma. Our study illustrates the importance of careful follow-up of patients with DTM to monitor for recurrences and possible disease-related deaths. To obtain better monitoring and recurrence detection, TT/NTT followed by RAI ablation should be the optimal treatment for patients with DTM. Simple follow-up may be appropriate for those who undergo unilateral lobectomy based on preoperative assessment as low risk.

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