# Nodal Capsular Invasion as a Risk Factor for Subsequent Early Recurrence after First Recurrence of Well Differentiated Thyroid Cancer

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## Abstract:

**Introduction:** Although thyroid cancer is the most prevalent endocrine malignancy, however it's responsible for less than 0.5% of cancer related death. Large number of researches had examined different factors that may affect recurrence such as age, sex, thyroid tumor size, histological types, and lymphatic invasion, which had all been used as an indicator for poor outcome. In our study, Lymph node (L.N.) capsular invasion by tumor had been assessed as a factor affecting recurrence in well differentiated thyroid cancer patients (WDTC) after first recurrence.

**Aim:** To assess the effect of neck L.N. capsular invasion in well differentiated thyroid cancer on subsequent recurrences

**Patients and methods**: This retrospective cohort study was carried on 40 patients with neck recurrence of WDTC who were referred to National cancer institute (NCI) between June 2014 and June 2015. Data was collected regarding initial disease stage, type of recurrence, time till recurrence, investigation done, and previous treatment. Adequate management of those patients was done (further investigation and surgical treatment), histopathology are obtained and documented

**Results:** Of the 40 patients included in the study, 35 patients showed nodal affection in their first recurrence, with 15 of them showed
L.N. capsular invasion. Of these 15 patients, 7 patients showed subsequent second recurrence (46.7%), 3 of them with nodal affection and 4 with operative bed only recurrence. L.N capsular invasion was found in 3 patients of the 7 with second recurrence. Of the 25 patients with no L.N. capsular invasion in their first recurrence only 8 showed second recurrence (32%).

**Conclusion:** Among those patients with multiple recurrence of WDTC, males that aged over 40 years with aggressive primary tumor and advanced stage, and those with L.N. capsular invasion, have a significant risk of multiple recurrence and possibly poor outcome. L.N. capsular invasion showed that it may be an important factor for further recurrences which may put those patients among higher risk group that need more aggressive management and more precise follow up.

**Keywords:** Well differentiated thyroid cancer (WDTC), recurrence, neck nodes, capsular invasion.

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## Introduction:

Thyroid cancer is the most prevalent endocrine malignancy, estimated to account for 94% of cancers of the endocrine system, and 66% of deaths due to cancers of the endocrine system [1]. Well differentiated thyroid carcinoma (WDTC) was found to be the most commonly diagnosed thyroid malignancy; it accounted for 2% of all cancers in the body and was reported to be responsible for less than 0.5% of cancer related deaths [1].

Combination therapy with thyroidectomy and Iodine 131 (I 131) was found to be the treatment of choice in most cases, and the majority of patient have excellent prognosis, with disease specific survival rates at 10 years greater than 90% [2]. However, 8-23% of patients were found to fail initial therapy and develop recurrence of the disease [1-4]. Mortality rates among patients with

recurrence have been reported to be as high as 38-69% [4-6].

In a previous study by Palm et al. [7] showed that WDTC patient who had either no recurrence of disease or only one recurrence after initial therapy had no difference in disease specific survival (100% vs. 94%) or overall survival (80% vs. 83%). In addition, patients with multiple treatment failures had significantly reduced disease specific survival (60%) and overall survival (58%) [7].

Several studies have attempted to classify patient into low, intermediate, and high risk groups based on the presence of these factors. Prognostication was therefore used to identify patients at high risk who require close follow up, and prompt therapy for any evidence of recurrence. [10,12-18]

In a recent study, of 685 patients with (WDTC) in a cohort study, 75 patients developed cervical structure recurrence (11%), 36 patients developed distant metastasis (5.2%) (with 2.8% of them had local and distant disease), and 14% died from their disease in a period ranged between 26 and 156 months from their initial diagnosis [26]. Rates of persistent / recurrent disease were 3.6% low risk patients, 13.6% for intermediate risk patients, and 71.4% for high risk patients. [26]

In the end of the follow up period that ranged between (4 to 243 months), (mean 71 months) 0.3% of low risk group patients, 0.9% of intermediate, and 15.2% of the high risk group patients had died from their disease. [26]

Till now there are no clear reports in literature delineating prognostic factors to predict disease outcome in patients who had suffered multiple reoccurrences and treatment failures of WDTC.

Thus, the purpose of this Study was to examine L.N. capsular invasion as an important factor for early subsequent recurrences after first recurrence in patient with well differentiated thyroid cancer.

## Patients and Methods:

*Study design*

This retrospective cohort study was carried on t h e 40 consecutive patients with neck recurrence of well differentiated thyroid cancer who were referred to National Cancer Institute between June 2014 and June 2015 and fulfilled the inclusion criteria. Thirty five of them had associated nodal recurrence that had developed after management of their primary disease. 20 patients had radioactive iodine (RAI) as part of their management plan while the other 15 didn't receive (RAI).

*Population of study & data collection*

For all patient with recurrent disease, data was recorded on demographics, investigation done, initial stage of the disease, number and location of recurrence, time till recurrence, and treatment received. Data were retrieved from the patient records in Epidemiology and Biostatistics department of National Cancer Institute.

Patients with recurrent disease were identified by evidence of disease in imaging study, or elevated thyroglobulin level postoperatively or during follow up.

Surgery was done for recurrent disease as indicated. Study included patients who had done hemithyroidectomy and had other lobe, operative bed or nodal recurrence, patients who had done total thyroidectomy and had operative bed or nodal recurrence, and patients who had done thyroidectomy with neck dissection and had nodal or operative bed recurrence.

Completion thyroidectomy was done for other lobe recurrence, neck dissection was done for nodal recurrence in patients without previous neck dissection (therapeutic for clinical nodes and prophylactic for high risk patients) and excision of affected group of nodes was done for patients with previous neck dissection. Excision of recurrence was done for resectable operative bed recurrence. Follow up of these patients was taken by history and physical examination, laboratory tests (thyroglobin level) and neck imaging (U.S., C.T, MRI).

Histopathology and risk factors were documented. Patterns of recurrence in thyroid cancer, and associated risk factors for each type of recurrence, (age, sex, most common site of recurrence, level of L.N. affection, number of recurrences, recurrence in less than 12 months) were identified. Surgical management of recurrent thyroid cancer patients was described regarding type of surgery, extent of resection, outcome of surgery in the form of completeness of resection, microscopic or macroscopic residual, and recurrence in less than 12 months.

All patient meeting selective criteria of the study were included in a one year starting from June 2014 to June 2015. Last patient will be followed up for 12 months.

*Eligibility Criteria*

*Inclusion criteria:*

All patients with well differentiated thyroid cancer (WDTC) who were treated or referred to National Cancer Institute because of recurrent or persistent disease after having their initial treatment at other medical centers.

*Exclusion criteria:*

All patients with incomplete previous management data, or undifferentiated pathology.

*Statistical methods:*

Data management and analysis were done using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY, USA). Numerical data were summarized using means and standard deviations or medians and ranges, as appropriate. Categorical data were summarized as numbers and percentages.

Time till recurrence was calculated using Kaplan - Meier survival analysis methods to detect different factor affecting time till recurrence. Cox regression analysis was used to detect predictors of second recurrence.

## Results:

The study was conducted on 40 patients and 35 of them had first recurrence in lymph nodes as demonstrated in table (1). Only 15 (42.5%) patients of 35 patients had nodal capsular invasion.

Mean age of 15 patients with first recurrence was 45.1 years old as demonstrated in table (2). Second recurrence occurred in 7 patients (during first year) and third recurrence occurred in 1 patient.

In primary surgery in table (3), most patients (73.3%) underwent total thyroidectomy. Only 4 patients had infiltration of nearby tissue. Most patients had papillary classic histology (73.3%). Right and left lobe affection occurred in equal number of patients (46.7%) and one patient had bilobar infiltration by tumor. Very few lymph node infiltrations during primary surgery. Most patients (78.6%) had complete resection in primary surgery.

All fifteen patients with first recurrence had lymph node recurrence in levels other than 6th level and six of them had lateral and central lymph node affection. Only 2 (13.3%) patients had infiltration of nearby tissue.

In table (5), 7 (46.7%) patients had second recurrence and 3 of them had lymph node affection. All 3 patients had 6th level nodal affection and one of them had 6th and level other than the 6th level. Lymph node capsular invasion occurred in 2 patients during the second recurrence. Of the 25 patients as shown in table (6) with no L.N capsular invasion, only 8 (32%) had subsequent recurrence, with all of them had nodal recurrence, and one with associated operative bed recurrence.

*Recurrence free survival:*

Second recurrence occurred in 15 patients as shown in table (7). Time till recurrence was calculated by survival analysis methods to detect cumulative survival at (3) year and it shows number of cases remaining without recurrence after years of follow up. Age showed statistically significant difference between 2 groups (p value < 0.001).

Patients on thyroxine was statistically different regarding recurrence free survival (p value = 0.021) as demonstrated in table (8), while other surgical features in primary surgery showed no statistically significant difference.

Recurrence free survival in relation to surgical characteristics of operations performed on first recurrence is shown in table (9). Patients with lymph node capsular invasion showed no statistically significant difference from patients without capsular invasion (p value = 0.306). Level of lymph node affection showed significant difference between these with both central and lateral and patients with lateral affection in first recurrence.

Cox regression model was performed to detect predictors of subsequent recurrence in table (9). Factors with significance level < 0.1 was entered in model except level of lymph node affection due to missing cases and L.N. capsular invasion was entered to model due to its clinical importance. Method of entry was forward likelihood ratio and was found that age more than 45 years old had 10.37 times higher risk of recurrence than in patients ≤ 45 years old. Patients with lymph node capsular invasion in 1st recurrence had 3.74 times more risk than patients without lymph node capsular invasion.

## Discussion:

Although the overall prognosis of well differentiated thyroid cancer is good, however local recurrence after initial surgery stay an important issue in management of this patients, especially with pathological factors predicting local recurrence remain unclear [13]

Prophylactic lymph node dissection during surgery also showed controversy.[14,15]. While some author advised for it to achieve reduction in post operative thyroglobulin (Tg) levels, and a decrease morbidity rate which is obtained in first surgery in compare to further surgery, some other authors suggested that this procedure may increase the risk for near by tissue injury like the parathyroid gland and recurrent laryngeal nerve.[19-22]

Various results are reported in the literature regarding the effect of lymph node metastases on DTC recurrence. Some studies indicate that lymph node metastases do not affect PTC recurrence [19]. However, some researchers have found that the number and size of lymph node metastases, and L.N. ratio may affect postoperative recurrence or metastasis. Thus, lymph node metastasis has become an important factor affecting the prognosis and recurrence of thyroid carcinoma [20].

Zhu et al. in his research revealed statistically significant differences in lymph node metastases between the recurrent and non-recurrent groups. He noted that Patients with lymph node metastases at the time of initial surgery are more likely to suffer recurrence than those without metastases.[21] The correlation of cervical lymph node metastases with recurrence needs to be confirmed through large-sample and long-term studies.

He also showed that recurrence in patients with positive nodes in first surgery, was observed to occur within a short period of time with the majority of DTC patients, showed recurrence within two to five years from surgery. Furthermore, recurrence may also occur more than once. Therefore, DTC patients must have regular reexamination with frequent follow-ups within five years after the first treatment.

In our study from the 40 patients who did surgical management for their disease 35 patients showed L.N, affection , 15 (42%)of them showed first recurrence with all of them showed L.Ns affection, and of the 15 patients 7 (46.6%) showed 2nd recurrence , 3 of them showed nodal affection

Table (1): Site of recurrence of thyroid cancer

| Site of recurrence | N=40 (%) |
|---|---|
| Nodal | 20 (50.0) |
| Nodal and extranodal | 15 (37.5) |
| Extranodal | 5 (12.5) |

Table (2): characteristics of patients with nodular capsular invasion in first recurrence

| Factors | | N=15 (%) |
|---|---|---|
| Age | Mean ± SD | 45.1 ± 11.4 |
| Gender | Male | 6 (40.0) |
| | Female | 9 (60.0) |
| Number of recurrences | 1 | 8 (53.3) |
| | 2 | 6 (40.0) |
| | 3 | 1 (6.7) |
| Patient on thyroxine | Yes | 6 (40.0) |
| | No | 9 (60.0) |

Table (3): Primary surgery of thyroid cancer

| Factors | | N=15 (%) |
|---|---|---|
| Type of previous thyroidectomy | partial | 4 (26.7) |
| | Total | 11 (73.3) |
| Infiltration of nearby tissue | Yes | 4 (26.7) |
| | No | 11 (73.3) |
| Size of tumor (N=10) | ≤ 2 cm | 1 (9.1) |
| | > 2cm | 9 (91.9) |
| Histology | Papillary (classic) | 11 (73.3) |
| | Papillary (tall cell) | 1 (6.7) |
| | Papillary (columnar cell) | 1 (6.7) |
| | Follicular (insular) | 2 (13.3) |
| Site of tumor in thyroid gland | Right | 7 (46.7) |
| | Left | 7 (46.7) |
| | Bilobar | 1 (6.7) |
| Capsular invasion in thyroid tumor | Yes | 8 (53.3) |
| | No | 7 (46.7) |
| Number of total L.N. removed | Median (range) | 0 (0-4) |
| Number of positive L.N. | Median (range) | 0 (0-4) |
| Side of L.N. affected | Right | 1 (6.7) |
| | Left | 1 (6.7) |
| | Bilateral | 13 (86.7) |
| Resection margin (N=14) | Complete | 11 (78.6) |
| | Microscopic residual | 1 (7.1) |
| | Macroscopic residual | 2 (14.3) |

L.N.: Lymph Node

Table (4) Surgical data in first recurrence

| Factors | | N=15 (%) |
|---|---|---|
| Level of lymph node affection | Lateral | 9 (60.0) |
| | Central and lateral | 6 (40.0) |
| Site of L.N. (N=13) | Right | 6 (46.2) |
| | Left | 7 (53.8) |
| Number of L.N. removed | Median (range) | 33 (1 - 96) |
| Number of positive L.N. removed | Median (range) | 6 (1 - 32) |
| Infiltration of nearby tissue | Yes | 2 (13.3) |
| | No | 13 (86.7) |

L.N.: Lymph Node

Table (5): Surgical data in second recurrence

| Factors | | N=6 (%) |
|---|---|---|
| Second recurrence (N=15) | Yes | 7 (46.7) |
| | No | 8 (53.3) |
| L.N. affection (N=7) | Yes | 3 (42.9) |
| | No | 4 (57.1) |
| Level of lymph node affection | Central | 2 (66.7) |
| | Central and lateral | 1 (33.3) |
| Site of L.N. affection | Right | 1 (33.3) |
| | Left | 2 (66.7) |
| Number of L.N. removed | Median (range) | 17 (4 - 19) |
| Number of +ve L.N. | Median (range) | 3 (1 -9) |
| L.N. Capsular invasion | Yes | 2 (66.7) |
| | No | 1 (33.3) |
| Site of 2nd recurrence | Operative bed | 3 (50.0) |
| | Lymph nodes | 1 (16.7) |
| | Operative and lymph nodes | 2 (33.3) |

L.N.: Lymph Node

Table (6): Patients without nodal capsular invasion

| *Factors* | | *N=25 (%)* |
|---|---|---|
| Subsequent recurrence | Yes | 8 (32.0) |
| | No | 17 (68.0) |
| Site of second recurrence (N=7) | Lymph nodes | 5 (71.4) |
| | Operative bed and lymph nodes | 2 (28.6) |

Table (7): Recurrence free survival in relation to demographic factors in patients with first recurrence:

| Factors | No. of case s | No. of events | Cumulative Survival % at 1 year | Cumulative Survival % at 2 years | Cumulative Survival % at 3 | Median survival time (months | P value |
|---|---|---|---|---|---|---|---|
| Whole group | 40 | 15 | 93.9 | 69.3 | 63 | NR | |
| Age at first | | | | | | | |
| ≤ 45 | 21 | 4 | 100 | 94.4 | 88.9 | NR | < 0.001 |
| > 45 | 19 | 11 | 86.7 | 37.5 | 30.0 | 22.0 | |
| Sex | | | | | | | |
| Male | 11 | 5 | 90.0 | 70.0 | 46.7 | 31.0 | 0.505 |
| Female | 29 | 10 | 95.7 | 69.9 | 69.9 | NR | |

NR= Not Reached

Table (8): Recurrence free survival in relation to clinical and surgical factors of patients

| Factors | No. of cases | No. of event s | Cumulative Survival % at 1 year | Cumulative Survival % at 2 years | Cumulative Survival % at 3 | Median survival time (months | P value |
|---|---|---|---|---|---|---|---|
| Patient on thyroxine | | | | | | | |
| Yes | 16 | 9 | 92.3 | 46.2 | 38.5 | 23.0 | 0.02 |
| No | 24 | 6 | 95.0 | 79.7 | 79.7 | NR | |
| Type of previous thyroidectomy | | | | | | | |
| Partial | 6 | 3 | 83.3 | 66.7 | - | 25.9 | 0.68 |
| Total | 34 | 12 | 96.3 | 69.8 | 66.0 | NR | |
| Capsular invasion (thyroid tumor) in 1ry surgery | | | | | | | |
| Yes | 17 | 5 | 93.3 | 79.4 | 72.2 | NR | 0.24 |
| No | 23 | 10 | 94.9 | 61.1 | 65.6 | 43.0 | |
| Infiltration of nearby tissue in 1ry | | | | | | | |
| Yes | 8 | 2 | 100.0 | 80.0 | 80.0 | NR | 0.65 |
| No | 32 | 13 | 92.9 | 67.5 | 60.0 | NR | |

NR= Not Reached

Table (9): Recurrence free survival in relation to surgical factors in first recurrence

| Factors | No. of cases n=40 | No. of events | Survival % at 1 year | Survival % at 2 year | Survival % at 3 year | Median Survival time (month | P Value |
|---|---|---|---|---|---|---|---|
| Site of first recurrence | | | | | | | |
| Nodal | 20 | 8 | 93.8 | 68.8 | 56.3 | 43 | 0.588 |
| Nodal & extranodal | 15 | 5 | 92.9 | 70.7 | 70.7 | NR | |
| L.N. Capsular invasion in 1st recurrence | | | | | | | |
| Yes | 15 | 7 | 100.0 | 66.6 | 51.9 | 43.06 | 0.306 |
| No | 25 | 8 | 90.0 | 75.0 | 70.0 | NR | |
| Level of L.N. affection (N=32) | | | | | | | |
| Central & Lateral | 16 | 2 | 100.0 | 91.7 | 91.7 | 22.0 | 0.006 |
| Lateral | 16 | 9 | 85.7 | 49.0 | 40.8 | | |

Table (10): Cox regression model to detect predictors of subsequent recurrence

| Factors | Hazard ratio | 95% Confidence interval | P value |
|---|---|---|---|
| Age | 10.37 | 1.955-20.017 | 0.001 |
| L.N. capsular invasion in 1st recurrence | 3.74 | 1.14-12.89 | 0.030 |

We found a statistically significant difference between patients with central compartment affection only, and those with central and lateral neck compartment affection ($p<0.006$) with incidence of recurrence was higher in those with both compartment affection, which may be attributed to higher tumor burden, larger number of L.N. affection, or higher incidence of tumor lymphovascular invasion.

DTC is the most common but least aggressive histological subtype of thyroid cancer. Most patients with DTC have excellent prognosis. However, recent studies have demonstrated increasing incidence of recurrent DTC [22,23].

Many factors can affect thyroid cancer recurrence, but final conclusions have not been reached. The results of some studies show that the age, staging, degree of extra thyroid invasion, lymph node metastatic rate, pathological type, and initial surgery approach are related to thyroid cancer recurrence [24, 25].

Studies investigating the effect of age as a risk factor for recurrence in patients with well differentiated thyroid cancer showed that age less than 20 and more than 70 years have a poor prognosis independent of stage of disease [27,28]. Sharifi A et all. showed that incidence of regional L.N. recurrence was higher in patients with age equal or higher than 45years [29]

In our study age was found to be a statistically significant factor regarding regional nodal recurrence ($p<0.001$) in patients with age 45 years or older with higher incidence of shorter time for recurrences, multiple neck nodes level affection, and more poor prognosis.

Tumor staging and extrathyroid extension were found also significant factors affecting regional recurrence. Larger tumor size at presentation is believed to be Assossiation with higher risk for recurrence [30, 31]. Some studies showed that tumor greater than 0.5 cm is strongly associated with regional L.N. recurrence. Other studies showed thyroid tumors larger than 4 cm is more likely to show regional L.N. recurrence.

In our study tumor size larger than 2 cm was found to be associated with higher incidence of regional L.N. recurrence. From the 35 patients with nodal recurrence 25 (71.4%) patients had tumor larger than 2 cm in their

first presentation, with 9 of them was associated with L.N, capsular invasion in their first recurrence.

Wu et al. Showed that extra nodal extension of tumor has negative effect on disease free and cause specific survival, with progression to high thyroglobulin, nodal persistence, systemic disease, and more poor prognosis. [32]

Our research showed that L.N. capsular invasion is statistically significant factor for subsequent recurrences after first recurrence in patients with well differentiated thyroid cancer (P-value < 0.05)

Multiple recurrences were found in 80% of patients with L.N. capsular invasion, while 20% of them showed single recurrence only. Also 70% of patient without L.N. capsular invasion showed single recurrence only, while the other 30% showed more than one

In the 35 patients with associated L.N. affection in their first recurrence, 15 patients (42.8%) showed L.N. capsular invasion, while the other 20 patients didn't show that (57.2%). Mean age of patients with L.N. capsular invasion in first recurrence was 45.1 years

Of the 15 patients 6 were males and 9 were females, 8 patients suffered 1 recurrence, 6 suffered two recurrences, and one patient suffered 3 recurrences (during first year). Six patients were regular on thyroxine therapy, while nine patients were not. On further follow up, twelve patients from those with capsular invasion in first recurrence showed subsequent early recurrence within two years. (75%). Seven patients of them (58.3%) showed recurrence in less than 12 months, and 5 patients showed recurrence in less than 2 years (41.6%).

In the fifteen patients with L.N. capsular invasion, eleven patients underwent total thyroidectomy, and four hemithyroidectomy. Only four of them showed infiltration of nearby structures, nine of them with thyroid tumors more than 2 cm, and eleven of them with papillary classic pathology.

In the 15 patients with L.N, capsular invasion in first recurrence, 9 of them lateral neck was affected (60%), and 6 patients with central and lateral neck affection (40%), with median number of removed nodes 33, and median number of positive nodes 6.

In the seven patients who suffered second recurrence in less than one year, nodal recurrence was found in 3 patients (42.9%), and 4 patients with extranodal recurrence (57.1%). Two of the patients with nodal recurrence suffered central group affection (66.7%), and one both central and lateral (33%), with median number of removed nodes 17, and median number of positive nodes [3]. L.N. capsular invasion was found in two of the three patients with nodal affection in second recurrence.

In the other five patients with recurrence after one year and less than two years, all of them suffered nodal recurrence with one suffered both nodal and extranodal recurrence.

From the 15 patients with L.N. capsular invasion in first recurrence, 8 patients showed extrathyroidal tumor extension in the thyroid gland when first removed (53.3%), while the other 7 patients showed no extrathyroidal tumor extension (46.7%).

Finally we found that non regular uptake of thyroxine treatment was associated with higher incidence of regional recurrence (statistically significant $p<0.02$). This may be due to insufficient suppression of TSH levels, which stimulate any unreserved thyroid tissue, or any metastatic cells in the circulation which retain some endocrine activity to uptake iodine in the circulation, with higher stimulation of thyroid tissue regeneration, and higher incidence of recurrence

As TSH promote the growth of thyroid tissue, the levels of this hormone are suppressed in the initial period following surgery in patients with well differentiated thyroid cancer, with effectiveness of this approach in improving long term clinical outcome following surgery compared with those without suppression therapy [33], although it became clear that stringent suppression of TSH does not improve long term clinical outcomes in patients with other than high risk presentations of well differentiated thyroid cancer.[34], so patients with lower risk of disease recurrence do not require complete suppression of TSH, and adequate treatment should optimize the balance between suppression to prevent disease recurrence, and the potential for adverse effects on bone and heart [35]

Adequate assessment of patient with well differentiated thyroid cancer is of great important, and defining risk factors is part of their management. Precise assessment of factor relating to LN. affection may predict patients who require more aggressive treatment modalities, and may modifiey more accurate methods for follow up and early diagnose of recurrence. Also close follow up of patients compliance to treatment is important to achieve expected results of adequate management, and improve disease free survival of those patients.

## Conclusion:

Patients with multiple recurrences of WDTC follow a poor clinical course, with multiple treatment failures and decreased survival. Among this subgroup of patients with multiple recurrences, males, those aged 40 years or more with aggressive primary tumors (ETS) and advanced stage disease (Stage III/IV) and L.N. extracapsular tumor extension have a significantly higher risk of multiple recurrences.

In addition, time to first recurrence within 12 months of initial therapy conveys a worse prognosis. One potential explanation is that these patients have a more biologically aggressive variant of WDTC which does not readily respond to treatment of the primary tumor or the initial recurrence.

Although the failure to cure these cases after several attempts may cause frustration in both the treating physician and the patient, close follow-up and aggressive treatment of further recurrences is still warranted, as approximately 30% of these will go on to be free of disease after subsequent therapies.

Further research is needed into the biological and molecular markers of tumor severity in order to provide an understanding of why some patients with WDTC have an excellent prognosis with complete cure, while

others are plagued by multiple treatment failures and eventual death.

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