

## Prognostic Factors and Survival of the Differentiated Thyroid Cancer Retrospective Study

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### Abstract

The Differentiated Thyroid Cancers (DTCs) is referred to the Papillary (PTC) and follicular (FTC) thyroid cancers. The thyroid cancer incidence was increased in recent years 1. Thyroid cancer is approximately represented 1% of all diagnosed cancer cases yearly 2. The Prognosis of thyroid malignancies is ranged from the most frequently seen differentiated carcinoma (papillary thyroid carcinoma – PTC, and follicular thyroid carcinoma – FTC), to the less common aggressive, but the most aggressively growing is an anaplastic type.

**The Aim of current work to explain the following:** The prognostic factors that are influence the long-term survival in patients with differentiated thyroid carcinoma either, the gender, age, size of the tumor mass, distant metastasis or not, lymph node metastasis or not, lymphocytic infiltration, degree operation effect, types of operative plan, histological characteristics-, iodine supply or deficiency, patients' TNM classification changes.

**Patients and methods used in our study:** The retrospective study was done at the surgical department, Zagazig University. Two hundred and fifty patients were operated for differentiated thyroid carcinoma between 2010 and 2018. All evaluated patients were divided into 167 for papillary carcinoma and 93 for follicular carcinoma. Data of 250 patients have been analyzed during our retrospective study. Survival data and risk factors have been concluded from follow-up documents, and from the patients reviewing.

**Results:** Follow-up 167 patients and their survival data underwent surgery for papillary carcinoma and follow 93 for follicular carcinoma, at the surgical department, Zagazig university. The 10 years survival was 87.9% and 84.0%, respectively. Follow up period about 10 years for both. In 167 patients of papillary carcinoma (average age: 42.7+/-16.0ys, male: 47, female 120: (female ratio 1:2.5), but in 93 patients were operated on for follicular carcinoma (average age: 48.5 +/- 14.9 years, male: 29, female: 64, male: female ratio 1:2.2). Our results clarified a continuous increase in patient numbers, with increased papillary carcinomas percentage, and during this time of period of our study their increase of early rate which correlated well with our statistics.

**Conclusions:** The clinical course and outcome of papillary and follicular thyroid carcinomas are relatively good with low tumor-related mortality, and the survival rates have been improved during the past 10 years as the result of wide spread modern diagnostic and therapeutic protocols. After determining the prognostic factors of survival gives us to make the suitable decision for every individualized surgical plan and the extent of the surgical intervention plane, whose needing for follow-up treatment, the number or frequent follow-up care visits or outpatients clinics.

**Keywords:** Thyroid Cancer; Retrospective Study; PTC; FTC

### Introduction

The thyroid cancer is count for approximately 1% of all diagnosed cancer patients yearly 1. Thyroid cancer range from the most frequently differentiated carcinoma; papillary thyroid carcinoma (PTC), and follicular thyroid carcinoma (FTC) to less common and most aggressively nature undifferentiated anaplastic types.

The differentiated thyroid carcinoma has a good favorable course that relative to another differentiated thyroid tumor. The tumor specific mortality is the low mortality rate, and the life expectancy continues to be improved during the recent 10 years, due to the advanced diagnostic and therapeutic protocols tools 2. However, some cases have poor prognosis in this group, because of late diagnosis and ignorance and lower educated types of patients 3.

The major differences in the treatment of the thyroid malignancy are about the different planes of the surgery intervention; extend of excision indicating different protocols of postoperative 131I-treatment. The

surgery is the primary treatment, and lymph nodes metastases degree that affecting the patients survival rate.

Among these most important complications, the recurrent laryngeal nerve paralysis, and hypoparathyroidism. The incidence of these complications is less common in the first operation. It is important to determine the extent of the surgical intervention before or during operation sitting 4. The most radical procedure, total thyroidectomy for all patients, after pre- and intraoperative diagnostic methods when the result of the histology reveals carcinoma, the option will total thyroidectomy after frozen results.

The post-operative treatment, the follow-up care, and the changes in the patient's life quality that underwent surgery for the differentiated thyroid carcinoma type is an important public health subject. So, these patients will require long life follow-up care.

It is necessary to adhere to an individualized long-term follow-up system in our age of cost-oriented health care plane, as the number of lost workdays is significant /certain diagnostic procedures are unusual or

unsuitable to use routinely, because of either their high cost such as CT, MRI, PET, or as they can also affect the patients adversely with it 3.

The side effect of performing whole-body 131I scan, or 131I therapy, after one-month suspension of thyroid substitution, can adversely make hypothyroidism that affecting the patients' quality life, or vocal cord affections complications. The matching and dividing patients into groups based on the available specific data, and prognostic factors preoperative can be helpful to clarify those cases that requiring more detailed and therapy .

Due to the long survival period, a good plane of surgery requires the long-term follow-up. Therefore, they were claimed by retrospective studies; data from prospective studies that not yet published. The survival depends on tumor size, lymph node and distant metastases , determined by TNM classification, also other factors. The study included papillary, follicular, or both types. The long-term good prognosis of differentiated thyroid carcinomas is still unknown reasons. The response of the immune system is a possible explanation of the lymphocytic infiltration that is not understood completely. The effects of iodine deficiency with above-mentioned factors have not been reported. The effects of ionizing radiation on the pathogenesis of the thyroid carcinoma, is not understood good and were examined by many investigations.

**Our aim explains to the following questions:**

A- What prognostic factors influence the long-term survival in patients with differentiated thyroid carcinoma?

1. A factor of gender and the age
2. The tumor mass size, distal metastasis and lymph nodes number and metastasis
3. Histological characteristics of the tumor?
4. Lymphocytic infiltration and iodine supply, iodine deficiency complications affecting the morphological characteristics of thyroid tumor
5. TNM classification changes after surgical treatment and radioactive iodine during the study period?

**Patients and methods**

At the zagazig university surgical department, 250 patients were operated on for the differentiated types of thyroid carcinoma between 2010 and 2018; 176 for papillary carcinoma and 93 for follicular carcinoma. The data of all 250 patients have been analyzed during the period of the retrospective study.

Survival data and complications have been obtained from the operating and post-operative documentation. The multifocality, multicentricity, lymphocytic infiltration, and iodine deficiency or supply, all have been examined in our retrospective study in both the papillary and follicular groups.

The tumor size, lymph node number extend and the distant metastases, total thyroidectomy (the complete removal of the gland) or near total (when only small suspected normal tissue about 0.5-1 cm3 of either thyroid lobe is spared), close to the rear capsule to be followed by 131I ablation, to avoid recurrent laryngeal nerve injury and parathyroid removal or deprivation of blood supply.

The histology specimens were re-evaluated again and the diagnosis was revised based on the classification guideline were analyzed. The extent of lymphocytic infiltration in the tumor was important and also evaluated that associated with good prognosis. Others studies clarified that the iodine intake correlated good with the iodine level in Hungary period. The survival curve calculations were done by the SPSS in our Windows program and the data were then analyzed by Cox regression. TNM analyzed changes and the operation types in two separate periods of our retrospective period, also we compared incidence and age distribution of

the histologically and degree of differentiation of the different carcinomas types.

**Results**

Follow-up 167 patients and their survival data underwent surgery for papillary carcinoma and follow 93 for follicular carcinoma, at the zagazig university surgical department. The 10 years survival for papillary and follicular carcinoma was 87.9% and 84.0% respectively , with average follow-up period 9.6 + for papillary type /- and 6.9 years for follicular type. In 167 patients of papillary carcinoma (average age: 42.7+/-16.0ys, male: 47, female 120: (female ratio 1:2.5), but in 93 patients were operated on for follicular carcinoma (average age: 48.5 +/- 14.9 years, male: 29, female: 64, male: female ratio 1:2.2).

The TNM stage distribution among our patients as usual. Most patients in stage T2 (PTC: 33%, FTC: 49%). In the follicular cancer group, all cancer-related deaths occurred in the first decade of the follow-up. Based on the Kaplan-Meier survival curves, distant metastases, extra thyroidal invasion, lymph node invasion, and infiltrating versus good non invaded, encapsulated form of the tumor had any negative influence on survival. The gender of patients, the age over 40 years, type of surgery (total vs. near-total thyroidectomy), and lymphocytic infiltration or multifocality that did not affect the survival rate.

Papillary carcinomas that early lymphatic metastasized to the primary neck lymph nodes. At the time of surgery, the primary, 58 (34.7%) of the 167 patients had nodal metastases, including 12 patients with stage N1b, bilateral metastases. But follicular carcinomas gave mostly distant metastases (to the bone and lungs), in 10.4% of our patients. Patients died of the primary disease in the group of 167 papillary patient group2 of these patients had stage T4M1 tumors, 3 had distant metastases (T1-3M1), and another 8 had extrathyroidal (T4M0) tumors. In the follicular group, 8 patients died of the 53. Of these, 2 had T4M1 stage. Another 2 had known distant metastases (T2-3M1) at the time of surgery, and 2 patients had stage T4M0. In the follicular cancer group all cancer related deaths occurred in the first decade of the follow-up also.

Gender	0.28 - 0.20
Age	<0.0001 - 0.047
Size	0.47 - 0.20
T1-2-3-4	<0.0001- <0.00009
Metastasis	<0.00009 - <0.0001
Node	0.009 - 0.046
Infiltration	0.38 - 0.28
Surgery	0.46 - 0.12
Multifocality	0.46 - 0.5
Encapsulation	0.04 - 0.07
Iodine	0.65 - 0.7

**Table 1** Survival factors of papillary and follicular cancer patients (Kaplan Meier curves - p value ( Papillary cancer , Follicular cancer).

Gender - sex of patient; Age – age of patient over 40; Size- tumor size if no extrathyroidal invasion present; T1-2-3-4 - tumor sizes (intrathyroideal v.s. extrathyroideal tumor); Met- distant metastasis; Node - lymph node metastasis present; Infiltr - lymphocytic infiltration present; Surg- extent of surgery (total or near total thyroidectomy vs. less than near total thyroidectomy); Multif - multifocal tumour; Encaps – encapsulated form of tumor v.s. infiltrative; Iodine - iodine intake Patients.

With stage T4 tumors, spreading out the anatomical borders or outside the capsule of the gland, had significantly worse the survival than of stage T1, T2, or T3 tumors, either in the papillary and the follicular groups. We can't did any procedure for stage T4 patients except only palliative resection., there is no any significant difference between the survival of stages for T1, T2 and T3 patients only If we were excluded patients of distal metastasis ( stage T4 tumors) from our analysis data. 5 patients with papillary carcinomas and 4 in the follicular group had at early diagnosis of primary metastasis. (died during the follow-up period) in both groups. survival changes very badly if associated with distal metastasis in all patients groups. The presence of lymphocytic infiltration had a good prognosis in both groups but not significantly affects the survival in both types.

Age of patients 40<	0.002 - 0.001
Tumour size	<0.0001 - 0.002
Metastasis	<0.0001- <0.0001
Node	<0.0001 - 0.170

**Table 2** Prognostic risk factors: Cox regression analysis (p) Papillary cc. Follicular cc.: Papillary cc. Follicular cc.

If lymph node metastasis and extra thyroidal invasion metastasis were present in the period of our study, the number of the absolute and relative frequency of PTC cases was increased in the past decade as opposed to the FTC among all cases. This due to the increasing the patient's number of their treated at our hospital. The proportion of early T1 and T2 stage between such cases that increasing gradually ,also in between PTC patients we found the degree of lymph node metastasis was decreased, from 40.6% to 30.8%, whereas less frequent distant metastases in both groups.

**Discussion**

The survival of differentiated thyroid carcinoma was affected by several factors other than those determined by the commonly accepted TNM classification as tumor mass size or lymph node metastases site, number, and distant metastases 8. Various scoring factors and systems have been created based on the results of the retrospective studies done before. In Table 3, we compare our data to those factors that considered major affection factors by most other authors.

The two types of the differentiated carcinomas papillary and follicular have to be examined separated due to their different biological behavior. The age at the time of discovery or patients examination is the most important prognostic factor in both types groups, with their recurrence and mortality rates that increasing after age 40, recurrence appears early stage, and death sooner after recurrence, indicating faster tumor growth and mitotic rate and tumor behavior. Furthermore, these tumors had less differentiated, and 131I isotope uptake is low uptake and effects by both the primary tumors and their metastases. Our results indicate a little or

continuous increase in the patient numbers, with an increased proportion of papillary type of carcinomas that more frequent presence of early stage tumors during the time period of our study. As Improved diagnostic techniques, and widespread use of ultrasound imaging and fine needle-guided and its increasing use as a screening techniques.

Byar (1979)	All 507 M M M
Cady (1988)	DTC 755 M M M
Sanders (1998)	DTC 1019 M M M n.s. n.s.
Mazzaferrri (1994)	DTC 1355 M M M M M M M
Sellers (1992)	DTC 212 n.s. M n.s. M M n.s. n.s.
Simpson (1987)	PTC 1074 n.s. n.s. M n.s. n.s. n.s. n.s.
Hay (1987)	PTC 860 n.s. M M M n.s. n.s.
Hay (1993)	PTC 1779 n.s. M M M n.s. n.s. n.s. M
Akslen (1993)	PTC 173 M n.s. n.s. n.s. n.s. n.s. n.s. n.s.
Kashima (1998)	PTC 1533 n.s. n.s. n.s. M n.s. M
Simpson (1987)	FTC 504 n.s. M M M M M
Mueller-G. (1990)	FTC 149 n.s. n.s. M n.s.
Shaha (1995)	FTC 228 n.s. M M M n.s.
Hay ID (2008)	PTC 900 n.s. n.s. n.s. M M n.s. n.s. n.s.
Eustatia- Rutten CF (2004)	FTC 322 n.s. M n.s. M M M
Hughes DT (2011)	PTC 160 n.s. m n.s. M M M M
Kithara CM (2016)	FTC 301 n.s. n.s. n.s. M M n.s. n.s. n.s.
Present study	FTC 106 n.s. n.s. M M n.s. n.s. n.s. n.s. n.s.

**Table 5** Prognostic factors affecting survival Author Type N Gender Size pT4. Met. Node. Multif. Infiltr. Surg. Iodine

All types of the thyroid cancer; DTC - differentiated thyroid cancer, FTC - follicular cancer, Infiltr - lymphocytic infiltration present, Iodine - iodine intake; Met - distant metastasis, Multif - multifocal tumour, N - Number of patients; Node - lymph node metastasis present, n.s. - non significant, pT4 - tumour size if extrathyroidal invasion present, PTC – papillary cancer, Gender -sex of patient, Size- tumour size if no extrathyroidal invasion present, Surg- extent of surgery (total or near total thyroidectomy vs. less than near total thyroidectomy), M-significant (p< 0.05) .

Cancer patients usually surgically treated at earlier stages because of advancement and widespread of fine-needle aspiration biopsy and ultrasound-guided aspiration cytology last decades. So, with the increasing the number of patients with papillary carcinomas, the proportion of stage T4 increased .This was explained by the relatively increased number of patients admitted and operate in our department. On the other hand, unfortunately, it still primarily among the older, those patients go to medical advice after the tumor has already persisted for nearly 10 years.

The most common operation for all endocrine disease is performed for thyroid lesion as the multinodular goiter or for a solitary node. In the solitary thyroid nodules, it is important to exclude the possibility of

malignancy during the treatment, to achieve the best survival when thyroid carcinoma is operated on at an early stage 3 2. By the help of fine-needle aspiration cytology guided by US has an important role in the evaluation of the dominant nodes and so the influence of the surgical plan but if the nodules were usually 1cm or above. For cases (C3-C5) where preoperative proven cytology or high suspected malignancy, the following operative procedures done at our hospital:

- Fine-needle aspiration cytology if negative we proceed to the removal of the enlarged thyroid lobe or that containing the node, with the isthmus, with preserving the recurrent laryngeal nerve and the parathyroid glands. The lobe and the isthmus were then sent for intraoperative frozen section.
- If the quick-frozen sample indicates malignancy, we proceed to total thyroidectomy. But if the fine-needle was done only preoperative and it was conclusive we proceed to the total thyroidectomy from the start without frozen section.

- we had two conditions If the result of the frozen section is uncertain or preoperative fine needle aspiration cytology uncertain, or if the opinions of the two pathologists are contradictory, and the diagnosis uncertain, the operation is finished as a lobectomy and isthmoidectomy, and the other side was kept, if the result of pathology of removed part is positive for malignancy we proceed for removal of the other lobe in the same week to ended by total thyroidectomy. It so-called “completing” operation. (The same as guideline-2015).

The recurrent laryngeal nerve and parathyroid glands can be identified with certainty, and preserved which is important in order to avoid the two most severe complications. Stage T1, solitary papillary carcinomas without metastases require also completing operations.

The primary radical operations were performed on about on 90 PTC patients in our hospital during the study period: 29 total and 59 near-total thyroidectomies, and 2 cases lobectomies. 42 patients needed completing operations. 17 patients were highly risk and they were referred to us for the second operation. The completing operations were total thyroidectomies in 6 cases after proved the frozen section, also near-total thyroidectomies in 14 cases, if another lobe was free by biopsy frozen section, and 1 lobectomy. in 12 cases the residual thyroid tumor tissue was found (27%). 50 patients underwent only lobectomy or subtotal resection in our period of study, that not considered enough option according to present therapeutically guidelines. because of patients' refusal to a second operation relative high number resulted. The total was done (in 7 patients) or near-total resection was done in (8 patients) but total thyroidectomy was performed in 29 patients with FTC as the first option. The completing operations were done in 16 patients.

Among these patients, 7 were suffered the second operation after the first operation. Of the other 9 patients, histopathology results conclude proven residual tumor examination in 3 of the specimen removed during 7 total removal of all residual thyroid gland and 9 near-total thyroidectomies. The percent of recurrent laryngeal N. paresis is 2.4-3.6% and persistent hypoparathyroidism in 2.1 – 6.9% among the groups.

The frequency of lymph node metastases is between 33-62% in PTC, and lower (14-18%) significantly in FTC patient. papillary “microcarcinomas” – tumors smaller than 1 cm, seen in childhood. that first clinical symptom of the disease, leading to the diagnosis. Among our 167 PTC patients, 58 had lymph node metastases (34.7%). Another benefit of Ultrasound imaging of the neck should be a part of the routine diagnostic of the cervical lymphadenomegaly nowadays, followed by ultrasound-guided cytology. This approach could decrease the number of cases that biopsied first is first, and later, based on the histology results, who have to undergo a second operation to bring a final surgical solution. The surgical treatment of cervical lymph node metastases can deal with either by the local dissection (LD), or modified radical neck dissection (MRND) with therapeutic or prophylactic. MRNDs lymph node metastases reveal up to 70% of negative palpation findings. If only the lymph nodes on the side of the thyroid cancer in most cases.

We performed 44 LDs and 22 MRNDs in our PTC patients. Depending on the cervical lymph nodes was not adherent to neighboring tissues and only their palliative removal was possible. Subsequent operations removal of recurrent lymph nodes metastasis in 31 patients. 16 patients needed one stage, 10 patients needed two stages operations, and 3 patients required three stages and another 2 required four subsequent operations. The number of patients with re-operations for recurrent lymph node involvement was 9 cases but after following LDs, and also, 16 after MRNDs. In 15 patients (%11.9) who were categorized to be in stage N0 by imaging and histology at the time of the first diagnosis, follow-up examinations revealed positive lymph node metastases. No worse relapse rate can be detected in patients with only LDs than in those patients who underwent MRNDs, but we change our approach during the past 10 years, and recommend performing MRNDs for preventing the relapse rate. Some author finds the prognostic significance of the autoimmune response to the thyroid carcinoma depends on high antibody levels against TSH or the thyroid gland itself a promoter of malignant transformation 19. But others found good outcomes for those cases with papillary carcinoma or Hashimoto thyroiditis as lymphocytic infiltration 20. The immune system plays in keeping the disease under control in differentiated thyroid carcinoma immune system. Among the patients with PTC, the more lymphocytic infiltration, the less metastasis and good prognosis. Another reason for the need to carefully plan the extent of operations, keeping the different prognostic factors in mind, is the spread of minimally invasive operation in the thyroid surgery.

## Summary

Clinical courses of papillary and follicular thyroid carcinomas are relatively good and favorable. With low tumor-related mortality, and survival rates have been increasing during the past 10 years as the result of modern diagnostic and therapeutic systemic protocols and guidelines. Determining and applying the prognostic factors of survival and early diagnosis gives us a chance to design an individualized of choice for types and ideal surgical plan concerning with the extent of the surgical intervention, the need for follow-up of the resulted treatment, the frequency and extent (invasiveness, cost) of follow-up of the care visits or clinic visit. No changes in demographic parameters of the population, we studied with the differentiated thyroid carcinomas compares with those previously published from other geographic areas with similar results and condition. Cox regression analysis found that in the papillary carcinoma cases, age over 40 years old, pT4 staging tumor, distant metastases or secondary, and lymph node metastases, while in patients had follicular carcinoma, age factor, extra thyroidal growth rate, and distant metastases are significant determinant prognostic factors. Lymphocytic infiltration that had better prognosis in both the papillary and follicular group of patients, but without any significant difference in survival rate. Also Iodine intake had any significant influence survival either with papillary or follicular carcinomas. But the increase in iodine intake we found a significant increase in the frequency of papillary carcinoma cases if compared to that of follicular carcinoma cases. The increasing use of ultrasound imaging as a screening tool, play important roles in this finding and cytological analysis by the guided US. the lowest incidence of complications (recurrent laryngeal nerve paresis, and hypoparathyroidism. in reoperation their no one hundred percent reliable, either separately, or in combination. Ultrasound imaging of the thyroid gland should be an important part of the routine diagnostic examination in cases of cervical lymph nodes affection nowadays, followed by cytology ultrasound-guided, if needed. This approach could decrease the number biopsied first to bring a final surgical solution to the cancer of the thyroid.

## Conclusions

1. Based on long-term follow-up data concluded on patients with papillary and follicular thyroid carcinomas, we found by Cox regression analysis that in papillary carcinoma cases, age over 40 years, pT4 stage tumor, distant metastases, and the lymph node metastases, while in patients with follicular carcinoma, age, extrathyroidal tumor growth, and distant metastases are affecting significant prognostic factors. In this latter population, the effect of lymph node metastases was not significant effect.
2. Lymphocytic infiltration had no significant survival effect in both types of differentiated thyroid tumor in either the papillary or the follicular carcinoma group of patients.
3. Survival either among patients with papillary or follicular carcinomas Iodine intake does not influence significantly outcome. But the increase in iodine intake in papillary than follicular.
4. No statistically significant difference in the survival of patients with radical (total or near-total thyroidectomy) versus less radical operations in the past years (lobectomy, subtotal resection, with affected lobe and free another lobe).
5. The multifocal appearance of papillary carcinomas (32.4%) did not affect the survival significantly, but significantly more residual tumors found in multifocal than solitary.
6. Prognostic factors need to be well weighed when patients are chosen for minimally invasive operations. Or biopsy
7. No difference in rate in relapse between patients undergo undergoing local lymph node dissection (LD) when compared to those patients who had modified radical neck dissection (MRND), but we recommend performing MRNDs, until our data are verified in a larger number of patients, or compared to other researchers.

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