Geospatial Analyses of Thyroid Cancer Incidence in Kelantan, Malaysia

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Abstract
Geographical Information System (GIS) has been widely used in evaluating health data. GIS-based disease mapping can act as a tool for an effective form of communication in public health and planning disease surveillance strategies. Yet, there is limited data on spatial distribution of cancer in Malaysia. In the present study, GIS was employed to map the thyroid cancer incidences, analyse the spatial distribution of the cases and assess their geographical accessibility to public hospitals. Registries of patients diagnosed with thyroid carcinoma from the year of 2013 to 2020 were retrieved and information regarding the year of diagnosis, age, gender, residential addresses and histological subtypes were obtained. The coordinates of residential addresses and public hospitals were obtained using Global Positioning System (GPS) and the radius of public hospitals were set within and beyond 10 km. Then, all data were inserted into ArcGIS 10.2 software and spatial analysis was performed. A total of 90 cases with thyroid carcinomas were recorded and mapped. The spatial distribution of thyroid cancer cases in Kelantan represented a clustered pattern (NNR: 0.549377, p-value <0.001) with most cases concentrated at northern part of Kelantan. Buffer analysis revealed that most of the cases (60%, 54 cases) were located within 10 km radius from public hospitals and the remaining 36 cases (40%) were situated beyond 10 km radius from public hospitals. In conclusion, thyroid cancer cases in Hospital USM were clustered with most cases concentrated at the northern part of the state. Majority of the cases have a good geographical access to public hospitals. These study findings provide useful information for health practitioners in planning public health intervention by targeting locations with poor geographical access to health facilities in order to improve overall health population in Kelantan.

1. Introduction

Thyroid cancer is one of the most common endocrine malignancies (Horner et al., 2009), representing 2% of all cancers with approximately 2 fold of incidence rate in the past 25 years (Goodarzi et al., 2018). It is one of the rapid growing types among all cancers worldwide (Jung et al., 2012). Asia continent recorded the highest incidence with 349,897 (59.7%) cases out of 586,202 new cases and highest mortality rates with 25,668 (58.8%) cases out of 43,646 cases recorded worldwide (Globocan, 2020). A rapid surge in the incidence rate of thyroid cancer has been reported in the past several decades in many countries (Kilfoy et al., 2009, Enewold et al., 2009, Liu et al., 2001 and Reynolds et al., 2005). Northern European countries, Australia and Japan experienced a relatively low incidence and a little increase (La Vecchia et al., 2015 and Franceschi and Vaccarella, 2015) whereas steep upward trends of thyroid cancer were observed in southern European countries (Busco et al., 2013 and Colonna et al., 2015), the United States (Davies and Welch., 2006, 2014 and Chen et al., 2009) and most markedly in the Republic of Korea (Ahn et al., 2014). In China, a strong increase in the incidence was also reported by previous studies (Du et al., 2014, Xie et al., 2012; Xie et al., 2014). This rapid increase has caused widespread public concern about thyroid cancer. In Malaysia, thyroid cancer ranked eighth most frequent cancer among female in Malaysia with age standardized rate of 3.2 per 100,000 population between 2012-2016 (Azizah et al., 2019). In Kelantan state, thyroid cancer is the fourth common cancer and recorded much higher age-standardized rate (5.1%) than the national average (Othman et al., 2008). A recent study highlighted that thyroid cancer incidence in Kelantan is at an alarming rate, with annual cases increment of approximately 2.7% over 10-year period from 2006 to 2015.

Incorporating spatial information in cancer data can examine the occurrence of cancer incidence in relation to the geographic variation and environmental parameters (Wang et al., 2008 and Levine et al., 2009). These spatial components can track new cases as well as demonstrate the geographic distribution, location and pattern of cases (Moore and Carpenter, 1999 and Rushton et al., 2006). However, the data kept by National Cancer Registries are in the tabular form which only provides the statistical data of the cases. The spatial data can be integrated into the existing tabular data by using Global positioning system (GPS) to include the geographical location based on the addresses of patients (Wang et al., 2008) which will be mapped using Geographical Information System (GIS) software.

Emergence of GIS as a great tool in geospatial technology is becoming more prominent in healthcare implementation (Musa et al., 2013). Spatial data analysis using Geographic Information System (GIS) is increasingly being used to determine the cluster of cases, identify disease pattern and evaluate the environmental and socioeconomic factors on the geographical distribution of disease (Hanley et al., 2015). It is also used to analyse the accessibility to public health facilities (Kuupiel et al., 2019). GIS-based disease mapping act as a tool for an effective form of communication in public health and planning disease surveillance strategies (Samat et al., 2013). Many studies have applied GIS technology and spatial data analysis in assessing health data (Levine et al., 2009 and Rushton et al., 2006). In western countries, data retrieved from the cancer registry can be utilized to relate the cancer incidences with geographical and demographic factors (Higgs et al., 2005 and More and Carpenter, 1999).

Currently, the diagnosis and management of thyroid cancer in Malaysia is good, owing to a number of guidelines that have been recently proposed. However, the thyroid cancer incidences in Malaysia are increasing in trend and patients still present with advanced stage of disease. Within the period of 2007-2011 and 2012-2016, there is an increment of 650 thyroid cancer cases recorded and male patients are more commonly observed with stage III and IV of the disease with 58.3% in 2012-2016 (Azizah et al., 2019). This is due to the risk factors of thyroid cancers that may vary accross different populations and geographical area. Since thyroid cancer has also been linked to environmental factors, the use of spatial techniques in determining the relationship will give a new pespective into this issue. The commonly used spatial techniques for health research include disease mapping, distance calculations, spatial aggregation, clustering, spatial smoothing, and spatial regression (Tsai, 2012 and Scott et al., 2002). However, there is limited data on spatial distribution of cancer in Malaysia. Hence, in this study, we aim to investigate the spatial distribution of thyroid cancer cases in Kelantan state and to determine whether there are associations with the geographical accessibility to public hospitals. This will contribute to better planning of health care services and programs to the community in order to improve the overall health population.

2. Material and Method

2.1 Study Design and Study Population

This is a retrospective study, covered all thyroid cancer patients between the periods of 2013 to 2020 in Hospital Univeriti Sains Malaysia (USM). Hospital USM is a referral centre for thyroid cancer management. Patients with confirmed histopathologic diagnosis of thyroid carcinoma were included. Information regarding the year of diagnosis, age, gender, and residential addresses were extracted from the patients registries in medical record office. These registries were carefully examined to ensure no duplicate entry. The histological subtypes of cancers were obtained from histopathological report in Pathology Department. A total of 90 cases with complete data were included in this study.

2.2 Study Location

This study involved 15 districts, including 9 districts from Kelantan and 6 districts from Terengganu, near the Kelantan's border. The districts involved in Kelantan are Kota Bharu, Bachok, Pasir Mas, Pasir Puteh, Machang, Tumpat, Tanah Merah, Kuala Krai and Gua Musang. Whereas, the districts from Terengganu are Besut, Kuala Terengganu, Kemaman, Setiu, Kuala Nerus and Marang. A total of 9 public hospitals involved in this study, which are Hospital Gua Musang, Hospital Kuala Krai, Hospital Tengku Anis, Hospital Machang, Hospital Tanah Merah, Hospital Pasir Mas, Hospital Universiti Sains Malaysia, Hospital Raja Perempuan Zainab II and Hospital Tumpat. The addresses of these public hospitals in Kelantan were obtained from Kelantan Health Department. All data obtained were recorded in Microsoft Excel format.

2.3 Spatial Analysis

The analysis of spatial data was performed using ArcGIS 10.2 software. Prior to analysis, the geographic coordinates of residential addresses and public hospitals in Kelantan were obtained using Global Positioning System (GPS). The Spatial global pattern analysis by average nearest neighbour ratio was carried out to determine the spatial distribution of thyroid cancer cases. The Average Nearest Neighbor tool measures the distance between each feature centroid and its nearest neighbor's centroid location. It then averages all these nearest neighbor distances. If the average distance is less than the average for a hypothetical random distribution, the distribution of the features being analyzed is considered clustered. If the average distance is greater than a hypothetical random distribution, the features are considered dispersed. The average nearest neighbor ratio is calculated as the observed average distance divided by the expected average distance (with expected average distance being based on a hypothetical random distribution with the same number of features covering the same total area).

The Average Nearest Neighbor ratio is given as:

$$\mathrm{ANN} = \frac{D_O}{D_E} \qquad \text{Equation 1}$$

where D_O is the observed mean distance between each feature and its nearest neighbor:

$$D_O = \frac{\sum_{i=1}^{n} d_i}{n} \qquad \text{Equation 2}$$

and D_E is the expected mean distance for the features given in a random pattern:

$$D_E = \frac{0.5}{\sqrt{n/A}} \qquad \text{Equation 3}$$

In the above equations, d_i equals the distance between feature i and it's nearest neighboring feature, n corresponds to the total number of features, and A is the area of a minimum enclosing rectangle around all features, or it's a user-specified Area value.

The average nearest neighbor z-score for the statistic is calculated as:

$$z = \frac{D_O - D_E}{SE} \qquad \text{Equation 4}$$

where:

$$SE = \frac{0.26136}{\sqrt{n^2/A}} \qquad \text{Eqaution 5}$$

3. Results

3.1 Geographical Distribution of Thyroid Cancer Cases

Figure 1 showed the geographical location mapping of all thyroid cancer cases from 2013 to 2020 in Hospital USM (n=90). Thyroid cancer cases were distributed throughout the state with high concentration in the northern part of Kelantan.

3.2 Spatial Distribution of Thyroid Cancer Cases

Spatial analysis showed that cancer cases in Hospital USM represented a clustered pattern (NNR: 0.549377, Z-score: -8.18, p-value <0.001). (Figure 2).

3.3 Geographical Accessibility of Thyroid Cancer Cases to Public Hospitals

Figure 3 shows the mapping of geographical location for all thyroid cancer cases (n=90) from all public hospitals in Kelantan (n=9). Majority of cases were located within 10 km radius from public hospitals and have good access to these hospitals. Meanwhile, the remaining cases were located beyond 10 km radius and have poor access to the public hospitals (Figure 3). It was found that 54 cases (60%) were located within 10 km radius from public hospitals. Out of 54 cases, 31 cases were found to overlap between two hospitals and 1 case overlapped between three hospitals. The remaining 36 cases (40%) were situated beyond 10 km radius from public hospitals, as shown in Figure 4.

3.4 Types of Thyroid Carcinoma

Based on histopathological diagnosis, most of the cases were papillary (71%), followed by follicular (17%), anaplastic (10%) and poorly differentiated carcinoma (2%), as illustrated in Figure 5.

3.5 Thyroid Cancer Cases According to Districts

The number of cases were reported according to districts. A total of 9 districts from Kelantan state and 6 districts from Terengganu state were involved in this study, as shown in Table 1.

4. Discussion

The spatial analysis revealed that distribution of thyroid cancer cases were spatially clustered and most of the cases were concentrated at the northern part of Kelantan, where the state capital city, Kota Bharu was located. Similarly, previous local study also reported most of the cases were found in Kota Bharu district (Othman et al., 2018).

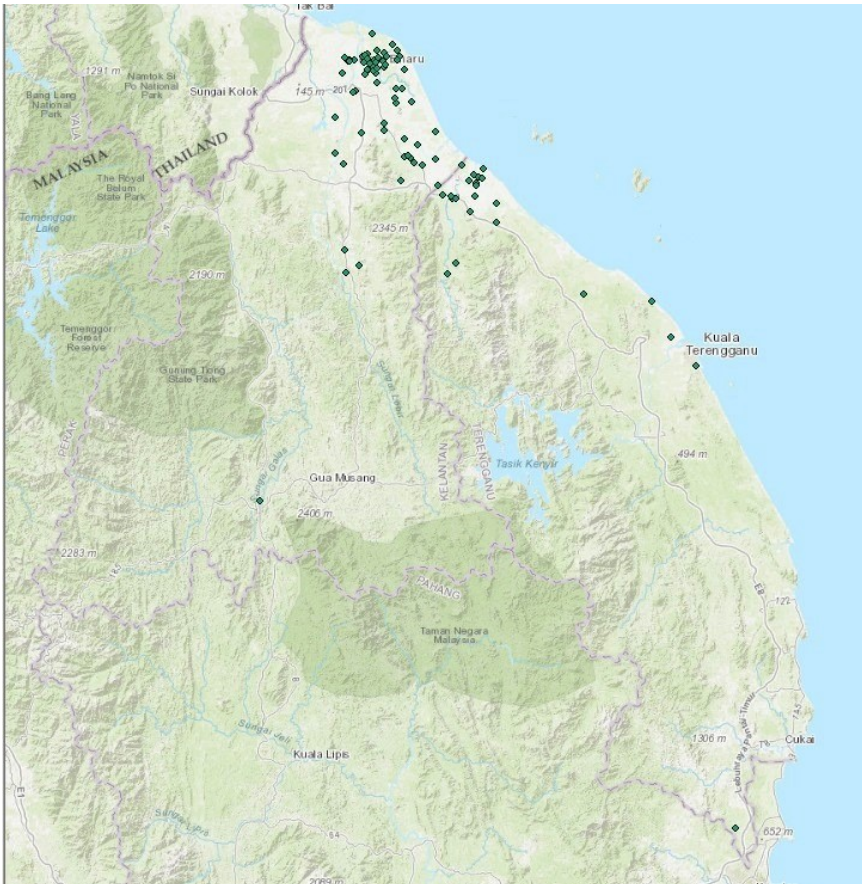

Figure 1: Geographical distribution of thyroid cancer cases

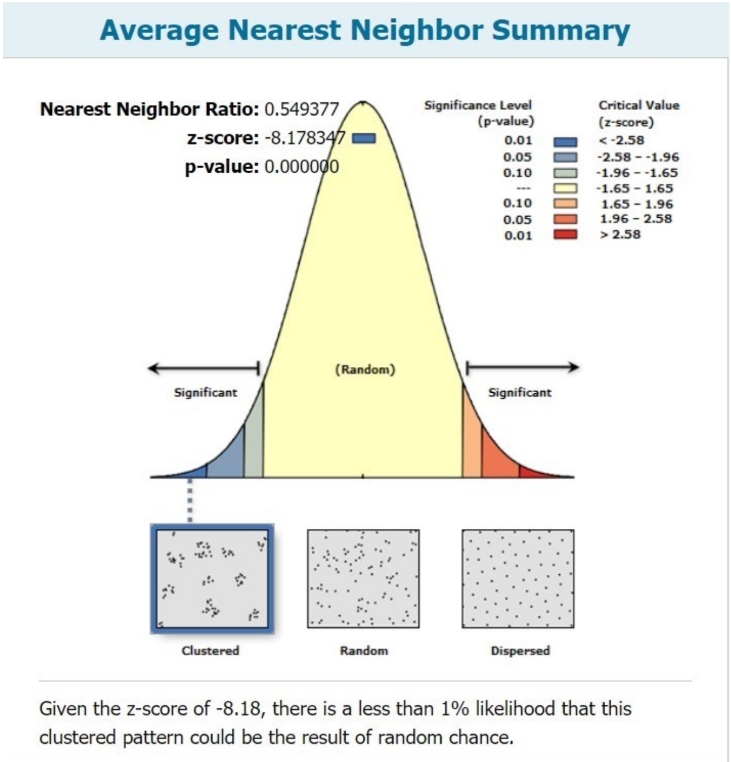

Figure 2: Spatial distribution of thyroid cancer incidences

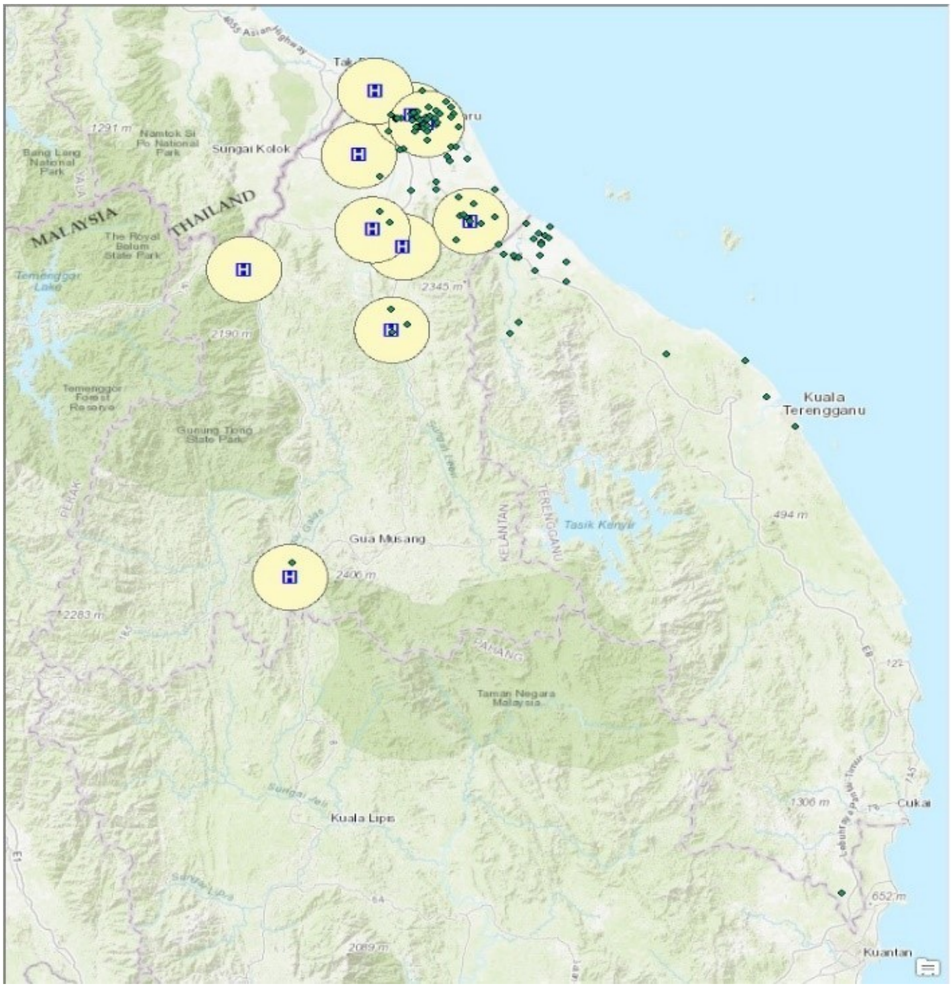

Figure 3: Geographical distribution of all thyroid cancer cases within and beyond 10 km radius from public hospitals

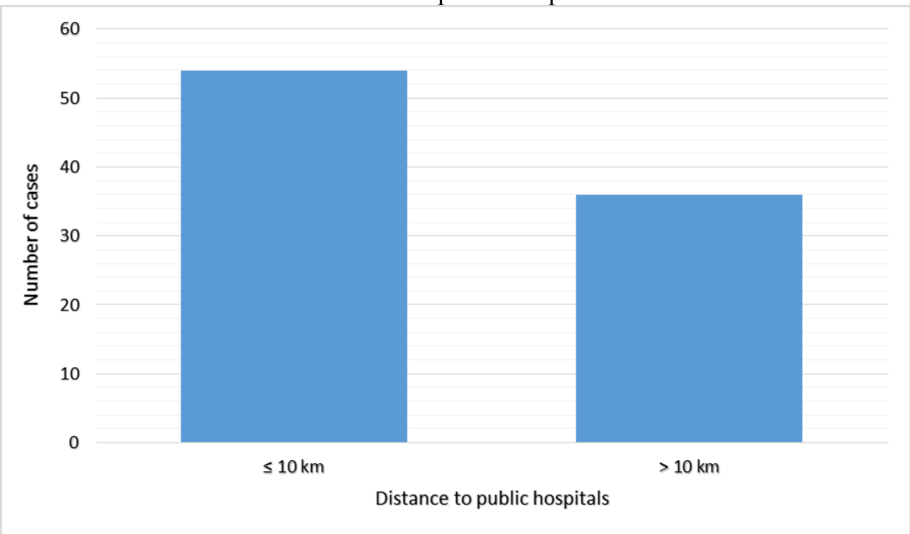

Figure 4: Number of thyroid cancer cases according to the distance with radius of ≤ 10 km and > 10 km to public hospitals

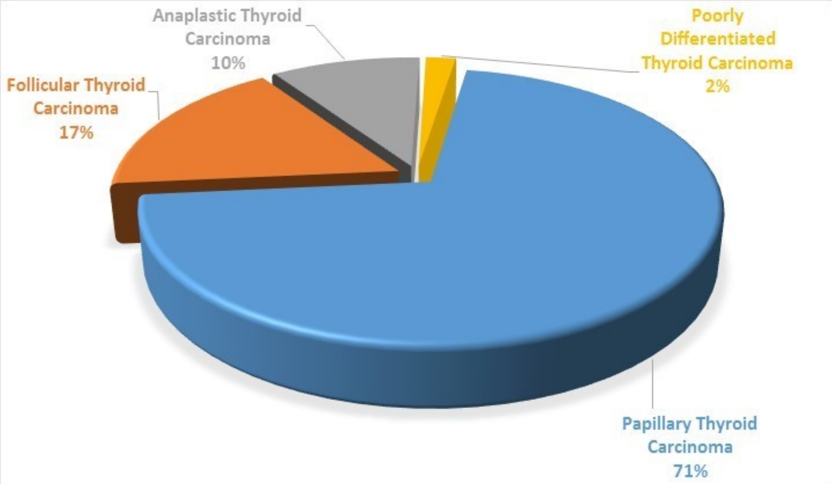

Figure 5: Percentage of thyroid cancer cases according to tumour types in Hospital USM from year 2013 to 2020

Table 1: Number of thyroid cancer cases according to all districts in Kelantan and few districts in Terengganu

Districts	Number of Cases
Kota Bharu	30
Bachok	12
Pasir Mas	2
Pasir Puteh	11
Machang	1
Tumpat	5
Tanah Merah	1
Kuala Krai	3
Gua Musang	1
Besut	19
Kuala Terengganu	1
Kemaman	1
Setiu	1
Kuala Nerus	1
Marang	1
Total	90

Furthermore, other cancer also found to be distributed at major town centres as reported by two local studies in Penang state (Samat et al., 2010, 2013). This probably due to the highest concentration of Malay population in this area, which made up the largest ethnic group in Kelantan. According to Malaysian National Cancer Registry, Malay ethnic are more likely to have thyroid cancers with an age-standardised incidence rates of 3.8 per 100,000 population (Azizah et al., 2019). Similarly, our data also suggested that Malay ethnic were more predominant in thyroid carcinoma cases observed. This is line with previous study which reported that the Malays (Abdullah, 2002) and the Ibans (Htwe et al., 2009) have a higher tendency to have thyroid cancer compared to other races.

Apart from that, risk factors associated with thyroid carcinomas might be one of explanatory factors. Known risk factors for thyroid cancer are radiation exposure (Cardis and Hatch, 2011), genetics (Soares et al., 2011 and Przybylik-Mazurek et al., 2011), obesity (Kitahara, 2011) and iodine deficiency (Liu et al., 2009, Dal Maso et al., 2009 and Franceschi, 1998). Previous study showed that Kelantan population have chronic iodine deficiency, with the overall urinary iodine excretion is lower than normal at 57 μ/day (Mafauzy et al., 1995) . In addition, it was found that those who live in districts near coastlines (Bachok, Kota Bharu, Pasir Puteh, and Tumpat) had higher frequency of thyroid cancers and are expected to be less-iodine deficient than those in districts located far inland (Othman et al., 2018). Since the districts near the coastlines were located at the northern part of Kelantan, we hypothesised that iodine deficiency is one of the risk factors which may explain the high concentration and clustering of cases observed. Papillary thyroid carcinomas were more frequent among other cancers associated with iodine deficiency (Othman et al., 2018). Our data suggested that papillary thyroid carcinoma is the most common histological subtype which accounted for 64 cases (71%) out of total cases. The similar pattern were also reported in other studies (Htwe et al., 2009 and Othman et al., 2018).

In addition, genetics might play a significant role. A previous study was done on goitrous patients in Kelantan, about 22.7% Chronic Multi-Nodular Goitre (MNG) or nodular hyperplasia expressed RET protein, the protein known to be involved in thyroid cancer (Omar and Othman, 2003). The cause of MNG is chronic iodine deficiency. RET gene mutation is associated with thyroid cancer (Nikiforov and Nikiforova, 2011). Possibly, this gene mutation occur more frequent among populations in the northern part of the state due to higher exposure of carcinogenic environmental factors. It is known that more factories were located in the northern region of the state. Furthermore, greater number of health facilities available (Samat et al., 2010) and population's ease of access to health facilities might play significant roles. In northern part of the state, there were 6 public hospitals in ratio to a total of 1492.4 populations as compared to southern part with only 4 public hospitals in ratio to 467.3 populations. This high hospital to population ratio in the northern region of the state indicated ease of access to health facilities, which might explain our finding. As reported by Dangisso et al, (2015), higher case notification rates were observed in locations where people have good access to treatment facilities (Dangisso et al., 2015). Apart from that, registration of cases possibly more complete in these areas as compared to other part of the state and faster or more refined diagnostic technique might also be one of the potential factors (Ahmadi et al., 2018). Being a referral centre, Hospital Universiti Sains Malaysia (HUSM) is located in the northern region of the state. All cases of thyroid cancers seen in other hospitals in Kelantan and adjacent states were referred to HUSM for futher management. Hence, the high number of cases registration in this hospital might contribute to high cases concentration and clustering pattern seen in the northern region of the state. However, we could not identify the high-risk areas as there were no statistically significant hotspot areas reported in this study.

In terms of accessibility of cases to public hospitals, the geographic accessibility was measured as: 0-10 km = good geographical access; and > 10 km = poor geographical access (Kuupiel et al., 2019). Majority of patients (60%) had good geographic access to the public hospitals as they were located within 10 km of radius from public hospitals. Among these patients, most of them resided in the northern part of Kelantan. Hence, we postulated that the greater availability of public hospitals in this region as compared to the southern part might be an explanatory factor. Since the good geographical access areas were located in the northern region, this give an indication that the distribution of public hospitals in this region are good. Patients who lived in these areas were more likely to utilize the health facilities as they were located nearby in comparison to those lived far away (Mizen et al., 2015). This will increase the chance of getting early diagnosis and treatment for the cancer.

Furthermore, it was noted that 40% of patients had poor geographic access to public hospitals. However, most of these patients resided in the neighbouring state, where they came to our hospital as referral cases for further management of the diseases. This finding implied that these patients had to travel far to seek for health care services. Travelling more than 10 km from resident area to health facilities was reported to cause delay in receiving treatment (Yimer et al., 2005) and associated with higher health risks or unfavourable outcomes (Becher et al., 2004). This might be due to longer travel time required to reach the nearest health facilities for treatment (Ursulica, 2016). Several studies demonstrated that time required to travel were related with delay in returning for treatment (Finnie et al., 2011 and Ross et al., 2015). In addition, a local study showed that patients who presented with late stage of cancer were also poor, not educated and from rural areas (Leong et al., 2007). Furthermore, other studies also showed that poor geographical access and socio-economic factors (SES) cause late stage detection of cancer diagnosis (Lyons, 2004 and Rushton et al., 2006). However, in this study, we do not correlate the sociodemographic factors and educational background of the populations with geographic accessibility. Hence, further study is recommended to be conducted to find the correlation between these factors.

5. Conclusion

From the findings, this study proved that the spatial distribution of thyroid cancer cases were clustered with most of the cases were concentrated at the northern part of Kelantan, where the state capital city, Kota Bharu was located. Presence of more risk factors such as iodine deficiency, genetic mutations and exposure to carcinogenic environmental factors in the northern region might be the cause. Considering the chronic iodine deficiency in

Kelantan populations, more iodized salt supplementation might be needed in the diet of population and more awareness programs regarding thyroid cancer risk and factors should be conducted in this region.

Furthermore, majority of the cases have good geographical access to the public hospitals where these cases are also located in the northern region of the state. These findings give an indication that the distribution of public hospitals in the northern part of Kelantan are good. Hence, giving the idea that more health care services should be provided as well as more efforts need to be directed in the locations of poor geographical access in order to minimize the thyroid cancer incidences in Kelantan. In near future, these efforts will help to improve the overall health population in Kelantan.

6. Limitation of Study

This study mapped the confirmed cases of thyroid carcinomas in Hospital USM and evaluate their spatial distribution. Hence, it could not properly explain the spatial distribution of the disease in Kelantan state as a whole.

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