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Should Multifocality be an Indication for Completion Thyroidectomy in Papillary Thyroid Carcinoma?

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Abstract

Background—Multifocality in papillary thyroid carcinoma (PTC) is common. The aim of this study is to determine whether patients with multifocal disease (MFD), treated with lobectomy alone, have an increased risk of contralateral lobe PTC, regional recurrence, and poorer survival.

Methods—After institutional review board approval, PTC patients managed, from 1986 to 2015, with lobectomy alone were identified from an institutional database. PTC patients with pT3–T4 classification, nodal disease, or distant metastases were excluded. After excluding 40 patients who underwent an immediate completion thyroidectomy, 849 were included in the analysis; 619 (72.9%) had unifocal disease (UFD), and 230 (27.1%) had MFD.

Contralateral lobe PTC-free survival (CLPFS), recurrence-free survival (RFS), disease-specific survival (DSS), and overall survival (OS) were calculated using the Kaplan-Meier method.

Results—With a median follow-up of 58 months, UFD and MFD patients had similar rates of contralateral lobe PTC, regional recurrence and OS (10-year CLPFS 98.6% vs. 97.8%; RFS 99.5% vs. 99.4%; OS 91.6% vs. 93.1%, respectively). There were no disease-related deaths.

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Conclusion—Select MFD patients, managed with lobectomy alone, have rates of contralateral lobe PTC, regional recurrence and overall survival comparable to UFD patients. MFD should not be an indication for completion thyroidectomy.

Keywords

Papillary Thyroid Carcinoma; Multifocality; Multicentricity; Lobectomy; Completion Thyroidectomy

Introduction

Multifocality in papillary thyroid carcinoma (PTC) is common. It occurs in approximately 20%–30% of PTC cases, but this estimate varies significantly depending on the methodology used and extent of histopathological sampling.^{1, 2} The current literature on multifocal disease (MFD) and its role in PTC is inconsistent. Some retrospective studies have reported MFD to be a risk factor for recurrence.³ However, other studies have reported no difference in outcome between MFD and unifocal disease (UFD) PTC patients.⁴ The conflicting evidence has meant the prognostic significance of MFD remains controversial.

Total thyroidectomy and radioactive iodine (RAI) ablation has previously been the mainstay of treatment in PTC patients. However, the 2015 American Thyroid Association (ATA) management guidelines have emphasized the role of thyroid lobectomy in the management of well-differentiated thyroid cancer (WDTC).⁵ Bilimoria et al. reported an increased risk of recurrence and poorer survival following less-than-total thyroidectomy in PTC.⁶ However, multiple studies since have supported the practice of lobectomy alone as definitive treatment in low- to intermediate-risk PTC, with no effect on rate of recurrence or survival.^{7–10}

Given the high survival outcome in PTC, with an estimated 5-year disease-specific survival (DSS) > 98%,¹¹ disease-specific death is not an adequate measurement of treatment success. Similarly, total thyroidectomy and RAI ablation may result in the over-treatment of many low-risk patients. The extent of initial surgery requires a discussion with each individual patient, based on their understanding of the risk of surgery, risk of recurrence, and feasibility of long-term monitoring.

Multifocality may present clinically as part of macroscopic bilateral disease or, more commonly, occur incidentally as microscopic foci diagnosed on histology report. In this study, T1–T2 N0M0 PTC patients, with no evidence of contralateral lobe abnormalities, managed with lobectomy alone were examined. The aim of this study is to determine whether patients with MFD in this cohort have an increased risk of contralateral lobe PTC, regional recurrence, and poorer survival.

Methods

After institutional review board approval, PTC patients treated with lobectomy alone were identified from an institutional database of 6,261 patients undergoing initial surgery for WDTC from 1986 to 2015. Patients with non-papillary histology, macroscopic extrathyroidal extension (ETE), bilateral macroscopic disease, a primary tumor > 4 cm,

pathological N1 disease, and distant metastasis at presentation were excluded. Eight hundred eighty-nine patients met the inclusion criteria. The decision to proceed with an immediate completion thyroidectomy was based on initial histology and done to facilitate RAI ablation. An immediate completion thyroidectomy was defined as performed within 12-months of initial surgery. Documented reasons for an immediate completion thyroidectomy were recorded. Immediate completion-free survival (ICFS) was calculated in months from initial thyroid lobectomy. After excluding those who had an immediate completion thyroidectomy, 849 patients were included in the outcome analysis. Patients were classified as having UFD, defined as one focus of PTC, or having MFD, defined as 2 or more foci of PTC, determined on histopathology.

Clinical End Points

Patient and tumor characteristics were recorded for each group. Over the 30-year period of this study, the post-operative protocol of monitoring patients has evolved. For the first 20 years, structural recurrences were detected clinically and supplemented with intermittent ultrasounds. Since 2005, patients have been followed at 6- to 12-month intervals with thyroid ultrasound, serum Thyroglobulin (Tg) and Tg antibody measurements. The presence of a contralateral lobe PTC and local, regional, or distant recurrence were recorded. Postoperative thyroid stimulating hormone (TSH) suppression was based on the estimated risk of recurrence for each individual patient.

Contralateral lobe PTC-free survival (CLPFS), recurrence-free survival (RFS), DSS, and overall survival (OS) were calculated in months from date of initial surgery. The disease-specific follow-up interval was to the date of last appointment, with a member from the institution's disease management team.

CLPFS and RFS was calculated to the first date indicating a contralateral lobe PTC or structural recurrence. Findings on imaging were considered a contralateral lobe PTC or structural recurrence if identified as, 'consistent with', 'suspicious for', or 'probably' a PTC metastasis/recurrence. The use of these keywords on imaging reports aim to give a level of diagnostic certainty > 75%. Actionable findings were confirmed on cytology reports. Outcomes were separated into contralateral lobe PTC and local (ipsilateral thyroid bed), regional, or distant recurrences.

Statistical Methods

Statistical analysis was carried out using SPSS (version 25.0, IBM Corporation, Armonk, NY). Pearson's chi-squared tests were used to compare variables between groups. Survival outcomes were analyzed using the Kaplan-Meier method and reported at 5- and 10-years post-operatively. Univariate analysis was carried out by the log-rank test. Unadjusted hazard ratios were calculated using the Cox proportional hazard model. A P value < 0.05 was considered significant.

Results

Eight hundred eighty-nine PTC patients were initially managed with a lobectomy. Forty patients had an immediate completion thyroidectomy. The 1-year estimated rates of

immediate completion thyroidectomy were similar in the UFD (5.0%) and MFD (5.2%) groups. Only 11 MFD patients underwent an immediate completion thyroidectomy. The reason for completion thyroidectomy in these patients was documented as size of primary tumor in 5 patients (median = 2.5 cm, range = 1.7 – 3.5 cm), patient or endocrinologist preference in 3 patients, contralateral lobe nodules in 2 patients and other histological features in 1 patient. After excluding those with an immediate completion thyroidectomy, 849 patients were included in the outcome analysis, which consisted of 619 UFD patients (72.9%) and 230 MFD patients (27.1%) (Figure 1).

Table 1 demonstrates the patient and tumor characteristics of the groups. Patients with UFD and MFD were similar in age ($P = 0.465$), tumor size ($P = 0.955$), and presence of vascular invasion ($P = 0.465$). However, patients with MFD were more likely to have microscopic ETE ($P = 0.009$) and microscopic positive margins ($P = 0.009$).

All patients were classified as Stage I according to the American Joint Committee on Cancer 8th Edition TNM staging system,¹² as shown in Table 1. Pathological tumor classification and ATA risk stratification⁵ were similar in the UFD and MFD groups ($P = 0.241$ and $P = 0.251$, respectively).

Do patients with MFD have worse CLPFS?

Contralateral lobe PTC was detected in 9 UFD patients and 5 MFD patients during the study period. Five- and 10-year CLPFS rates were 99.1% and 98.6% in the UFD group and 97.8% and 97.8% in the MFD group ($P = 0.270$) (Figure 2). Table 2 shows the 14 patients who had a contralateral lobe PTC, with details on time of diagnosis, subsequent management, and outcome.

Do patients with MFD have poorer rates of regional recurrence, RFS or disease-specific death?

Patients with MFD had rates of structural recurrence comparable to UFD patients (Figure 3). During the follow-up period, there were no local or distant recurrences in either group. In the UFD group, 2 patients developed regional recurrence; in the MFD group, 3 patients developed regional recurrence during the study period. The 5-year and 10-year RFS were 100.0% and 99.5% in the UFD group and 99.4% and 99.4% in the MFD group ($P = 0.061$). Of the 5 patients who developed regional recurrence, all underwent salvage surgery and had no evidence of disease at last follow-up (Table 3). According to the ATA response to therapy classification¹³, 2 patients had an excellent response, 2 patients an indeterminate response, and 1 patient an unknown response at final follow-up. Table 3 shows the 5 patients who developed regional recurrence, with details on time of diagnosis, subsequent management, and outcome.

There were no disease-specific deaths in either group (5- and 10-year DSS was 100% in both groups). The 5- and 10-year OS were 96.6% and 91.6% in the UFD group and 96.5% and 93.1% in the MFD group (Figure 4). Univariate analysis showed that multifocality was not a predictor for OS ($P = 0.467$).

Discussion

Role of Lobectomy

The 2015 ATA guidelines expanded the role of thyroid lobectomy in the management of WDTC.⁵ Previously, thyroid lobectomy played a limited role, and its use was primarily restricted to papillary microcarcinomas. Some studies have shown that the extent of surgery may effect recurrence and survival in PTC.⁶ Therefore, there was hesitation to move towards more conservative treatment. Since then, convincing evidence has demonstrated thyroid lobectomy to be a safe alternative to total thyroidectomy for disease ≤ 4 cm confined to one lobe of the thyroid gland.^{7–9, 14} The ATA guidelines consider thyroid lobectomy alone to be adequate treatment for unifocal, intrathyroidal carcinomas but does not specifically address the risk of recurrence associated with multifocality in its risk stratification system. Instead, there is a suggestion that some patients, “may require completion thyroidectomy to provide complete resection of multicentric disease and to allow for efficient RAI therapy.”⁵

Some studies have demonstrated a lower risk of loco-regional recurrence following total thyroidectomy compared to lobectomy.^{6, 15} However, Nixon et al. and Vaisman et al. have shown low rates of contralateral lobe PTC (4.2%)¹⁰ and loco-regional recurrence (< 1%)⁹ in properly selected PTC patients managed with lobectomy alone. In addition, depending on the post-operative protocol of monitoring patients, with serial neck ultrasounds and Tg measurements, the necessity for completion thyroidectomies in low- to intermediate-risk patients may be significantly diminished. The few recurrences that develop during long-term follow-up can be appropriately managed with no evidence of impact on survival.^{5, 9, 10} The ATA guidelines have concluded, “in properly selected low- to intermediate-risk patients..., the extent of initial thyroid surgery probably has little impact on disease-specific survival.”⁵

Benefits of Lobectomy

The risks and post-operative sequela of total thyroidectomy are greater than that of lobectomy. A recent meta-analysis reported a pooled relative risk (RR) significantly greater following total thyroidectomy compared to lobectomy for permanent recurrent laryngeal nerve (RLN) injury (RR = 1.9) and permanent hypoparathyroidism (RR = 3.2).¹⁶ Hauch et al. reported on 62,722 patients from the Nationwide Inpatient Sample database and found total thyroidectomy to be associated with an increased risk of complications compared to lobectomy (20.4% vs. 10.8%, respectively, $P < 0.0001$); even high-volume thyroid surgeons had an overall higher complication rate following total thyroidectomy compared to following lobectomy (14.5% vs. 7.6%, respectively, $P < 0.0001$).¹⁷ Furthermore, thyroid lobectomy eliminates the rare but severe complication of bilateral RLN injury requiring tracheostomy. Total thyroidectomy necessitates life-long TSH replacement. However, following thyroid lobectomy alone, TSH suppression is done on an individual's estimated risk of recurrence.

Institutional Philosophy on Lobectomy

At our institution, the treatment of intrathyroidal PTC has long favored a conservative approach. The extent of surgery, total thyroidectomy versus thyroid lobectomy, has been guided by tumor size, status of contralateral lobe, and gross extrathyroidal extension.^{9, 14}

The presence of ipsilateral MFD has not precluded patients from thyroid lobectomy nor mandated completion thyroidectomy over the past 30 years.¹⁴ It is against this backdrop that we have compared the outcomes of lobectomy patients with MFD to those with UFD to determine if any evidence supports immediate completion thyroidectomy for patients with MFD.

MFD and its Histopathological Features

MFD has been associated with more aggressive histopathological features in many studies.^{3, 18} In our study, MFD patients were found to have higher rates of microscopic ETE ($P=0.009$) and microscopic positive margins ($P=0.009$), compared to UFD patients. We hypothesize this difference is due to the presence of clinically occult, microscopic, intrathyroidal disease not appreciable intraoperatively. However, as previously reported by our institution, microscopic ETE and positive margins have no obvious significance on subsequent risk of recurrence or survival.^{19, 20} These histological findings rarely changed subsequent management or follow-up. A meta-analysis of 1,598 papillary microcarcinoma patients reported a significantly greater risk of regional metastasis in MFD patients, compared to UFD (odds ratio = 1.9).²¹ In a study of 2,418 patients with PTC, Kuo et al. also found higher rates of nodal metastasis and ETE as well as distant metastases at initial presentation in patients with MFD.²² However, despite the evidence of more aggressive clinical and histological features in MFD patients, the prognostic significance of MFD remains controversial.

MFD and its Prognostic Significance

Some retrospective studies have reported MFD to be a risk factor for recurrence³ and others conclude MFD requires more aggressive management.²³ Kim et al. found MFD to be an independent risk factor for disease persistence / recurrence in patients with PTC > 1 cm, which was not apparent in patients with MFD PTC ≤ 1 cm.²⁴ Within the ATA low-risk PTC category, the ATA guidelines provide an estimated risk of structural recurrence: UFD PTC ≤ 1 cm (1%–2%), MFD PTC ≤ 1 cm (4%–6%), and intrathyroidal PTC 2 cm–4 cm (~5%).⁵ Therefore, the size of the primary tumor or macroscopic foci in patients with MFD may play a role in prognosis. However, La Greca et al. showed multifocal macroscopic PTC had a low risk of recurrence following total thyroidectomy and RAI therapy.²⁵ Potentially, MFD in the presence of other aggressive histological features, most notably gross ETE and nodal metastasis, may influence outcome.

In our study, we aimed to eliminate, other than MFD, any other reason for an immediate completion thyroidectomy in order to identify the role of MFD alone in low- to intermediate-risk PTC. In our cohort, MFD patients had similar rates of immediate completion thyroidectomy ($P=0.943$) compared to UFD patients. Of the patients treated with lobectomy alone, there was no difference in the rates of contralateral lobe PTC between the two groups (10-year CLPFS 98.6% vs. 97.8%, respectively ($P=0.270$)). MFD patients were not more likely to develop structural recurrence; the 10-year RFS rates were 99.5% vs. 99.4% for the UFD and MFD groups, respectively ($P=0.061$). MFD patients had a similar rate of OS compared to UFD ($P=0.467$), and there were no disease-specific deaths in either group. In spite of multiple differences observed in patient and tumor characteristics between

the two groups in our study, including sex, histological subtype, margin status and presence of microscopic ETE (Table 1), no detrimental impact on recurrence or survival was identified.

Given salvage surgery and active surveillance are effective management options in the few patients who recur, accepting a low risk of contralateral lobe PTC and regional recurrence may be an appropriate strategy for select MFD patients initially treated with lobectomy. The management team's and each patient's preferences need to be taken into account when considering the extent of initial surgery. Complications of surgery, individual risk of recurrence, and method of post-operative monitoring also need to be considered.

Limitations

Like all retrospective studies, this data has limitations. Given individual physician and patient preferences, the role of selection bias requires discussion. Conservative surgery for PTC has long been emphasized at our institution, however, this philosophy has evolved during the study period. Our institution has previously reported that the presence of microscopic ETE¹⁹ and positive margins in the absence of gross ETE are not associated with an increased risk of recurrence and therefore, has not mandated completion thyroidectomy. However, the management team has sometimes, albeit rarely, chosen to proceed with further surgery in these cases, taking into account the patient's and endocrinologist's preferences. Selection bias in this cohort cannot be excluded.

Data regarding the number and size of foci in the MFD patients was not available. Therefore, we have been unable to determine whether certain subgroups of MFD patients may be at increased risk of structural recurrence. Further studies are required to assess the impact of extensive MFD disease with a large volume and number of foci.

Our approach to monitoring patients post-operatively has progressed during the time period studied. This limits the conclusions that can be drawn from our results and potentially results in an underestimation in our reported rate of recurrence. In the first 20 years of the study period, most recurrences were clinically evident rather than sonographically identified. In contrast, since 2005, recurrent disease has been detected using serial ultrasounds and Tg measurements as part of a standardized follow-up protocol.

Conclusion

In our study, properly selected MFD patients do not have an increased probability of developing contralateral lobe PTC, regional recurrence, or disease-specific death. Thyroid lobectomy alone appears to be a safe alternative to total thyroidectomy in T1-T2 N0M0 PTC patients with unilateral disease, in spite of the presence of incidental multifocality.

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Figure 1.
Inclusion/exclusion criteria

Figure 2.
Kaplan-Meier estimates of contralateral lobe PTC-free survival (CLPFS) by multifocality

Figure 3.
Kaplan-Meier estimates of recurrence-free survival (RFS) by multifocality

Figure 4.
Kaplan-Meier estimates of overall survival (OS) by multifocality

Table 1.

Comparison of patient and tumor characteristics between UFD and MFD patients

	Total <i>n</i> = 849	UFD* <i>n</i> = 619 (72.9)	MFD† <i>n</i> = 230 (27.1)	<i>P</i> value
Age				
< 55	610 (71.8)	449 (72.5)	161 (70.0)	0.465
≥ 55	239 (28.2)	170 (27.5)	69 (30.0)	
Sex				
Female	612 (72.1)	460 (74.3)	152 (66.1)	0.018
Male	237 (27.9)	159 (25.7)	78 (33.9)	
Pathological T Classification				
T1a	401 (47.2)	292 (47.2)	109 (47.4)	0.241
T1b	275 (32.4)	193 (31.2)	82 (35.7)	
T2	173 (20.4)	134 (21.6)	39 (17.0)	
Tumor Size				
≤ 1 cm	401 (47.2)	292 (47.2)	109 (47.4)	0.955
> 1– 4 cm	448 (52.8)	327 (52.8)	121 (52.6)	
PTC Subtype				
Follicular Variant	333 (39.2)	258 (57.5)	75 (48.1)	0.040
Classical Variant	192 (22.6)	130 (29.0)	62 (39.7)	
Tall Cell Variant	43 (5.1)	30 (6.7)	13 (8.3)	
Other	37 (4.4)	31 (6.9)	6 (3.8)	
Unknown	244 (28.7)	-	-	
Microscopic ETE‡				
Not Identified	770 (90.7)	571 (92.4)	199 (86.5)	0.009
Present	78 (9.2)	47 (7.6)	31 (13.5)	
Unknown	1 (0.1)	-	-	
Vascular Invasion				
Not Identified	719 (84.7)	516 (96.4)	203 (95.3)	0.465
Present	29 (3.4)	19 (3.6)	10 (4.7)	
Unknown	101 (11.9)	-	-	
Margin				
Negative/Close	740 (87.2)	536 (98.5)	204 (95.3)	0.009
Positive	18 (2.1)	8 (1.5)	10 (4.7)	
Unknown	91 (10.7)	-	-	
ATA§ Risk				
Low	721 (84.9)	531 (85.8)	190 (82.6)	0.251

	Total <i>n</i> = 849	UFD* <i>n</i> = 619 (72.9)	MFD[†] <i>n</i> = 230 (27.1)	<i>P</i> value
Intermediate	128 (15.1)	88 (14.2)	40 (17.4)	
AJCC^{//} Stage				
Stage I	849 (100.0)	619 (100.0)	230 (100.0)	n/a

* UFD – unifocal disease;

[†] MFD – multifocal disease;

[‡] ETE – extrathyroidal extension;

[§] ATA- American Thyroid Association;

^{//} AJCC –American Joint Committee on Cancer

Table 2.

Details and outcomes of patients with contralateral lobe PTC

Patient	Multifocality Status	Time to Contralateral Lobe PTC* (years)	Management of Contralateral Lobe PTC	Final Outcome - ATA [†] response to treatment
1	MFD [‡]	1.1	Surgery	NED [§] - Unknown
2	UFD [§]	1.3	Surgery	NED - Excellent
3	UFD	3.0	Surgery	NED - Unknown
4	UFD	3.0	Surgery	NED - Excellent
5	UFD	3.5	Surgery	NED - Unknown
6	UFD	4.9	Surgery	NED - Unknown
7	UFD	6.1	Surgery	NED - Unknown
8	MFD	10.6	Surgery	NED - Excellent
9	UFD	11.3	Surgery	NED - Indeterminate
10	MFD	11.9	Surgery	NED - Unknown
11	UFD	12.9	Surgery	NED - Indeterminate
12	MFD	13.3	Active Surveillance	ALD [¶] - Structural Incomplete
13	UFD	13.5	Active Surveillance	ALD - Structural Incomplete
14	MFD	23.5	Surgery	NED - Indeterminate

* PTC – Papillary Thyroid Carcinoma

[†] ATA – American Thyroid Association[‡] MFD – multifocal disease[§] UFD – unifocal disease[§] NED – no evidence of disease[¶] ALD – alive with loco-regional disease

Table 3.

Details and outcomes of patients with regional recurrence

Patient	Multifocality status	Histological details	Time to recurrence (years)	Level of recurrence	Management of recurrence	Final Outcome - ATA [*] response to treatment
1	MFD [‡]	Classical Variant, 1.3 cm, no VI [§] , mETE , negative margins	1.2	Ipsilateral Level 3	CT [¶] + MRND [#]	NED ^{††} - Excellent
2	UFD [‡]	Classical Variant, 1.4 cm, focal VI, no ETE, negative margins	6.0	Ipsilateral Level 2	CT + MRND	NED - Indeterminate
3	MFD	Classical Variant, 0.8 cm, no VI, no ETE, positive margins	10.6	Contralateral Level 2,4	CT + MRND	NED - Excellent
4	MFD	Follicular Variant, 1.8 cm, no VI, no ETE, positive margins	11.3	Contralateral Level 6	CT + TEGD ^{**}	NED - Indeterminate
5	UFD	Classical Variant, 1.7 cm, no VI, no ETE, negative margins	15.3	Ipsilateral Level 4	CT + MRND	NED - Unknown

^{*} ATA – American Thyroid Association

[‡] MFD – multifocal disease

[‡] UFD – unifocal disease

[§] VI – vascular invasion

^{||} mETE – microscopic extrathyroidal extension

[¶] CT – completion thyroidectomy

[#] MRND – modified radical neck dissection

^{**} TEGD – tracheoesophageal groove dissection

^{††} NED – no evidence of disease