Primary versus Tertiary Care Follow-Up of Low-Risk Differentiated Thyroid Cancer: Real-World Comparison of Outcomes and Costs for Patients and Health Care Systems

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Keywords

Thyroid cancer · Follow-up · Primary care · Tertiary care · Outcomes · Cost

Abstract

Background: An unprecedented rise in the prevalence of low-risk well-differentiated thyroid cancer (TC) has been reported in several countries, which is partly due to an increased utility of sensitive imaging techniques. The outcome of these cancers has generally remained excellent and the overall 5-year survival is almost 100%. However, the extended follow-up strategy for these patients remains unclear and while the initial management is done in specialist centres some experts opt to follow them on a long-term basis while others discharge them to primary care after the initial management. The effectiveness of one strategy versus the other has not been studied. **Methods:** We conducted a real-world comparison to assess the outcome of low-risk TC (AJCC stage I) with undetectable thyroglobulin (TG) 2 years after radioiodine (I-131) therapy. The outcome from Halifax (NS, Canada) and London (ON, Canada), where all TC patients are rou-

tinely followed by the tertiary care team, was compared with that from Edmonton (AB, Canada), where patients are routinely discharged to primary care. **Results:** All patients were diagnosed between January 1, 2006, and December 31, 2011. The mean follow-up in primary care after discharge was 62.2 months and in tertiary care it was 64.6 months ($p = 0.43$). Rates of recurrence were similar in both groups, i.e., 1.1% in primary care and 1.3% in tertiary care ($p = 0.69$). Ultrasound surveillance was conducted in 56.5% of the patients in primary care and 52.6% of the tertiary care group ($p = 0.26$). The rate of annual unstimulated TG testing per patient was 0.58 (range 0–14) in primary care and 0.96 (range 0–6) in tertiary care ($p = 0.06$). More patients in primary care (86%) than in tertiary care (29.9%) consistently had thyroid-stimulating hormone levels within the target range ($p < 0.001$). The mean healthcare cost, based on a single follow-up visit with a blood test and ultrasound in the primary care group was CAD 118.01 and in the tertiary care group it was CAD 164.12. **Conclusion:** Our study shows that extended follow-up of low-risk TC patients is perfectly feasible in primary care and provides significant economic benefit for the healthcare system.

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Introduction

Well-differentiated thyroid cancer (TC) is the most common thyroid malignancy, comprising over 90% of all TC [1]. Furthermore, data from various countries including Canada [2], the USA [3–5], and European countries [6–8] show a rapidly rising incidence of TC. This may partly be due to radiation exposure [9, 10] and a family history of TC [3], but there is also evidence suggesting that the more widespread utility of sensitive imaging techniques has led to increased detection of small, sub-clinical tumours which contribute to the rising incidence of TC [11]. Regardless, the outlook of TC is generally excellent, with an overall 5-year survival of 97.9%, and that of low-risk TC (stage I and II) is almost 100% [12]. Although long-term follow-up of TC is recommended [13], it is becoming increasingly unfeasible to provide such follow-up for all TC patients in a multidisciplinary tertiary care setting. Thus, the optimal approach to long-term follow-up remains to be determined. It has been suggested that low-risk TC patients who are free of disease at 5 years may be followed by primary care physicians and nurse-led clinics [14]; however, the effectiveness of such a practice remains unclear. The objective of the present study was to compare outcomes and costs for low-risk TC patients followed by multidisciplinary clinics in tertiary clinics versus those discharged at 24 months for follow-up in the primary care setting using real-world data.

Methods

This was a multi-centre, retrospective study comparing the outcomes of TC in 3 tertiary care centres: Halifax (NS, Canada), Edmonton (AB, Canada), and London (ON, Canada). These centres readily participated because they maintained a comprehensive computerized TC registry. The Halifax and London centres routinely follow all TC patients in their tertiary center. In Edmonton, all TC patients with a primary tumour <2 cm, AJCC stage I, with an undetectable stimulated thyroglobulin (TG) 24 months after radioiodine therapy (I-131) are discharged to their respective primary care physicians. Specific guidelines to follow patients are provided and include a neck ultrasound (US) scan every 12–24 months, unstimulated TG annually, and the recommendation to maintain serum thyroid-stimulating hormone (TSH) levels in a range of 0.3–2.0 mU/L. Family physicians are directed to refer the patients back to the tertiary care clinic if there is evidence of recurrence on US or if TG becomes detectable.

For the purpose of this study, we identified all patients seen at these 3 centres who met the following criteria: (1) initial diagnosis between January 1, 2006, and December 31, 2011, (2) primary tumour (or largest tumour in the case of multifocal TC) <2 cm, (3) AJCC stage I, (4) undetectable stimulated TG 2 years after I-131 ablation treatment, and (5) Nx, N0, and N1a lymph node status

only. Patients were excluded if they had not received I-131 ablation treatment or had an aggressive tumour pathology including evidence of tall cells, columnar cells, and/or a diffuse sclerosing variety. The timelines were chosen to obtain at least 2 years of follow-up after discharge to primary care follow-up.

Follow-up data on patients seen in primary care was obtained through the provincial healthcare database which contains all biochemical and radiological test results, as well as, by contacting the primary healthcare providers and patients. The recommended TSH in the tertiary care group was also 0.3–2.0 mU/L. The frequency of follow-up visits was variable across the centres due to their local practices and ranged between 12–18 months. Approximately 300 patients were seen in Edmonton during the study period, of whom 93 (around 30%) met the inclusion criteria, whereas in the combined tertiary care group (London and Halifax) around 900 patients were followed during the same period, of whom 224 (around 25%) met the inclusion criteria.

We collected the following variables for each patient: age at diagnosis, gender, residential postal code, date of diagnosis, tumour type (papillary vs. follicular), primary tumour size, TNM stage, date of the final surgery, type of surgery (partial vs. total thyroidectomy), lymph node dissection, lymph node dissection type (central, lateral, or both central and lateral), number of lymph nodes removed, number of lymph nodes positive for metastatic disease, dose of I-131, follow-up TSH, follow-up US, follow-up TG (stimulated or unstimulated), recurrence, date of recurrence (if occurred), location of recurrence (local or distant), mode of diagnosis of recurrence (US, TG, or both), and death and cause of death (if known). A calculation of the impact on healthcare and patient costs was conducted on the basis of certain assumptions. The costs were calculated based on the assumption that patient monitoring occurred according to the local practice guidance, US costs were calculated based on US studies that were actually performed. All cost components were based on Ontario information even though in reality they may vary by province. Healthcare costs were estimated using Ontario Health Insurance Plan (OHIP) schedule of benefits and fees J 105 and are based on 2017 costs. All costs have been adjusted based on OHIP reductions (fee reductions imposed by the provincial government), and therefore only the actual estimated cost incurred is represented (may vary by province). Physician fees and investigations were assessed by year. Physician fees were based on re-assessment (rather than consult) fees and the assumption of 1 visit per year, even though in practice some primary care centers may see patients up to 3 times per year. US fees consisted of technical and professional components. TC follow-up instructions provided by the Edmonton site to family physicians recommend US every 2 years rather than once yearly, which typically occurs in the tertiary care centers; therefore based on the yearly evaluation we divided the US costs into 2 for primary care centers. Biochemistry is assumed to be performed once per year, including all TC markers, TSH, free T4, free T3, TG, and anti-TG. The cost of the rhTSH 2-dose regimen kit was CAD 1,990 in Ontario in 2017.

The patient cost estimation was based on the time and distance travelled using postal codes of participants and their tertiary care center. The London Health Sciences Centre was used for Ontario patients, the QEII Health Sciences Centre was used for Halifax patients, and the Cross Cancer Institute was used for Edmonton patients. Travel costs and times were calculated based on the distance travelled to and from the tertiary center; the distance to the pri-

Table 1. Baseline characteristics

Variable	Tertiary care (n = 224)	Primary care (n = 93)	p value
Females	195 (87)	77 (83)	0.32
Mean age at diagnosis, years	47.7±13.1	46.0±12.6	0.87
Mean follow-up, months	64.6±20.6	62.2±26.2	0.43
Papillary thyroid cancer	216 (96.4)	87 (93.5)	0.06
T stage ^a			
T1	222 (99.1)	85 (91.4)	0.001
T2	2 (0.9)	8 (8.6)	
N stage ^a			
N0	97 (43.3)	46 (49.4)	<0.001
N1	39 (17.4)	0	
Nx	88 (39.3)	47 (50.6)	
Mean tumour size, cm	1.26±0.53	1.35±0.80	0.08
Primary tumour size			
<1 cm	88 (39.2)	41 (44.1)	<0.01
1–2 cm	136 (60.8)	52 (55.9)	
Central lymph node dissection	137 (61)	46 (49)	0.05
Mean I-131 dose, GBq	3.88±0.83	1.85±0.13	<0.01

Values are presented as numbers (%) or means ± SD. ^a Fisher's exact test p value are presented.

mary center was not calculated but it can be estimated to be 5 km 1 way (10 km 2 ways) based on Ng et al. [15]. Patients residing out of province were excluded from the travel analysis. The cost of distance was estimated at CAD 0.40/km based on the current practice in the London hospitals (2017). This study was approved by the respective research ethics boards.

Statistical Analysis

This study represents a real-world clinical experience comparing 3 tertiary care centres. Descriptive statistics were reported to present the study variables. Means and SD were reported for normally distributed continuous variables, and medians and ranges were reported for nonnormally distributed continuous variables. Frequencies and proportions were reported for categorical variables. χ^2 tests were used to compare 2 categorical variables, and Fisher's exact tests were used when the cell frequency was less than 5. An independent Student *t* test was conducted to compare the means of 2 groups for normally distributed continuous variables. Mann-Whitney tests were used to compare 2 groups with non-normal continuous variables. $p < 0.05$ was considered statistically significant. SPSS version 15 (IBM company) was used to conduct all of the statistical analyses. Two-sided tests were used for all of the statistical comparisons.

Results

There were 317 patients in total, of whom 224 were followed in tertiary care centres (70 in Halifax and 154 in London), whereas 93 were being followed in the primary

care setting (Edmonton). The primary characteristics of these patients are summarized in Table 1. There was an overall female preponderance in both primary (77/93; 83%) and tertiary (195/224; 87%) groups ($p = 0.32$). The mean age of the patients in the primary and tertiary care groups was 46.0 (SD = 12.6) and 47.7 years (SD = 13.1), respectively ($p = 0.87$). Papillary TC constituted the most common pathological variety of TC in the primary (93.5%) and tertiary care (96.4%) groups, while the remaining cases were follicular TC ($p = 0.06$). The mean follow-up for the primary care group was 62.2 months (SD = 26.2) and for the tertiary group it was 64.6 months (SD = 20.6) ($p = 0.07$).

Tumour Characteristics at Presentation

These are summarized in Table 1. With respect to the TNM staging at presentation, most patients presented with T1 cancers in both primary (91.4%) and tertiary care (99.1%) ($p = 0.01$); however, there were differences in the N stage at presentation such that 49.4% presented as N0 and 50.6% presented as Nx in the primary care group, whereas in the tertiary care group 43.3% presented as N0, 17.4% presented as N1, and 39.3% presented as Nx ($p = 0.001$). The mean tumour size at presentation in the primary care group was 1.35 cm (SD = 0.80) and in the tertiary care group it was 1.26 cm (SD = 0.53; $p = 0.08$). In terms of the tumour size at presentation, 41 out of 93

Table 2. Outcomes of tertiary versus primary care groups

Variables	Tertiary care (n = 194)	Primary care (n = 93)	p value
Recurrence rate ^a	3 (1.5)	1 (1.1)	0.4
Patients undergoing routine US	118 (52.6)	56 (60.2)	0.22
TSH target			
Patients within the target TSH	58 (29.9)	80 (86.0)	<0.001
Patients below the target TSH	113 (85.2)	9 (9.7)	
Patients above the target TSH	23 (11.8)	4 (4.3)	

Values are presented as numbers (%). ^a Fisher's exact test p value are presented.

(44.1%) patients had a primary tumour of <1 cm and 52 out of 93 (55.9%) patients had a primary tumour of 1–2 cm in the primary care group, whereas in the tertiary care group 88 out of 224 (39.2%) patients had a primary tumour of <1 cm and 136 out of 224 (60.8%) patients had a primary tumor of were 1–2 cm.

Initial Management Strategies

All patients had undergone total thyroidectomy at presentation. However, 61% of the tertiary care cohort had undergone lymph node dissection as compared to 49% in the primary care group ($p = 0.043$). Following surgical excision, all of the patients received I-131 therapy, with a mean dose of 1.84 GBq (SD = 0.13) in the primary care group and 3.88 GBq (SD = 0.83) in the tertiary care group ($p < 0.001$). The mean serum unstimulated TG after final surgery, but before I-131 therapy, was available in 17 (18.3%) cases in primary care and 148 (66%) cases in tertiary care group; they were 0.89 (SD = 1.30) and 0.92 (SD = 0.93), respectively ($p = 0.93$).

Follow-Up Strategies and Outcomes

The mean follow-up of patients in the primary care group was 62.2 months (SD = 26.2) and that in the tertiary care group was 64.6 months (SD = 20.6) ($p = 0.43$). Key outcome data are summarized in Table 2. The risk of recurrence was very low in both groups at 1.1% in the primary care group and 1.5% in the tertiary care group ($p = 0.69$). All recurrences occurred locally in the neck; 3 were identified initially through neck US and rising TG in the tertiary care group, while 1 recurrence in the primary care group was initially identified through rising TG and the patient was referred back to tertiary care where local recurrence was confirmed by neck imaging. There were a total of 3 deaths, all in the tertiary care cohort. None of these deaths were deemed to be related to TC. During follow-up, 52.6% of the patients in the tertiary care group

underwent routine US surveillance, whereas 56.5% of those in the primary care group underwent surveillance US ($p = 0.26$).

Patients in the tertiary care group had a mean of 5.25 visits to the specialist clinic during the entire follow-up. During routine follow-up in tertiary care the mean number of annual unstimulated TG tests per patient was 0.96 (range 0–6) and in the primary care group it was 0.58 (range 0–14; $p = 0.06$). On the other hand, stimulated TG was done in 38 (17%) of the patients in the tertiary care group and 5 (5.4%) of those in the primary care group ($p < 0.01$).

When looking at maintenance of serum TSH values within the recommended target range of 0.3–2.0 mIU/L, in the primary care group 80 out of 93 (86.0%) cases were consistently within the recommended range, whereas the rest had one of more readings outside of the range; of these, 9 (9.67%) had TSH values below and 4 (4.30%) had TSH values above the target. Consistent TSH values at each visit were available in 194 patients in the tertiary care group, of which 58 (29.89%) were consistently within the target TSH range, 123 (58.24%) had 1 or more TSH values below the target range, and 23 (11.85%) had 1 or more values above the target range ($p < 0.001$).

Economic Impact of Primary versus Tertiary Care Follow-Up

The economic impact of the 2 strategies on patients and the healthcare system is summarized in Table 3. The mean travel time and distance travelled for the primary care group were 8 min and 10 km, respectively, whereas, for the tertiary care group they were 154 min and 215 km. The mean cost of travel to the appointment for the primary care group was CAD 4.00, whereas that for the tertiary care group was CAD 86.00. The mean healthcare cost per year, based on a single follow-up visit with a blood test and US in the primary care group was CAD 118.01 and in the tertiary care group it was CAD 164.12.

Table 3. Cost analysis and patient impact

	Tertiary care	Primary care
A Healthcare costs		
Physician visit	89.85	38.35
US		
Technical component	47.30	47.30
Professional component	23.70	23.7
Patients undergoing US annually, %	52.6	56.5
Cost of US per patient per year	42.74	37.35
Laboratory		
TSH	5.20	5.20
Free T4	3.20	3.20
Free T3	5.82	5.82
TG	11.00	11.00
Anti-TG antibody	11.70	11.70
Healthcare cost per patient per year	164.12	118.01
Stimulated TG		
rhTSH	38/224 (17.0%)	5/93 (5.4%)
Stimulated TG cost per patient ^a	822.39	44.93
B Patient impact^b		
Travel time, min	140 (6–826)	8
Distance travelled, km	191.5 (2.2–1,358)	10
Cost of travel (CAD 0.40/km)	76.6 (0.88–543.2)	4

Costs are in CAD. Patient impact values are medians (range). ^a The cost of stimulated TG over the entire follow-up period is based upon costs for rhTSH, TG, and anti-TG and averaged over all patients in the group. ^b For primary care, the patient impact is based upon assumptions rather than actual calculations (see Methods).

Both tertiary care centres routinely used recombinant TSH for the stimulated TG test, which cost CAD 1,990 for a single kit containing the 2-dose regimen. A recombinant TSH stimulated TG test was done in 17% of the patients in tertiary care and 5.4% of the patients in primary care ($p < 0.01$). The cost of stimulated TG tests averaged over all of the patients in each group and calculated over the entire follow-up period was CAD 822.39 per patient in the tertiary care group and CAD 44.93 in the primary care group.

Discussion

Our study shows that low-risk TC patients followed in the primary care setting have similar outcomes to those in the tertiary care setting. To our knowledge, this is the first study that has specifically assessed the outcomes of patients followed in primary versus tertiary care settings. The unprecedented rise in the prevalence of TC is largely attributed to an increased detection of small TC, which has led to tripling of the TC incidence in the USA from 3.6 cases/100,000 individuals in 1973 to 11.6 per 100,000

persons in 2009 [16]. This diagnosis now accounts for almost 90% of cases in newly diagnosed TC in some countries [4]. These small TC have an excellent prognosis and the 5-year survival rate is almost 100% [12]. In fact, a recent observational study from Japan suggested that patients with small TC who underwent careful US surveillance without surgery or additional therapy did well and did not progress to developing symptoms or dying of TC [17]. Despite that, a lifelong follow-up of these patients is recommended [13] due to some risk of late recurrence that can often be salvaged successfully. However, the optimal follow-up strategy for these patients is not well defined. Follow-up care patterns vary and, while certain agencies recommend discharging disease-free patients to primary care physicians after 5 years [14, 18], the effectiveness of such a strategy in this patient group has remained unstudied. Previously, a randomized clinical trial comparing primary versus tertiary care follow-up of women with breast cancer in remission showed no delay in the diagnosis of recurrence or health-related quality of life [19]. Similarly, randomised trials have suggested that follow-up of prostate cancer patients in the primary care setting is also an effective alternative to hospital-based

follow-up [20]. Based on these data, it would seem feasible to consider alternative care pathways for patients with low-risk TC.

Our study is the first to compare the outcomes of primary versus tertiary care patients with TC. Our data suggest that primary care follow-up of low-risk TC is feasible. We compared rates of recurrence and cancer-related mortality between 2 groups and found no differences in these outcomes. The rate of recurrence, as expected, was low in both populations and there was no excess mortality in either group. It is noteworthy that TG testing in both cohorts was calculated on an annual basis but not all patients underwent annual TG testing because some patients were followed in tertiary care once every 18 months and also some patients in the primary care cohort did not undergo TG testing strictly every 12 months.

There were differences in management within the 3 centres as more patients followed in the tertiary care centres underwent lymph node dissection at the initial surgery compared to the primary care cohort (61 vs. 49%) and they received a larger dose of I-131 (3.88 vs. 1.84 GBq). However, significant diversity in therapeutic approach has previously been reported [21] and facilitates the real-world application of the study results. Despite these variations, no significant differences in the outcomes of these patients was identified during the follow-up period.

In addition, the utility of US during follow-up was relatively low and around 40% patients in both groups did not undergo routine US surveillance during follow-up. However, it was largely due to the existing practice paradigm in our centres during that time which was based on earlier studies showing an increased risk of non-specific and false-positive findings on routine US [22] and recommendations against routine US in low-risk DTC [23, 24]. Another study previously reported similar trends in US surveillance for patients followed jointly in tertiary and primary care settings and it reported that almost 40% of patients never underwent routine US follow-up [25].

With respect to health care costs and patient impact, our findings indicate increased healthcare costs for tertiary care follow-up as compared to primary care follow-up. In addition, the tertiary care centers used stimulated TG more frequently, resulting in significantly higher health care costs for patients followed in tertiary care versus primary care. However, the availability of the second-generation TG assay [26] will likely result in a significantly lower utility of recombinant TSH, thus driving down this aspect of the healthcare cost. Regardless, our analysis shows that the costs of follow-up remain higher in tertiary care.

The cost impact on patients is quite substantial and follow-up in tertiary costs is associated with significantly increased travel time and travel costs. We realize that our approach has limitations in that we did not assess to what extent clinic visits, lab testing, and imaging studies were combined, which could further affect the travel time and distance. We also did not assess whether an increased travel time was associated with income loss due to taking time off work. Furthermore, there might be other costs associated with clinic visits (such as parking, meals, etc.), particularly for tertiary follow-up. Finally, except for US frequency, we calculated the costs related to following local guidelines, rather than the actual visits and investigations. Despite these limitations, it is clear that tertiary care follow-up is associated with increased costs for both health care systems and patients.

Patients in the primary care setting were more likely to be within the recommended TSH target range (~76%) as compared to those followed in the tertiary care setting (~41%). These data suggest that primary care physicians are more likely to maintain the TSH within the target range. These numbers are again in agreement with a previous study [21] showing that patients followed jointly by primary and tertiary care achieved the recommended TSH values in 68.1% of cases.

The management of DTC is rapidly evolving, with recent studies supporting a less aggressive initial management but a more intensive follow-up. These studies have suggested that “active surveillance” of select low-risk DTC [17, 27] instead of an aggressive initial treatment such as surgery and/or I-131 therapy does not change the outcome in the short to medium term. However, the long-term safety of this approach remains unclear and, furthermore, who will monitor these patients for many decades also needs to be carefully considered. It is conceivable that, with the ongoing refinement of the molecular TC markers, better prediction models of the disease prognosis may develop. Future studies will need to address these crucial questions. Our data suggest that at least those patients with low-risk DTC who have been aggressively managed and are disease free can be considered for discharge to primary care. In our centres, we have started discharging these patients to primary care and at the time of discharge we provide both patients and primary care physicians with clear written guidelines to monitor serum TSH every 3–6 months at the physicians’ discretion, with a target TSH between 0.3 and 2.0 mU/L, measure serum TG and palpate the neck on an annual basis, and conduct a neck US every 24 months and re-referral if TG becomes detectable or if there is evidence of recurrence on imaging.

In summary, our study suggests that primary care follow-up may be feasible for low-risk TC patients who have been previously treated with I-131, in the presence of clear guidelines for follow-up and re-referral in cases of recurrence. However, additional and preferably prospective studies are needed to further confirm these findings.

Disclosure Statement

No competing financial interests exist.

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