

Factors Predictive of papillary thyroid cancer (PTC) recurrence post total thyroidectomy & radioiodine ablation : a single-center experience in the Jordanian Royal Medical Services

*Abdullah Al Zreiqat**, *Hamzeh Aladwan**, *Ola Attieh**, *Eslam Jabali**, *Anas Zboun**, *Rania Al-asa'd***, *Mahmoud AlZoubi**, *Omar Shokaibi****, *Mais Halaseh**, *Khaled Alkhawaldeh**

ABSTRACT

Aim: to assess the factors predictive of PTC recurrence after total thyroidectomy and radioiodine ablation using a retrospective analysis of patients treated for thyroid cancer by the Jordanian Royal Medical Services (JRMS).

Methods: 243 patients (56 men and 186 women) were included in the study (at King Hussein Medical Center) between January 2009-December 2017 with a mean age of 40 years. All patients had papillary thyroid cancer. Fifty-eight percent (58%) underwent a one-stage total thyroidectomy, and 42% underwent a two-stage thyroidectomy and all patients received I131 Radio-Iodine ablation. Univariate regression analyses were used to study factors that may influence the risk of recurrent disease.

Results: There was no statistically significant difference for sex, initial thyroid surgical management, vascular invasion, positive surgical margin, or the dose of I131 Radio-Iodine ablation dose. Tumour recurrence was found in 27% of patients younger than 40 years old at the time of diagnosis, which was found to be significant ($P=0.009$). It was noted that disease recurrence was more frequent in patients with T2-T4 tumour stages [13% (12 out of 92 patients) with T2, 41% (32 out of 78 patients) with T3, and 80% (12 out of 15 patients) with T4 tumours]; this was statistically significant ($P=0.0001$). The last characteristic that showed a significant risk for recurrence was lymphatic invasion, which was noted in 51% (46 out of 90 patients with disease recurrence) ($P=0.008$).

Conclusion: Our cohort study results show that patients <40 years old, with large tumour size (T), and lymphatic invasion have a significantly higher recurrence rate. Gender, presence of vascular invasion, positive tumour margins, and radio-iodine ablation may have an impact on the chance of recurrence but were not statistically significant

Keywords: Differentiated Thyroid Cancer (DTC), papillary Thyroid Cancer (PTC), recurrence, Microscopic positive margins, tumor size, and lymphatic invasion.

RMS December 2021; 28(3): 10.12816/0059547

Introduction

Thyroid cancer is the most common malignant endocrine cancer, with a rising global incidence (1). Papillary thyroid cancer (PTC) is the most common type of well-differentiated thyroid carcinoma (WDTC), constituting around 70% of all follicular-cell derived thyroid malignancies (2).

From the departments of:

*Nuclear Medicine Division/Radiology Department/KHMC.

**Endocrine Division/Internal Medicine Department/KHMC.

***Department of laboratory medicine and pathology/ Princess Iman center.

Correspondence should be addressed to: Dr. Abdullah Al Zreiqat

, email:

The majority of PTC have a good prognosis with a five-year survival rate of 97% (3), and excellent overall survival rates depending on many factors such as age, tumour size, local invasion, and metastasis (4). The prognosis of PTC is usually good; however, a small number of patients have mortality related to the disease and morbidity due to recurrence (2).

PTC is a slowly progressing tumour, with excellent survival. Its incidence has been increasing, mainly due to the increased use of thyroid imaging (5). The primary management is surgical, followed in almost all patients by radio-iodine ablation (6). Higher recurrence rates of PTC are associated with many factors: age greater than 45 years, male gender, aggressive histopathological type, large tumour size, multifocality, capsular invasion, affected lymph nodes $\geq 30\%$, presence of thyroid-stimulating immunoglobulin, p53 mutation, and BRAF mutation (2, 7-9).

Our study aimed to assess the factors predictive of PTC recurrence after total thyroidectomy and radioiodine ablation using a retrospective analysis of patients treated for thyroid cancer by the Jordanian Royal Medical Services (JRMS).

PATIENTS AND METHODS

Patients

We start by retrospectively reviewing a total of 493 well-differentiated thyroid cancer (WDTC) patients that had been treated between 1995 and 2017. We excluded 250 patients with non-papillary thyroid cancer, distant metastases at the time of diagnosis, gross residual tumour, or incomplete thyroidectomy. Eventually, our study included a total of 243 patients. Patients were included if they had papillary thyroid cancer (regardless of histologic variants), with or without lymph node metastases, were diagnosed between 2009 and 2017 and had a least 36 months of follow-up.

We studied several factors: age at diagnosis, gender, histopathology reports, T stage of the tumour, type of surgery, radioactive iodine dose, and the last follow-up date. Twenty-three percent (23%) of the studied patients were males and seventy-seven were females, with a mean age of 40 years. Fifty-six percent (56%) of patients were below the age of 40 years old. Fifty-eight percent (58%) underwent a single-stage total thyroidectomy, and 42% underwent a two-stage thyroidectomy. All patients had papillary thyroid cancer.

The follow-up serum thyroglobulin levels were not available for a considerable number of patients in our sampled population and hence constituted a limitation to our study as we were unable to assess this factor.

The Jordan Royal Medical Services Research Ethics Board approved this study.

Recurrence definition

Recurrence was defined as any newly detected tumour or metastatic lesion in patients who had been previously free of disease following initial treatment.

Disease recurrence is not labelled as such in our system. Hence, we classified recurrence based on having undergone a second radio-iodine ablation (therapeutic radio-iodine dose), patients with positive biopsy results (Ultrasound-guided biopsies), or patients who underwent a positive whole-body radio-iodine scan. Combined with serum thyroglobulin measurements both stimulated and non-stimulated alongside antithyroglobulin antibodies measurements.

Statistical analysis

Categorical data are expressed as frequency and percentage, and continuous data are expressed as mean \pm SD. Univariate regression analysis was performed by the Cox proportional hazards model using SPSS version 25 (IBM Corporation, Armonk, NY, USA). A P value of <0.05 was used to indicate statistical significance.

RESULTS

The studied characteristics of the studied patients are illustrated in (**Table I**). Twenty-four percent (24%) had a T1 tumour, 36% had a T2 tumour, 32% had a T3 tumour, and 8% had a T4 tumour. Positive tumour margins were noted in 30% of patients. Lymphatic invasion was noted in 37% of patients and vascular invasion in 37% of patients. All patients received I¹³¹ radio-iodine ablation; 34% (83 patients) received less than 100 mCi, 61% (148 patients) received an iodine dose ranging from 101-150 mCi, and 5% (11 patients) received more than 150 mCi as the I¹³¹ radio-iodine ablation dose. Gender, initial thyroid surgical management, vascular invasion, positive surgical margin, or the dose of I¹³¹ radio-iodine ablation dose had no statistically significant effect.

Tumour recurrence was noted in 56 patients (18 of which had local recurrence, 28 had a regional nodal recurrence and 10 with distant metastases) and all of them received a 2nd radioiodine ablation dose ranging from 150-200 mCi according to their recurrence stage.

Tumour recurrence was found in 37 out of 135 (27%) patients younger than 40 years old at the time of diagnosis, which was found to be significant ($P=0.009$) (**Table II**). Based on the tumour size (T) categories illustrated in (**Table I**), which are in accordance with the AJCC Cancer Staging Manual (8th Edition) (10), it was noted that disease recurrence was more frequent in patients with T2-T4 tumour stages [13% (12 out of 92 patients) with T2, 41% (32 out of 78 patients) with T3, and 80% (12 out of 15 patients) with T4 tumours]; this was statistically significant ($P=0.0001$) (**Table II**). The last characteristic that showed a significant risk for recurrence was lymphatic invasion, which was noted in 51% (46 out of 90 patients with disease recurrence) ($P=0.008$) (**Table II**).

Table I: Clinical characteristics

Clinical characteristics	All patients n =243
Male	56 (23%)
Female	186 (77%)
Age at diagnosis (years, mean)	40
Categorical age group	
<40 years old	135 (56%)
>41 years old	108 (44%)
Initial thyroid surgical management	
Total thyroidectomy	142 (58%)
Two-part total thyroidectomy	101 (42%)
Histology	
Staging	
T1	58 (23%)
T2	91 (37%)
T3	77 (32%)
T4	14 (8%)
Lymphatic invasion	90 (37%)

Vascular invasion	91 (37%)
Positive margins	73 (30%)
I ¹³¹ radio-iodine ablation dose	
<100 mCi	83 (34%)
101-150 mCi	148 (61%)
>150 mCi	11 (5%)

Table II: Univariate analysis of factors affecting disease recurrence

Risk factor	Hazard ratio (95% CI)	P value
Gender (men)	1.442 (0.769-2.706)	0.254
Age at diagnosis (<40 years)	0.461 (0.258-0.826)	0.009
T staging	3.231 (2.161-4.831)	0.0001
Vascular invasion	1.009 (0.259-3.931)	0.989
Lymphatic invasion	6.725 (1.646-27.467)	0.008
Positive margins	1.098 (0.596-2.022)	0.764
I ¹³¹ Radio-Iodine ablation dose	1.007 (0.999-1.015)	0.080

DISCUSSION

Thyroid cancer is the most common malignant tumour of the endocrine system (11); 233 cases were diagnosed in Jordan in 2014 and is ranked the sixth among cancers in both genders and the third among female cancers, according to the records of the Jordan Cancer Registry for the year 2014 (12). Papillary tumours are highly treatable and usually curable. Many factors such as age, gender, T stage, distant metastases, extrathyroidal extension, and surgery are known to have a significant impact on prognosis and outcomes (13, 14).

Our long follow-up interval provided an adequate perspective to study the prognostic value of different patient-specific and tumour-specific factors in patients with papillary thyroid cancer. Papillary thyroid carcinoma is associated with good outcomes in most patients (11). The recurrence rates have been reported to be 20-30% (4, 15). Our recurrence rate was 23%, which is within the range of prior studies.

Many risk factors of metastasis and recurrence are described by the NCCN and AJCC/IUCC thyroid carcinoma practice guidelines (16). Gender and age are deemed as independent risk factors in WDTC, with a worse curve in males. In our study, 20.8% of females versus 30.3% of males had a tumour recurrence, although this showed no statistically significant difference from those who did not. In our patients, in contrast to a previous publication (17), we found that tumour recurrence was found in 27% of patients in the age group younger than 40 years old at the time of diagnosis, which was statistically significant (P 0.009).

Postoperative I¹³¹ therapy is an integral part of the WDTC treatment algorithm to achieve the ablation of the residual tumour and residual functioning thyroid tissue. Thus, accurate follow-up with whole-body

iodine scanning and serum thyroglobulin (sTg) levels is imperative. Radioiodine therapy in patients with WDTC has been shown to reduce the recurrence rate, irrespective of whether or not they had residual disease (18, 19). All our patients received radioiodine ablation, and no statistically significant difference was noted with regards to different radioiodine doses.

Tumour size (T) categories were also investigated, and we noted that disease recurrence took place more frequently in patients with T2-T4 tumour stages, i.e. 13% T2, 41% T3, and 80% T4 tumours, which was statistically significant ($P=0.0001$). This is compatible with most previously published meta-analyses (20).

The last factor that showed a significant risk for recurrence was lymphatic invasion, which was noted in 51% of cases ($P=0.008$) and which appears to be compatible with many other publications in this regard (21).

CONCLUSION

Our cohort study results show that patients <40 years old, with large tumour size (T), and lymphatic invasion have a significantly higher recurrence rate. Gender, presence of vascular invasion, positive tumour margins, and radio-iodine ablation may have an impact on the chance of recurrence but were not statistically significant.

Conflict of interest

The authors declare that no conflicts of interest could be perceived as biasing the objectivity of the reported research.

REFERENCES

- 1.Cabanillas ME, McFadden DG, Durante C.** Thyroid cancer. *Lancet.* 2016;388(10061):2783-95.
- 2.Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al.** 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid.* 2016;26(1):1-133.
- 3.Jemal A, Siegel R, Xu J, Ward E.** **Cancer statistics, 2010.** *CA Cancer J Clin.* 2010;60(5):277-300.
- 4.Mazzaferrri EL, Jhiang SM.** Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med.* 1994;97(5):418-28.
- 5.Li N, Du XL, Reitzel LR, Xu L, Sturgis EM.** Impact of enhanced detection on the increase in thyroid cancer incidence in the United States: review of incidence trends by socioeconomic status within the surveillance, epidemiology, and end results registry, 1980-2008. *Thyroid.* 2013;23(1):103-10.
- 6.Rivera-Robledo CG, Velazquez-Fernandez D, Pantoja JP, Sierra M, Perez-Enriquez B, Rivera-Moscoso R, et al.** Recurrent Papillary Thyroid Carcinoma to the Cervical Lymph Nodes: Outcomes of Compartment-Oriented Lymph Node Resection. *World J Surg.* 2019;43(11):2842-9.
- 7.Kim SJ, Park SY, Lee YJ, Lee EK, Kim SK, Kim TH, et al.** Risk factors for recurrence after therapeutic lateral neck dissection for primary papillary thyroid cancer. *Ann Surg Oncol.* 2014;21(6):1884-90.

- 8.Jauculan MC, Buenaluz-Sedurante M, Jimeno CA.** Risk Factors Associated with Disease Recurrence among Patients with Low-Risk Papillary Thyroid Cancer Treated at the University of the Philippines-Philippine General Hospital. *Endocrinol Metab (Seoul)*. 2016;31(1):113-9.
- 9.Qu H, Sun GR, Liu Y, He QS.** Clinical risk factors for central lymph node metastasis in papillary thyroid carcinoma: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)*. 2015;83(1):124-32.
- 10.Sneed DC.** Protocol for the examination of specimens from patients with malignant tumors of the thyroid gland, exclusive of lymphomas: a basis for checklists. Cancer Committee, College of American Pathologists. *Arch Pathol Lab Med*. 1999;123(1):45-9.
- 11.Statistics SC.** SEER Cancer Statistics Review (CSR) 1975-2016. 2019.
- 12.health JMo.** Jordan Cancer Registry Cancer Incidence in Jordan - 2014. 2014.
- 13.Sautter-Bihl ML, Raub J, Hetzel-Sesterheim M, Heinze HG.** Differentiated thyroid cancer: prognostic factors and influence of treatment on the outcome in 441 patients. *Strahlenther Onkol*. 2001;177(3):125-31.
- 14.Leung AM, Dave S, Lee SL, Champion FX, Garber JR, Pearce EN.** Factors determining the persistence or recurrence of well-differentiated thyroid cancer treated by thyroidectomy and/or radioiodine in the Boston, Massachusetts area: A retrospective chart review. *Thyroid Res*. 2011;4(1):9.
- 15.Coburn M, Teates D, Wanebo HJ.** Recurrent thyroid cancer. Role of surgery versus radioactive iodine (I131). *Ann Surg*. 1994;219(6):587-93; discussion 93-5.
- 16.Guidelines N.** NCCN clinical practice guidelines in oncology (NCCN Guidelines) Thyroid Carcinoma. 2020;version 2.2020.
- 17.Trimboli P, Piccardo A, Signore A, Valabrega S, Barnabei A, Santolamazza G, et al.** Patient Age Is an Independent Risk Factor of Relapse of Differentiated Thyroid Carcinoma and Improves the Performance of the American Thyroid Association Stratification System. *Thyroid*. 2020;30(5):713-9.
- 18.DeGroot LJ, Kaplan EL, McCormick M, Straus FH.** Natural history, treatment, and course of papillary thyroid carcinoma. *J Clin Endocrinol Metab*. 1990;71(2):414-24.
- 19.Mazzaferrri EL.** Treating differentiated thyroid carcinoma: where do we draw the line? *Mayo Clin Proc*. 1991;66(1):105-11.
- 20.Zhang TT, Li CF, Wen SS, Huang DZ, Sun GH, Zhu YX, et al.** Effects of tumor size on prognosis in differentiated thyroid carcinoma smaller than 2 cm. *Oncol Lett*. 2019;17(5):4229-36.
- 21.Sezer A, Celik M, Yilmaz Bulbul B, Can N, Tastekin E, Ayturk S, et al.** Relationship between lymphovascular invasion and clinicopathological features of papillary thyroid carcinoma. *Bosn J Basic Med Sci*. 2017;17(2):144-51.