

Prognostic Factors in Patients with Well-Differentiated Thyroid Carcinoma with Locoregional Recurrence Submitted for Salvage Treatment

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Abstract

Background: Well-differentiated thyroid carcinoma is characterized by an excellent prognosis; however, recurrence rates range from 5% to 23%, and mortality after salvage treatment ranges from 38% to 69%.

Objectives: To identify prognostic factors in patients who have undergone salvage therapy for well-differentiated thyroid carcinoma.

Patients and methods: This is a retrospective cohort series including 102 patients with respectable locoregional recurrences who underwent salvage treatment. One hundred twenty loco-regional recurrences were observed amongst 102 patients. Univariate survival analysis was performed using the Kaplan-Meier method.

Results: Five-year overall survival rates were significantly associated with age over 45 years (67.6%) ($p < 0.0001$), site of recurrence (local or regional recurrence and distant metastasis (65.8%), only local recurrence (88.8%), only regional recurrence (92.2%) ($p = 0.0267$), and histology (papillary carcinoma (90.3%) and follicular carcinoma, (72.2%) ($P = 0.0156$).

Conclusion: Age over 45 years, follicular carcinoma and location of recurrence were significant prognostic factors in patients with well-differentiated thyroid carcinoma who underwent salvage treatment.

Keywords: Thyroid cancer; Recurrence; Prognostic factors; Salvage treatment; Survival outcomes

WDTC with locoregional recurrences treated with salvage surgery with a curative intent.

Introduction

Well-differentiated thyroid carcinoma (WDTC) represents approximately 2% to 5% of all human cancers and accounts for less than 0.5% of all cancer deaths [1,2]. These tumors are treated with surgery, either associated or unassociated with adjuvant radioiodine, and the prognosis is usually favorable. However, despite the efforts to improve the management of this disease, recurrence rates have been reported to range from 8% to 23%, and in these cases, the mortality rates range from 38% to 69% [1,2]. Most of these recurrences are locoregional, for which 12% -17% of patients present recurrences in neck lymph nodes, and 4% -7% of patients present recurrences around the thyroid bed [2].

However, the treatment of recurrences is controversial [3]. Radical surgery is typically reserved for locoregional resectable lesions and is usually associated with adjuvant post-operative radioiodine therapy. For all lesions, non-iodine sensitive, surgical treatment can be complemented with post-operative radiotherapy [4-6].

The literature is scarce regarding recent results and survival outcomes after salvage treatment of locoregional recurrences of differentiated thyroid carcinoma [7,8]. The objective of this study is to both identify prognostic factors and analyze a series of patients with

Materials and Methods

This is a retrospective cohort study. The medical records of 2,356 patients with differentiated thyroid carcinoma registered at A C Camargo Hospital, Sao Paulo, Brazil were reviewed from January 1977 to December 2008. A total of 102 cases were selected for further analysis. The eligibility criteria for the study were patients with WDTC who displayed resectable locoregional recurrences. Exclusion criteria were patients who had undergone salvage treatment at another institution as well as patients with medical charts with incomplete clinical and pathological information. Among the 102 selected cases, 69 patients (67.4%) had undergone previous treatment at another institution and were referred after the diagnosis of tumor recurrence. The surgical procedures previously performed were as follows: 1 (1.0%) thyroid nodulectomy, 23 (22.6%) partial thyroidectomies, 75 (73.5%) total thyroidectomies and 3 (2.9%) extended total thyroidectomies. Demographic, clinical, pathological, treatment and follow-up data were obtained from medical records and then transcribed into a previously prepared form.

Clinical and image (ultrasound, CT scan or MRI) data were reviewed for all cases and then re-staged according to the UICC/AJCC TNM system [9]. rTNM classification served as the basis for both

classifying the extent of recurrence and developing the following proposed classification:

rT0 = no evidence of local recurrence

rT1a = recurrence in thyroid remnant

rT1b = recurrence in the thyroid bed

rT1c = relapse with involvement of adjacent organs

rN0 = no evidence of lymph node recurrence

rN1a = recurrence, level VI

rN1b = recurrence, levels II - V

rN1c = recurrence, level VI and II-V

rM0 = no distant recurrence

rM1 = distant recurrence

The time elapsed data following salvage surgery and information regarding the patient's clinical condition at the final objective follow-up (alive without disease, alive with disease, died due to the disease, dead due to other causes or lost for follow-up) were recorded and applied for survival analysis.

Statistical analysis was performed using STATA 10.0 version. Univariate analysis of survival after recurrence was performed using the Kaplan-Meier method. The log-rank test was used to compare the differences between the survival curves of the different categories of the same variable. Statistical significance was set at $p < 0.05$.

Results

A total of 102 patients were eligible for the study, 25 (24.5%) were male and were 77 (75.5%) female. The patients ranged in age from 9 to 82 years with a median age of 38 years. Regarding the ethnic groups, 94 patients were Caucasian (92.2%). The most frequently observed locations of the locoregional recurrences were as follows: 51 in the thyroid bed, 45 in ipsilateral the lateral neck lymph nodes (levels I to V) and 24 in the central neck compartment (level VI). Isolated recurrence in the thyroid bed was observed for 33 cases (32.4%), and recurrence associated with lymph node metastasis was observed for 16 cases (15.6%). Metastases localized exclusively in the central

compartment lymph nodes were observed for 10 cases (9.8%), and the association of local recurrence or locoregional recurrence with distant metastasis was observed for 9 cases (8.2%). The clinical and pathologic features are presented in Table 1. The Table 2 shows the local of recurrence according to initial treatment established.

Variable	Category/Measures	Freq (%) or Measures
Histology recurrence (surgery of)	Papillary carcinoma	90 (88.2)
	Follicular Carcinoma	11 (10.8)
	Hurthle cell Carcinoma	1 (1.0)
Tumor size	N	6
	Min - Max	0.4 – 12.0
	Median	0.9
	Mean \square SD	2.8 \square 4.5
Staging rT	rT0	51 (51)
	rT1a	26 (25.5)
	rT1b	22 (21.5)
	rT1c	3 (3.0)
Staging rN	rN0	35 (34.3)
	rN1a	16 (15.6)
	rN1b	31 (30.4)
	rNc	20 (19.7)
Staging rM	rM0	93 (91.2)
	rM1	9 (8.8)

Table 1: Clinical pathologic features of the 102 patients with recurrent well-differentiated thyroid carcinoma

Type of Thyroidectomy	Recurrence Topography		Lymph Node Recurrence		Distant Recurrence		Total
	Nodulectomy	Lobectomy	Lobectomy Istmectomy +	Partial Thyroidectomy	Total Thyroidectomy	Extended Total Thyroidectomy	Total
Local	0	13	4	0	15	1	33
Ipsilateral Lymph Nodes	0	0	0	0	25	1	26
Contra lateral Lymph Nodes	0	0	0	0	3	0	3
Level VI	0	0	0	0	10	0	10
Local+Ipsilateral Lymph Nodes	1	0	0	0	2	0	3
Local + Contralateral Lymph Nodes	0	1	0	0	1	0	2
Local + Level VI	0	0	0	1	5	0	6
Local + Lung	0	0	0	1	0	0	1

Ipsilateral+Contralateral Lymph Nodes	0	0	0	0	3	0	3
Ipsilateral + Level VI	0	0	0	0	3	0	3
Ipsilateral Lymph Nodes + Lung	0	0	0	0	3	0	3
Contralateral Lymph Nodes + Level VI	0	0	0	0	1	0	1
Local + Ipsilateral Lymph Nodes + Level VI	0	0	0	0	1	0	1
Local + Ipsilateral Lymph Nodes + Lung	0	0	0	1	0	1	1
Local + Lung + Central Nervous System	0	0	0	1	0	0	1
Ipsilateral + Contralateral Lymph Nodes + Level VI	0	0	0	0	2	0	2
Local+ Ipsilateral Lymph Nodes + Lung + Other Site	0	1	0	0	0	0	1
Local + Ipsilateral + Contralateral Lymph Nodes + Level VI + Lung + Central Nervous System	0	0	0	0	1	0	1
Total	1	15	4	4	75	3	102

Table 2: Initial Treatment vs Recurrence

Regarding the rT re-staging of 102 patients using the proposed rTNM classification, we observed 51 cases (51%) with rT0, 26 (25.5%) cases with rT1a, 22 (21.5%) cases with rT1b and 3 (3.0%) cases with rT1c. Concerning the rN stage, 35 (34.3%) cases were rN0, 16 (15.6%) cases were rN1a, 43 (42.1%) cases were rN1b, and 8 (7.8%) cases were rN1c. Only 9 cases (8.8%) displayed distant metastasis (rM1) in association with loco-regional recurrent disease (Table 3).

Site of recurrence (number of cases)	rT	rNn6	rNI	rNc	rM	N. of cases
rT (33)	•					33
rNn6 (16)		•				10
	•	•				6
rNI (33)			•			26
	•		•			3
		•	•			3
	•	•	•			1
rNc (11)				•		3
	•			•		2
		•		•		1
			•	•		3
		•	•	•		2
rM (9)	•				•	2

			•		•	3
	•		•		•	3
	•	•	•	•	•	1
Total	51	24	45	12	9	

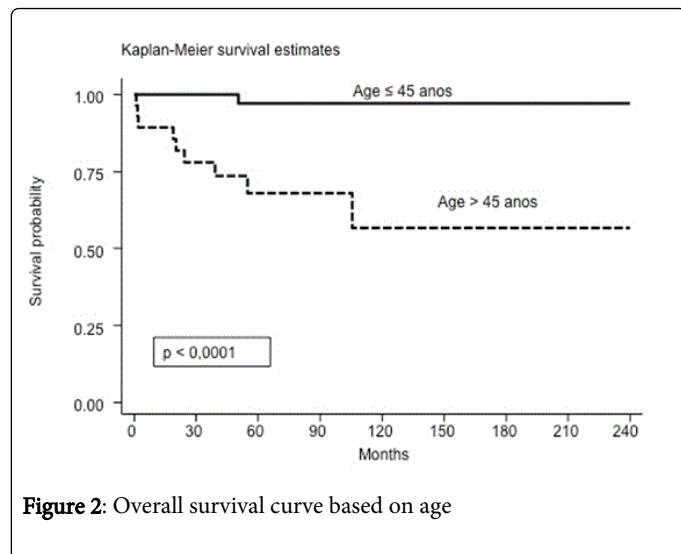
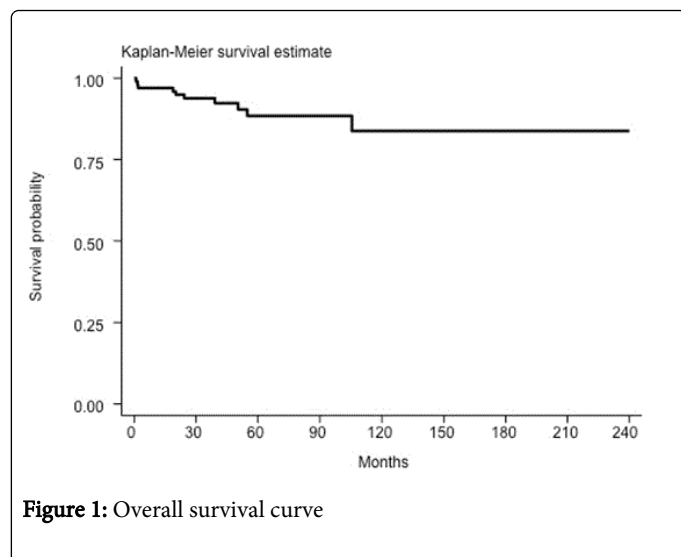
Table 3: Distribution of samples based on the site of tumor recurrence.* Legend: rT: local recurrence; rNn6: level VI recurrence; rNI: levels II-V ipsilateral; recurrence; rNc: levels II-V contralateral recurrence; and rM: distant recurrence

The surgical treatment for 51 local recurrences was wide local resection for 16 cases (15.6%). Eighteen patients (17.6%) were treated with a total thyroidectomy. Wide local resection associated with neck dissection was performed for 14 cases (13.7%), and extended local resections (including tracheal or recurrent nerve resection) were performed for only 3 cases (2.9%). Neck dissection represented the most frequently performed surgical procedure (66 patients (64.7%)). Of these, 38 (37.2%) patients underwent selective neck dissection of either levels II - V or levelsII - VI. For 28% of these patients, unilateral or bilateral dissection (levels VI or VI and VII) was performed.

Concerning the pathologic analysis of recurrence, 90 cases (88.2%) of recurrence displayed papillary carcinoma, 11 (10.8%) cases displayed follicular carcinoma and 1 (0.9%) patient displayed Hurthle cell carcinoma (1.0%). The recurrent lesion sizes ranged from 0.4 cm to 12.0 cmwith a median size of 0.9 cm.

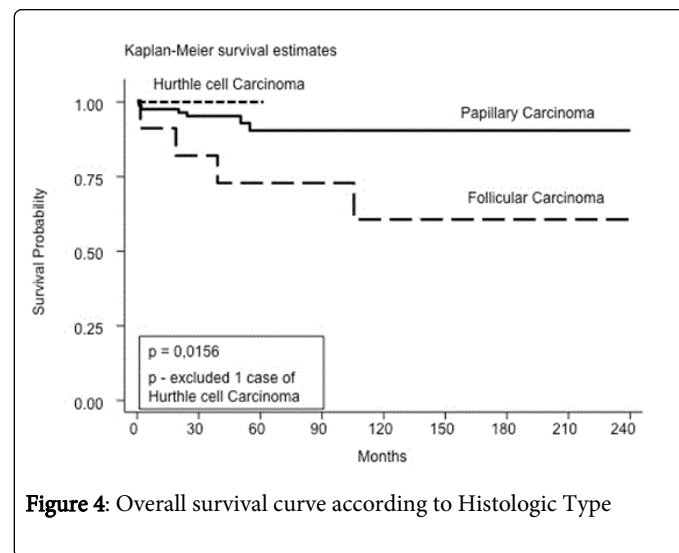
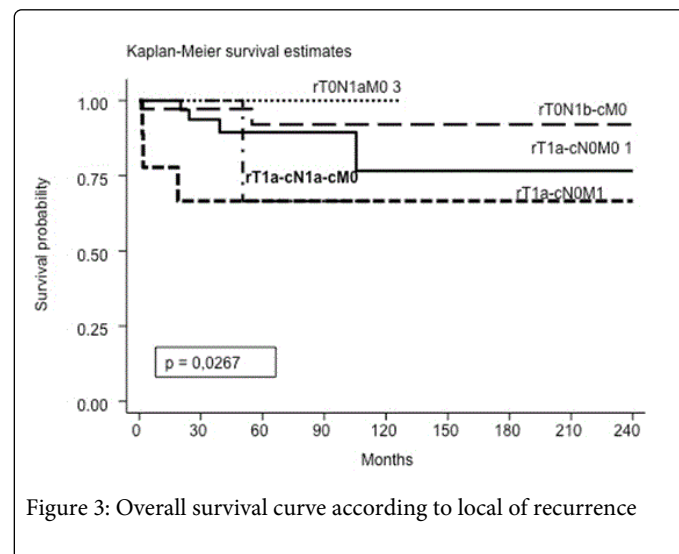
The time from salvage treatment until further recurrence or final follow-up ranged from 1 to 348.5 months with a median time of 36.5 months and mean time of 58.6 months. Regardingpatient status at the

end of the follow-up, 67 patients (65.7%) were alive without evidence of disease, 12 patients (11.8%) were alive with recurrent disease, 11 patients died (10.8%) and 12 patients (11.8%) were lost to follow-up. Overall survival at 3 and 5 years was 93.7% and 88.2%, respectively (Figure 1). There was no significant difference in overall survival in relation to gender ($p=0.2203$). Younger patients (aged less than or equal to 45 years) had an overall 5-year survival of 100%, while patients over 45 years of age had an overall 5-year survival of 67.6% ($p < 0.0001$) (Figure 2).



Univariate survival analysis regarding the site of recurrence was statistically significant ($p=0.0267$). The best survival rates at 5 years were observed among patients with recurrence at level VI (rT0N1aM0) (100%). The patients with recurrence at levels II-V lymph nodes (rT0N1b-cM0) had 5-year overall survival rates of 92.2%. The patients with local recurrence (rT1a-cN0 M0) had 5-year overall survival rates of 88.8%. The cases with local and regional recurrence (rT1a-cN1a-cM0) had 5-year overall survival rates of 66.7%. The patients with local recurrence or loco-regional recurrence associated with distance disease (rT1a-cN0 M1) had 5-year overall survival rates of 65.8% (Figure 3).

Regarding the histological types, the patients with papillary carcinoma had the best overall survival rates at 5 years (90.3%). Follicular carcinoma cases had a 5-year survival of 72.2% ($P = 0.0156$) (Figure 4).



Discussion

The survival expectation of patients with treated WDTC is high, while the risk of recurrences is moderate, and the risk of cancer-related death is low. Regardless of the type of initial treatment used, approximately 5% to 23% of patients present with cancer recurrence, which may be associated with a more virulent strain of the disease [10,11]. Although recurrences can be diagnosed decades later, most relapses occur within the first 5 years after treatment, and the first 18-24 months are considered the highest risk period for recurrence [12]. According to Palme et al., the male sex, advanced initial stage and the presence of extrathyroidal spread represent the most significant independent predictors of multiple recurrences in patients with WDTC. These patients usually have a poor prognosis [1]. Based on this study, we did not find significant differences in overall and cancer-specific survival among patients undergoing initial treatment with those who presented a single treated recurrence. However, for patients with multiple relapses, there was a considerable increase in the risk of death (ranging from 12% to 69%).

Recurrent thyroid carcinoma can usually be treated and controlled. In contrast, the treatment of recurrences is controversial [3]. For patients with progressive increases in thyroglobulin and no evidence of disease based on imaging studies, a therapeutic dose of I131 is indicated [13-15]. Radical salvage surgery is reserved for resectable locoregional lesions. The typical salvage surgical treatment for locoregional relapses consists of surgical removal associated with adjuvant therapeutic doses of radioiodine, generally 100-200 mCi. [2, 16-18]. For recurrent lesions with no iodine uptake, salvage surgical treatment can be complimented with post-operative radiotherapy [4-6].

Shah et al., have investigated the safety and efficacy of central compartment neck dissection in the treatment of 82 patients with recurrent WDTC. Central compartment neck dissection was performed in 36 patients (42%), while lateral neck dissection was required for the rest of the patients. Post-operative temporary hypoparathyroidism was performed for 17 patients (20%) and permanent was performed for 6 patients (7%). Unilateral recurrent laryngeal nerve injury was transient in 3 patients and permanent in 3 patients (2%). Seventeen patients (21%) experienced subsequent recurrences. The Tg levels were normalized for 15 patients (56%). Normalization occurred for 10 of the 20 patients (50%) who received sodium iodide I 131 ablation and in 5 of the 7 patients (71%) who did not [19].

Well-differentiated carcinoma is more frequent in females [17-20]. However, men display poorer prognosis. Kim et al., have shown in a multivariate analysis that male patients with papillary microcarcinoma and locoregional recurrences had statistically significant negative prognoses [8]. Similarly, Palme et al., have found that the male sex was one of the most significant independent predictors of developing multiple recurrences in patients with WDTC. These patients have a poor prognosis with a significant reduction in tumor-free survival [1]. However, in our study, there were no statistical significances in overall survival after recurrence regarding gender ($p = 0.2203$).

Duntas et al., have demonstrated that for WDTC, patient age greater than 45 years or less than 25 years represented a particularly strong independent prognostic factor [21]. According to ITO et al., age >55 years displayed a significantly negative influence on disease-free survival at 10 years [22,23]. According to this study, a larger proportion of patients under the age of 45 years survived for 5 years compared with the group of patients older than 45 years of age ($p < 0.0001$).

Furthermore, the present study demonstrates that the histology of the tumor has an important influence on survival after salvage treatment. A number of histologic variants of well-differentiated papillary carcinoma have been found to be associated with more aggressive tumor behavior. Tall cell, columnar cell, diffuse sclerosing, solid/trabecular, and insular variants of well-differentiated papillary thyroid cancer are all potentially more aggressive than conventional papillary thyroid cancer [24]. However, when assessed via multivariate analysis, the evidence that the histologic subtype of the tumor is an independent predictor of outcome is weak [25]. In our study, we observed that papillary carcinoma was the most frequent (88.2%), and patients with papillary carcinoma displayed higher survival rates ($p = 0.0156$) than those with follicular carcinoma.

The distribution of recurrences was as follows: 33.3% in the thyroid bed, 37.2% in lateral cervical lymph nodes, 15.6% at level VI

isolated, 4.9% local recurrence associated with lymph nodes and 8.8% local recurrences were associated with distant metastasis. This variable had a significant impact on overall survival in the univariate analysis ($p = 0.0267$). Patients with distant metastasis displayed the lowest survival rates in our series. Wasseem et al., have also observed that patients with distant recurrences had a poor prognosis with a significant reduction in the actuarial disease-specific survival rates [2].

Some authors have described a poor prognosis for patients with relapsing disease in the thyroid bed compared with those with recurrence in the thyroid remnant [1,2]. Grant et al., have divided 963 patients with thyroid surgery with local recurrence in the thyroid bed and recurrence in the thyroid remnant. They found that mortality rates were higher for patients with recurrence in the thyroid bed [26]. Disease-free survival rates for these cases appeared to be lower than patients with recurrent disease at the thyroid remnant [1,2].

In conclusion, the present study found that the significant prognostic factors in patients with recurrent WDTC submitted for salvage treatment were as follows: age over 45 years, histologic type (follicular carcinoma), local recurrence and the association of two anatomical sites of recurrence. This high-risk group of patients should be considered as candidates for adjuvant radioiodine or radiotherapy as well as for inclusion in clinical trials.

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