Importance of Number of Foci of Capsular Invasion in Follicular Thyroid Carcinoma

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Abstract The importance of capsular invasion in follicular thyroid carcinoma (FTC) has not been extensively studied. The aim of the present study was to correlate the clinical features and outcome of FTC with histology features particularly emphasizing on the importance of the number of foci of capsular invasion. This was a retrospective study. Histology of 123 FTC patients was reviewed. Patients were divided in three groups based on the number of foci of vascular and capsular invasion noted in primary tumor: group 1—capsular invasion at <6 and vascular invasion at <4 foci, group 2—either capsular invasion ≥ 6 or vascular invasion at ≥ 4 foci, and group 3—capsular invasion ≥ 6 and vascular invasion at ≥ 4 foci. Different prognostic factors and overall survival (OS) were compared among the groups. The incidences of distant metastases ($p = 0.008$) and OS ($p = <0.001$) were significantly different among the groups. On univariate analysis, age ($p = 0.001$), tumor size ($p = <0.0001$), distant metastases ($p = <0.0001$), vascular invasion ($p = 0.018$), and capsular invasion ($p = 0.003$) were significantly associated with OS. On multivariate analysis, age ($p = 0.020$), distant metastases ($p = 0.045$), and foci of capsular invasion ($p = 0.005$) were significant. The number of foci of capsular invasion seems to have significant prognostic value in widely invasive FTC.

Keywords Widely invasive FTC · Minimally invasive FTC · Angioinvasive FTC · Developing country

Introduction

Follicular thyroid carcinoma (FTC) is the second most common malignancy affecting the thyroid gland. The incidence of FTC carcinoma is decreasing all over the world, though it still remains high in the developing world [1, 2]. Despite being less common malignancy than papillary thyroid carcinoma, clinicians and researcher have shown considerable interest in FTC. There are several reasons for this. The chief reason is that preoperative diagnosis of this malignancy remains elusive despite many scientific advances, and even on histological examination, the diagnosis many times is not easy [2–6]. FTC is more aggressive in behavior and has greater propensity for distant metastases than PTC [6].

FTC is classified into two histologic categories, minimally (MIFTC) and widely invasive FTC (WIFTC) [1, 4–6]. MIFTC are considered indolent tumors, whereas WIFTC are aggressive and have poor prognosis [6–9]. The basis of dividing FTC into MIFTC and WIFTC groups is based on the degree of invasiveness. According to the WHO classification, “MIFTC” has limited capsular and/or vascular invasion. WIFTC shows “widespread infiltration of adjacent thyroid tissue and or blood vessels” [3]. But what constitutes limited and widespread invasion remains a contentious issue. Though not universally accepted, there seems to be a consensus among pathologists regarding cutoff of foci of vascular invasion ($<$ or ≥ 4 foci) for such division but the same is not true about the number of foci of capsular invasion which would differentiate between MIFTC and WIFTC [1, 4, 6, 10]. Previously published reports considered angioinvasion as the major prognostic factor and capsular invasion of not much significance. But some recent

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literature seems to suggest that the wide invasion per se and not particularly angioinvasion is an adverse prognostic factor [6–11]. The relative incidence of FTC among DTC is high in our country, and majority of these are WIFTC [1]. Patients who are in advanced stage have worse outcome than those in the developed nations. The aim of the present study was to correlate the clinical features and outcome of FTC with histologic features particularly emphasizing on the importance of the number of foci of capsular invasion.

Methods

This retrospective study consisted of histology-proven FTC patients managed between December 1990 and December 2010 in our hospital. The institute ethics committee approved the study (IEC code 2012-138-MCH-64). Hurthle cell carcinoma and mixed FTC and medullary thyroid carcinoma were excluded from the study. Patients for whom sufficient information was not available and those with non-evaluable histology material were also excluded. A total of 204 FTC patients were identified, and out of these, 123 had evaluable histology and were included in the final analysis. All the histology slides were reexamined by two independent pathologists. The diagnosis of FTC was reconfirmed based on the most recent WHO classification system [3]. In hematoxylin and eosin-stained sections of tumors, pathologists noted the presence and number of capsular and vascular invasive foci and presence of calcifications, necrosis, and extra-thyroidal extension. Lymph node involvement was noted separately. One section per centimeter of tumor was taken and examined in whole.

Clinical details, extent of surgical procedures, and follow-up findings were obtained from inpatient records and outpatient follow-up registers. Patients who had not been regularly coming for follow-up visits were contacted by postal mail, telephone, or email. All the details including histology findings were entered in a predesignated proforma and later entered into SPSS. All cases were reclassified according to the seventh edition of the AJCC classification of thyroid tumor [12].

FTC Management Protocol

All the patients of FTC barring few had total thyroidectomy as primary or secondary operative procedure. Few patients refused to undergo completion total thyroidectomy after undergoing hemithyroidectomy for preoperatively undiagnosed FTC. Patients having lymph node involvement (detected preoperatively or intraoperatively by frozen section examination) had therapeutic central compartment (CCLND) or lateral neck dissection (LND) performed, as indicated. All patients received thyroxine with the intent to keep serum TSH concentration suppressed to undetectable levels (<0.01 mIU/l). All patients undergoing total thyroidectomy were referred for whole body

radioiodine (WBRAI) scan followed by radioiodine (RAI) ablation or therapy as indicated. A diagnostic WBRAI scan was performed after stopping thyroxine for 4–6 weeks. A fixed dose policy for RAI administration has been followed at our institute, and accordingly, a dose of 50, 100, and 150 mCi RAI was administered to patients with thyroid bed, lymph node, and distant metastases uptake, respectively. A post-therapy scan was obtained 3–5 days after RAI therapy. WBRAI scan was repeated at 6-monthly intervals, and a further dose of RAI was administered if required. Serum thyroglobulin (Tg) estimation became available in our patients in 2002, and prior to that, patients with two consecutive negative scans were considered cured. Patients with increased serum Tg concentration and negative RAI scan were subjected to radiological examination of neck and thorax (USG followed by CT scan). An accessible and operable recurrence and metastasis was usually surgically excised. Only few of our patients could afford PET scan due to financial reasons. Patients were followed up after 6 months, and if serum Tg titer was increasing, further search for disease was made. If two WBRAI scans were negative and Tg is <1 ng/ml, the patients were considered cured and followed up with yearly serum Tg estimation. For gross inoperable locoregional disease and symptomatic bony metastases, external radiotherapy was considered.

Analysis of the Results

Patients were divided in three histologic groups according to the number of vascular and capsular foci present in the tumor: group 1—patients with capsular invasion at <6 and/or vascular invasion at <4 foci, group 2—patients with either capsular invasion ≥ 6 or vascular invasion at ≥ 4 foci, and group 3—patients with capsular invasion ≥ 6 and vascular invasion at ≥ 4 foci. An ROC curve was drawn and that showed capsular invasion at six or more foci had maximum sensitivity (60 %) and specificity (70 %) in predicting mortality. Therefore, we had taken six foci as cutoff point for dividing various groups. Since customarily foci of vascular invasion are taken as determinant for MIFTC and WIFTC, we also took this factor into account and thus we divided the patients into three groups and not two. The data were analyzed by SPSS software (version 22.0). Kaplan-Meier method was used for survival analysis. Log rank test and Cox-regression model was used to perform univariate and multivariate analysis to determine the factors affecting the overall survival (OS). A p value of <0.05 was taken as statistically significant.

Results

A total of 123 patients were included in the final analysis. The clinical profile of the whole cohort is summarized in Table 1. The mean age of the patients was 48.2 ± 13.4 years. Median

Table 1 Clinical profile of the whole cohort

Sl no.	Attributes	Value
1	Age ≥ 45 years: <i>n</i> (%)	82 (66.7)
2	Gender (M/F)	1:2.6
3	Tumor >4 cm: <i>n</i> (%)	64 (52.0)
4	Extra-thyroidal extension: <i>n</i> (%)	20 (16.3)
5	T stage: <i>n</i> (%)	
	Tx	05 (4.1)
	T1	05 (4.1)
	T2	29 (23.6)
	T3	64 (52.0)
	T4a	14 (11.4)
	T4b	06 (4.9)
6	Nodal metastasis: <i>n</i> (%)	15 (12.2)
	N1a	05 (33.3)
	N1b	10 (66.7)
7	Distant metastasis: <i>n</i> (%)	
	Synchronous	58 (47.2)
	Metachronous	02 (1.6)

duration of goiter was 48 (1–480) months. Mean primary tumor size was 5.2 ± 2.7 cm. Among those having distant metastases, skeletal, pulmonary, both skeletal and pulmonary, and brain metastases were noted in 76.6, 15, 6.7, and 1.7 % patients, respectively. Of the patients, 58.5 % belonged to high-risk category of AMES prognostic system [13]. On histology examination, vascular invasion was noted in 79.7 % and capsular invasion in 98.4 % tumors (78.0 % had both). The distribution of capsular invasion foci was $<6 = 51.2$, $6-10 = 33.3$, and $>10 = 15.5$ %. The distribution of vascular invasion foci was $<4 = 87.8$, $4-10 = 11.4$, and $>10 = 0.8$ %. According to the histologic classification used in the study 62 (50.4 %), 47 (38.2 %) and 14 (11.4 %) patients were in groups 1, 2, and 3, respectively. Twenty-one patients in group 1 had only capsular invasion (minimal invasive capsular), whereas 41 has angioinvasion (minimal invasive angioinvasive). All the patients except one in group 2 had less than four vascular invasion foci. Presence of poorly differentiated areas (PDA), necrosis, and calcification were observed in 64.2, 18.7, 46.3 % tumors, respectively. A summary of comparative profile of these groups is provided in Table 2. All the three groups were comparable in all the respects except that the incidence of PDA, distant metastases, and mortality were significantly high in groups 2 and 3.

One hundred and seventeen (95 %) patients underwent total thyroidectomy (primary 71.5 %, completion 23.6 %), 4.1 % hemithyroidectomy, and 0.8 % subtotal thyroidectomy. Fourteen (11.4 %) patients had lymph node dissection at initial surgery and 19.5 % had resection of metastatic lesion. Eighty-nine (72.4 %) patients received RAI ablative therapy. The median cumulative dose was 200 mCi (range 40–1295 mCi). Seven (5.7 %) patients received external radiotherapy in

addition to RAI therapy. Median follow-up was 53 months (2–241 months). Initial cure was noted in 26.8 % patients and the rest had persistent disease. Of patients, 5.7 % had recurrence and 41.5 % died in follow-up. Among those who died, 33.3 % were male, 82.4 % were older than 45 years, 74.5 % had metastasis, 21.6 % had extra-thyroidal extension, and 52.9 % had tumor measuring >4 cm. Vascular invasion was noted in primary tumors of 88.2 % of such patients and 66.7 % showed capsular invasion at ≥ 6 foci. Among those seven patients who had recurrence, six had only locoregional recurrence and one had locoregional recurrence along with pulmonary metastases. Five and 10 years OS of the whole cohort were 72.4 and 57.7 %, respectively. The survival was significantly different ($p = 0.001$) between the three groups (Fig. 1). In group 1, the OS of minimal invasive capsular ($n = 21$) and angioinvasive ($n = 41$) subgroups was not significantly different (5 and 10 years OS = 81 vs. 63.1 and 82.2 vs. 63.7; $p = 0.886$). On univariate analysis, age ($p = 0.001$), tumor size ($p = <0.0001$), metastases ($p = <0.0001$), vascular invasion ($p = 0.018$), and capsular invasion ($p = 0.003$) were significantly associated with OS. Presence of poorly differentiated areas ($p = 0.386$) and tumor necrosis ($p = 0.557$) was not significant for OS. On multivariate analysis, age ($p = 0.020$), distant metastases ($p = 0.045$), and foci of capsular invasion ($p = 0.005$) were found to be significant factors (Table 3).

Discussion

Our study showed that age, distant metastases, and foci of capsular invasion are significant independent factors for OS in FTC. It also reiterated the aggressive nature of WIFTC (groups 2 and 3) and relatively indolent nature of MIFTC (group 1). In the current study, a large proportion of patients had advanced FTC. The incidence of distant metastases (47.2 %) and extra-thyroidal invasion (16.3 %) was high, and median tumor size (5.2 cm) was more than the developed nations. More than half (58.5 %) of patients belonged to AMES high-risk category. The reported incidence of distant metastases at presentation and extra-thyroidal invasion ranges from 3 to 11 and <1 to 10.2 %, respectively [7, 9–11]. The reported median tumor size in literature ranges from 3 to 3.5 cm [10, 14]. If we consider the conventional definition of MIFTC, then the group 1 of our study would include both MIFTC (capsular) and angioinvasive categories of MIFTC. Going by this logic, about half (group 2 + group 3 = 49.6%) of patients in our study clearly had WIFTC. The incidence of WIFTC has ranged from 20 to 53.8% in various studies [7, 10, 15].

Distant metastases and patient age have consistently reported adverse prognostic factors for OS in FTC, and the same was also true for this study [9, 10, 13–16]. Tumor size and extra-thyroidal invasion have not consistently been associated with adverse outcome in FTC and none had significant association with survival

Table 2 Comparative profile of the three histologic groups

Sl. no.	Attributes	Group 1 ^a (n = 62)	Group 2 ^b (n = 47)	Group ^c (n = 14)	p value
1	Male gender: n (%)	15 (24.2)	16 (34.0)	3 (21.4)	0.449
2	Age in years: mean ± SD	47.5 ± 15.3	47.8 ± 11.8	52.7 ± 8.6	0.418
3	Age ≥ 45 in yrs.: n (%)	40 (64.5)	30 (63.8)	12 (85.7)	0.275
4	Tumor size in cm: mean ± SD	4.9 ± 2.9	5.5 ± 2.7	5.3 ± 2.2	0.573
5	Tumor size >4 cm: n (%)	27 (47.4)	29 (61.7)	08 (57.1)	0.335
6	Extra-thyroidal invasion: n (%)	08 (12.9)	09 (19.1)	03 (21.4)	0.584
7	Necrosis: n (%)	12 (19.4)	07 (14.9)	04 (28.6)	0.506
8	Poorly differentiated areas: n (%)	32 (51.6)	34 (72.3)	13 (92.9)	0.005
7	Lymphadenopathy: n (%)	06 (9.7)	06 (12.8)	03 (21.4)	0.473
8	Recurrence: n (%)	04 (6.5)	02 (4.3)	01 (7.1)	0.860
9	Distant metastases: n (%)	21 (33.9)	27 (57.4)	10 (71.4)	0.008
10	Mortality: n (%)	17 (27.4)	24 (51.1)	10 (71.4)	0.002

^a Group 1: capsular invasion <6 and vascular invasion <4 foci^b Group 2: capsular invasion ≥6 or vascular invasion ≥4 foci^c Group 3: capsular invasion ≥6 and vascular invasion ≥4 foci

in this study as well [10–14]. Patients (16.3 %) in this study had extra-thyroidal invasion; 75 % of whom were >45 years of age and 55 % had distant metastases. Probably, an incidence of extra-thyroidal invasion was not very high in our study so as to have a statistically significant difference in survival. The same could be true about vascular invasion. While 79.7 % tumors showed vascular invasion, only 12.2 % of those had ≥4 foci of invasion, which is considered a significant cutoff for prognostic analysis [5, 9, 11, 15]. But the significance of vascular invasion in relation to OS in FTC remains controversial. Vascular

invasion has been reported to be associated with poor survival in many previous reports [7–9, 11]. However, recent reports do not substantiate this fact fully and suggest that vascular invasion might be important in certain situation and not in all cases of FTC [10, 17, 18]. The importance of tumor necrosis and poorly differentiated areas has not been sufficiently studied to reach any definitive conclusion on their impact on OS [5, 19]. In our study, these were not significant factors. The reported 5- and 10-year OS of FTC has ranged from 88.4–94 to 75.3–85 %, respectively [6, 7, 10, 11, 15]. In the current study, the OS was worse across all the groups than that reported in literature. The main reason is that a large proportion of our patients presented with metastatic disease. The most likely reason for this seems to be delay in seeking medical attention. The median duration of goiter at presentation was 48 months in our patients. If we add this lag period to survival curve, the resultant OS figures would be at par with those reported.

- 5- year OS (Group, 1,2 3): 81.7 Vs. 63.0 Vs. 50.0%
- 10- year OS (Group, 1,2 3): 63.8 Vs. 27.7 Vs. 0%

Fig. 1 Overall survival in three groups**Table 3** Results of multivariate analysis

Sl. no.	Variables	Hazard ratio (95 % CI)	p value
1	Age in years	1.031 (1.005–1.058)	0.020
2	Male gender	1.839 (0.970–3.486)	0.062
3	Tumor size in cm	0.996 (0.884–1.112)	0.946
4	Lymph node	0.218 (0.024–1.963)	0.174
5	Extra-thyroidal extension	2.054 (0.923–4.572)	0.078
6	Distant metastases	2.174 (1.019–4.637)	0.045
7	Capsular invasive foci	1.081 (1.024–1.141)	0.005
8	Vascular invasive foci	1.090 (0.960–1.237)	0.184
9	Poorly differentiated areas	0.734 (0.362–1.485)	0.389
10	Necrosis	0.762 (0.328–1.767)	0.526
11	Calcification	0.845 (0.441–1.619)	0.612

WIFTC are known to have poor OS, but the impact of the extent of capsular invasion on OS has not been extensively studied. As per WHO definition, “WIFTC have widespread infiltration of adjacent thyroid tissue and or blood vessels.” So, in this current study, we tried to quantify the “widespread infiltration” and its effect on OS of FTC. On multivariate analysis, the number of capsular invasive foci was found to have independent prognostic significance. Based on ROC analysis, we had taken 6 as cutoff point for diving various groups. Tumors in 48.8 % of patients showed ≥ 6 capsular invasion foci in the current study. Because of the high proportion of such invasive cases, we could study the impact of capsular foci on OS. Many authors have advocated an individualized approach to the management of FTC based on the degree of capsular and vascular invasion [19–21]. Therefore, it makes sense to quantify the risk and select out the high- and low-risk patients separately. Such attempts have been made in the past based on the number of vascular invasion foci. We have attempted a similar approach towards quantification of risk in terms of capsular invasion foci.

The major weakness of the study is its retrospective nature because of which many cases had to be excluded from the histologic analysis and thus impact of some of the prognostic factors could be either under- or overrated. We could have divided group 1 in three subcategories one having only capsular invasion, second only angioinvasion, and third both. But since only two patients had exclusive angioinvasion in group 1, we did not and hence could not study the impact of angioinvasion in MIFTC. But at the same time, the truth is that this is the data we got and possibly could not change it.

Conclusions

Based on our study, we can conclude that apart from the other well-described prognostic factors, the number of foci of capsular invasion seems to have significant prognostic value particularly in WIFTC. The fact needs to be validated in prospective studies.

Compliance with Ethical Standards

Conflict of Interest The authors CK, AM, NK, NK, GC, GA, AA, and SKM declare that they have no conflict of interest.

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