Diffuse sclerosing variant of papillary thyroid carcinoma - an update of its clinicopathological features and molecular biology

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Short biography of the corresponding author

The corresponding author is an internationally recognized authority in diagnostic and molecular pathology of endocrine cancer with 25 years of activity this field. He has published more than 250 articles in peer reviewed journals and has written book chapters in the World Health Organization’s classification of tumours of the endocrine system. His publications have attracted high citations in the research field with the citation index (H-index) for his publications at 40 for 2014. He also serves on editorial boards for a few international peer reviewed journals.
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ABSTRACT

Diffuse sclerosing variant of papillary thyroid carcinoma (DSVPTC) is an uncommon variant of papillary thyroid carcinoma. The aim of this review is to critically analyse the features of this entity. A search of the literature revealed 25 clinicopathological studies with in-depth analysis of features of DSVPTC. Overall, the prevalence of DSVPTC varies from 0.7-6.6% of all papillary thyroid carcinoma. Higher prevalence of DSVPTC was noted in paediatric patients and in patients affected by irradiation. DSVPTC tends to occur more frequently in women and in patients in the third decade of life. Macroscopically, DSVPTC can involve the thyroid gland extensively without forming a dominant mass. Microscopic examination of DSVPTC revealed extensive fibrosis, squamous metaplasia and numerous psammoma bodies. The latter pathological feature can aid in the pre-operative diagnosis of the entity by fine needle aspiration and ultrasound. Compared to conventional papillary thyroid carcinoma, DSVPTC had a higher incidence of lymph node metastases at presentation. Distant metastases were noted in approximately 5% of the cases. Patients with DSVPTC were recommended to be managed by aggressive treatment protocols. It is likely that as a result of this, the prognosis of the patients with DSVPTC was noted to be similar to conventional papillary thyroid carcinoma. Overall, cancer recurrence and cancer related mortality have been reported in 14% and 3%, respectively, of patients with DSVPTC. In immunohistochemical studies, DSVPTC showed different expression patterns of epithelial membrane antigen, galectin 3, cell adhesion molecules, p53 and p63 when compared to conventional papillary thyroid carcinoma. On genetic analysis, the occurrence of BRAF and RAS mutations are uncommon events in DSVPTC and activation of RET/PTC rearrangements are common. To conclude, DSVPTC has different clinical, pathological and molecular profiles when compared to conventional papillary thyroid carcinoma.
1. Introduction

Papillary thyroid carcinoma accounts for approximately 75% of thyroid cancer [1]. The carcinoma comprises different histological variants of variable clinicopathological features and biological behaviour. Diffuse sclerosing variant of papillary thyroid carcinoma (DSVPTC) is an uncommon variant of papillary thyroid carcinoma, characterized by diffuse involvement of one or both lobes of the thyroid gland. This lesion often presents as a diffuse enlargement of the thyroid gland without specific mass [2]. It was first described as a case report by Vickery and colleagues in 1985 [3]. DSVPTC has different clinical and pathological presentation when compared with other thyroid cancers. As DSVPTC is not common, however, detailed study on its clinicopathological features and molecular characteristics have not been undertaken. In this review, we update the currently available data on the clinical, pathological and molecular features of this disease.

2. Methods

All the English language literature that reported features of DSVPTC from PubMed and Google Scholar databases from 1980 to 2013 were analysed. Following this, those series with demographic and clinical data were input into a unified database and analysed using the statistical software, SPSS (statistical package for social science) version 22 (IBM, New York, USA). Only series with three or more cases were included in this analysis. Also, cases that had been presented in more than one study were counted only once to avoid duplication.

Overall, 25 studies with a total of 641 patients with DSVPTC met the criteria for critical analysis of the clinical pathological data (Table 1) [4-32]. Amongst these, the largest series of
DSVPTC cases to date was reported in an epidemiological study by Kazaure and colleagues in which 261 cases over a period of 20 years were presented [29].

3. Epidemiology

The prevalence of DSVPTC varies from 0.7-6.6% of all papillary thyroid carcinomas [1, 23, 33, 34]. In regions affected by increased radiation exposure, the prevalence of this entity is different from other regions. For instance, a study on 119 patients diagnosed with papillary thyroid carcinoma in Belarus (the area affected by the Chernobyl accident) showed that the prevalence of DSVPTC in young patients was 13% [35]. The high prevalence of DSVPTC in this study population is attributed to the high levels of radioactive iodine released from the Chernobyl reactor in 1986. In another study, ten percent of the paediatric thyroid cancers that occurred following the Chernobyl nuclear accident in 1986 were DSVPTC [36]. Also, aside from the association with radiation, the prevalence of this entity is high in the paediatric population. Koo and colleagues in Korea reported that approximately half of papillary thyroid carcinoma diagnosed in patients less than 20 years old was DSVPTC [26].

DSVPTC tends to occur more frequently in women, similarly to conventional papillary thyroid carcinoma [18, 33]. In an early review of literature by Sywak and colleagues, DSVPTC was found to occur more often in patients in their third decade and the male to female ratio was approximately 1 to 5 [33]. These figures were collected after reviewing 65 cases of DSVPTC reported up until 2001. However, a recent epidemiological study on 261 DSVPTC cases from the USA showed the cancer could occur in older patients with a mean age of presentation at 47 years old [29]. Also, other larger series have shown the mean age of presentation for DSVPTC was 40 years old [19, 30]. Some cases of DSVPTC have also been reported in patients older than 60 years [18, 22, 23, 30, 37].
After pooling the data from the reported series in the literature, DSVPTC was most often seen in the third decade of life (Figure 1). The mean age at presentation of patients with DSVPTC was 30 and the median age at presentation was 28. The range of ages at presentation of patients with DSVPTC was from 6 to 78 years. Of the 641 patients, 81% were females (n=520) and 19% were males (n = 121). The female to male ratio was 4.3 to 1. There was no significant gender difference in age at presentation (p>0.05). It is worth noting that the mean age of occurrence of papillary thyroid carcinoma was in the fifth decade of life (mean age = 45 years) [1]. Thus, DSVPTC is more often seen in a younger age group than conventional papillary thyroid carcinoma. However, they can also be seen in patients with advanced age.

4. Clinical Features

DSVPTC patients mostly present with a mass lesion in the neck [24, 30]. However, unlike conventional papillary thyroid carcinoma, DSVPTC presents with diffuse involvement of one or both lobes of the thyroid gland without forming a dominant mass [2]. Associated symptoms were due to local compression of the neck organs such as dysphagia, hoarseness and dysphonia [17]. Sometimes, the tumours are discovered accidentally during a routine physical examination. In some instances, cases have been reported in association with hyperthyroidism and hypothyroidism [17].

5. Macroscopic Features

In DSVPTC, the thyroid gland is enlarged and appeared to be diffusely infiltrated without any encapsulation. The tumour appears lobulated, nodular and multifocal with a firm, pale to greyish white appearance [17]. It has been demonstrated that patients with DSVPTC tend to
have larger tumour size compared with conventional papillary thyroid carcinoma [18]. In concurrence with the histological features, the cut surface of the tumour shows a gritty appearance with specks of calcium impregnated throughout the tumour. In addition, the tumour is noted to be separated by bands of fibrosis [17].

6. Microscopic features

On microscopic examination, DSVPTC have characteristic nuclear features of papillary thyroid carcinoma. In addition, the carcinoma shows marked squamous metaplasia, numerous psammoma bodies, extensive interstitial fibrosis, and heavy lymphocytic infiltration with formation of germinal centres (Figure 2). Also, DSVPTCs show higher prevalence of extra-thyroidal extension and cervical lymph node metastasis [17.18]. In addition, vascular invasion by tumour cells may be seen [17]. Furthermore, presence of calcification/ossification in the stroma of thyroid carcinomas could be a feature of aggressive thyroid carcinomas [28]. Lam and Lo reported the presence of osseous metaplasia in a patient with DSVPTC, who eventually died of the disease [18].

Hashimoto thyroiditis and lymphocytic thyroiditis have often been associated with papillary thyroid carcinoma [39.40]. Lee and colleagues reported in a meta-analysis of 38 studies in the literature that histologically proven Hashimoto thyroiditis was identified in 23% of papillary thyroid carcinomas [39]. Hashimoto thyroiditis co-existing with papillary thyroid carcinoma was more often seen in females, multifocal disease, lack of extra-thyroidal extension, lack of lymph node metastases and long recurrence-free survival. Association of DSVPTC with Hashimoto’s thyroiditis has also been reported [24, 41]. Takagi and colleagues reported that 17 of 20 patients with DSVPTC, in which anti-thyroid antibodies were examined, had Hashimoto’
thyroiditis [24]. As Hashimoto thyroiditis and DSVPTC both present with goitre and with heavy infiltration of chronic inflammatory cells, the presence of co-existing Hashimoto’ thyroiditis could make the pre-operative pathological detection of DSVPTC difficult both by clinical examination or by fine needle aspiration.

7. Pre-operative diagnosis

Fine needle aspiration biopsy is the most popular way to diagnose papillary thyroid carcinoma before surgery [24]. The sensitivity of diagnosis of the DSVPTC by fine needle aspiration is usually higher than in the diagnosis of PTC in general [18, 24, 42, 43]. The presence of numerous psammoma bodies in the fine needle aspirate of thyroid lesions can be a clue to the diagnosis of papillary thyroid carcinoma. Also, the presence of numerous psammoma bodies when taken in combination with other clinical and pathological features could suggest a diagnosis of DSVPTC [18]. Takagi and colleagues listed out the cytological findings of DSVPTC as follows: (1) solid cell balls and/or hollow balls containing lymphocytes; (2) hobnail cells; (3) septate cytoplasmic vacuoles; (4) large unilocular vacuoles; (5) squamous differentiation; (6) abundant psammoma bodies; (7) lymphocytic background; and (8) the absence or relative lack of characteristic nuclear features of papillary carcinoma [24].

The sonographic findings of DSVPTC are characteristic, and are a useful tool in the diagnosis of the disease. In ultrasonography, hyper-echogenicity, diffuse scattered micro-calcification and cervical lymph node metastasis were the characteristic features in DSVPTC [28]. The calcification and extent of the disease can also be detected by specimen radiography [44, 45]. When DSVPTC is suspected by ultrasound examination, the aspiration cytology from a non-nodular area of the thyroid can lead to the diagnosis of DSVPTC [24].
8. Metastases

Compared to conventional papillary thyroid carcinomas, DSVPTCs had a higher incidence of lymph node metastasis [18]. Lam and Lo reported the prevalence of lymph node metastasis in DSVPTC as almost twice to that of conventional papillary thyroid carcinoma (80% vs 43%) [18]. A patient with DSVPTC presenting with 65 metastatic cervical lymph nodes has been reported [46]. After reviewing 65 cases of DSVPTC in the literature, Sywak and colleagues reported the occurrence of extra-thyroidal tumour spread in 40% and cervical lymph node metastasis in 68% of cases. Also, for a mean follow-up period of 8 years, 13% had local recurrence, 19% had distant metastasis and 2% had cancer related mortality [33].

On pooling the data from the literature, we found the prevalence of distant metastases to be 5% (33/641). Lung was noted as the commonest site of distant metastasis in many studies [18, 23, 25, 32]. Other sites of metastases included the bone, brain, liver and pericardium [18, 32, 47]. Distant metastases could also be reported in multiple sites. For example, Kuo and colleagues reported a DSVPTC with elevated carcinoembryonic antigen (CEA) and multiple metastatic sites including lung, brain, bone and liver [37].

9. Clinical management

The high propensity for lymph node involvement in DSVPTC suggests that adjuvant radioiodine therapy may be considered in all cases [34]. Initial radical surgery followed by radioiodine treatment and a long term follow-up are the common management strategies for DSVPTC. Before operation, radiological examination of the neck is helpful in detecting the involvement of any lymph node metastases in this disease entity. Also, a thorough search for suspicious lymph nodes should be performed at the initial operation. Modified radical lymph
node dissection could be performed if positive lymph nodes are found. In some instances, an en bloc resection of locally infiltrating structures combined with a modified neck dissection for regional lymphadenopathy is advised [34].

10. Prognosis

Although DSVPTC has pathologically aggressive features, many studies have shown that the prognosis of patients with DSVPTC was similar to conventional papillary thyroid carcinoma [14, 18, 23, 48]. On the other hand, a study by Regalbuto and colleagues in 35 patients with DSVPTC showed patients with DSVPTC have poorer prognosis compared to those with conventional papillary thyroid carcinoma [30]. Similar findings were also reported in some earlier studies [4, 6, 12]. It is likely that the adoption of more aggressive treatment protocol in the patients with DSVPTC when compared to those with conventional papillary thyroid carcinoma accounted for the variable prognostic outcomes. By analysing the pooled data from the literature, approximately 14% (n=89/641) of the patients with DSVPTC showed recurrence of cancer. Disease related mortality was noted in 3% (n=19/641) of the total DSVPTC cases.

11. Expression of common immunohistochemical markers

11.1 Common immunohistochemical markers

Like conventional papillary thyroid carcinoma, DSVPTC are positive for thyroglobulin and thyroid transcription factor-1 (TTF-1) [15, 49]. Cytokeratin 19 (CK19) is commonly strongly expressed in papillary thyroid carcinomas [50]. It is also positive in the squamous component in DSVPTC [15, 51]. Thus, CK19 could be a useful marker in identifying tumour
cells with squamoid differentiation in DSVPTC. These findings suggested that squamous metaplasia in DSVPTC arises from thyroid follicular epithelial cells [33]. In addition, Koo et al, showed higher protein expression of epithelial membrane antigen (EMA) in DSVPTC (40.8%) than in conventional PTC (20.0%) [25]. Furthermore, positive bcl-2 protein expression in DSVPTC has been reported to be associated with early cancer recurrence. The study by Koo et al also showed relatively lower prevalence of galectin-3 protein expression in DSVPTC (83.7%, 41 of 49) compared to conventional PTC (100%, 50 of 50) [25]. Both bcl-2 and EMA are associated with cancer aggressiveness. This finding concurs with the phenomenon that DSVPTC often presented in advanced pathological stages as well as with lymph node metastases. Although galactin-3 protein expression is lower than conventional PTC, its expression in DSVPTC was still very high. The result is also consistent with finding that galactin-3 is related to the biological aggressiveness of PTC. In addition, Kinoshita and colleagues have reported a DSVPTC case with positive staining for the oestrogen receptor and progesterone receptor [53].

11.2 Cell adhesion molecules

E-cadherin, neural cell adhesion molecule (N-CAM) and beta-catenin play a crucial role in cell to cell adhesion and maintaining epithelial morphology [53, 54, 55]. This cadherin/catenin complex also regulates cell motility and is believed to function as an invasion suppressor system [56]. The DSVPTC is a variant of papillary thyroid carcinoma that is locally invasive in which disruption of these cell to cell adhesion molecules might play a major role [56]. Accordingly, Rocha and colleagues analysed eight DSVPTC and showed pronounced reduction of E-cadherin protein expression in the cell membrane, which was accompanied by relocation of the protein staining to the cytoplasm [56]. In contrast to this, conventional papillary thyroid carcinoma
(n=18) showed heterogeneous loss of E-cadherin expression. In addition, they found 13% (n=1 of 8) of cases carried E-cadherin mutations, 60% (n=3 of 5) of cases showed methylation of the E-cadherin gene promoter and 38% (n=3 of 8) of cases had alterations in protein expression of beta-and/or gamma-catenin. Kinoshita and colleagues also showed reduction in the staining of E-cadherin protein in a case of DSVPTC [52]. These findings showed that the abnormalities of the E-cadherin/catenin complex appear to be more distinct in DSVPTC compared to conventional papillary thyroid carcinoma.

11.3 p53 and p63

Mutation of p53 is the most common mutation detected in human cancers [57, 58, 59]. In thyroid cancer, p53 expression was more often noted in undifferentiated carcinoma [38]. The papillary carcinoma component associated with undifferentiated carcinoma of thyroid was often reported to be negative for p53 protein over-expression.

Santoro and colleagues reported a lack of p53 mutation in DSVPTC cases detected via polymerase chain reaction [60]. Thompson and colleagues have reported p53 protein overexpression in the tumour cells of 80% of patients with DSVPTC [17]. Koo and colleagues reported p53 protein overexpression in 43% (21 of 49) of DSVPTC using tissue microarray [25]. This showed that the prevalence of p53 protein over-expression in DSVPTC was lower than that of conventional papillary thyroid carcinomas (76%, n=38 of 50). It is well known that p53 over-expression is not exactly equivalent to p53 mutation. Nevertheless, it is likely that p53 mutation in DSVPTC is also lower in prevalence than conventional papillary thyroid carcinoma.

p63 is a member of the p53 family of transcription factors. The p63 protein functions as a transcription factor, which means it attaches (binds) to certain regions of DNA and controls the
activity of particular genes. It interacts with other proteins to regulate the expression of many different genes at different times. Koo and colleagues reported higher expression of the p63 protein in 28.6% (14 of 49) of cases of DSVPTC, a very high value compared to conventional papillary thyroid carcinoma in which p63 protein expression was negative in all selected cases [25]. Higher rates of p63 protein expression, lower rates of p53 mutation and protein expression in DSVPTC indicates that there is a distinct molecular profile of tumour suppressor genes present in DSVPTC compared to conventional papillary thyroid carcinoma.

12. **RET/PTC rearrangement**

Rearrangement of the *RET* oncogene (also known as *RET/PTC* rearrangement) was the first common genetic alteration identified in papillary thyroid carcinomas [61]. *RET/PTC* rearrangement is more common in thyroid carcinomas in children and young adults and in papillary thyroid carcinomas associated with radiation exposure [62, 63]. Several forms of *RET/PTC* rearrangement have been identified so far, based on the involvement of the 5’ partner gene in the rearrangement [64]. Among the different forms, *RET/PTC1* and *RET/PTC3* are the most common accounting for > 90% of all rearrangements [64, 65]. *RET/PTC1* rearrangement has been reported at a higher frequency in DSVPTC compared to the solid/follicular variant of PTC, which showed high *RET/PTC3* re-arrangement [60]. Another study by Sheu and colleagues reported the occurrence of *RET/PTC* rearrangement in selected samples of DSVPTC (n=7) [22]. In this study, the *RET/PTC1* rearrangement was noted in 28% (n=2 of 7) and *RET/PTC3* in 14% (n=1 of 7) of the DSVPTC samples which suggested that other *RET/PTC* rearrangements may occur in DSVPTC [22]. Also, none of the seven cases of DSVPTC showed a *BRAF* mutation (see below), indicating a mutual inimitability between *RET/PTC* and *BRAF* in
this rare subtype of papillary thyroid carcinoma [22]. These studies signify that the activation of RET/PTC1 rearrangement is a common genetic event in the initiation and progression of DSVPTC. In addition, a higher incidence of RET/PTC1 activation in DSVPTC compared to other variants of PTC suggest that molecular pathogenesis in DSVPTC is different. The pathological aggressiveness of DSVPTC may be attributed to this molecular uniqueness.

13. **BRAF mutation**

*BRADF* mutation is common in human cancers and most often detected in melanoma and thyroid cancer [66]. Different profiles of *BRAF* mutations were observed in conventional, follicular variants, multifocal and DSVPTCs [40, 66, 67]. These variations might influence the clinical features of the papillary thyroid carcinoma [66, 67]. *BRAF* mutants show differential expression of genes in the *RAF/MEK/ERK* pathway compared with cells bearing mutations in *RAS, RET*, or other tyrosine kinases [68, 69]. Higher frequencies of *BRAF* mutations were reported in papillary thyroid carcinomas with large size tumours, suggesting its role in the aggressiveness of papillary thyroid carcinoma [66]. *BRAF* mutation was also noted in high-staged thyroid cancers, female patients and in cancers with lymphocytic thyroiditis [40]. A multi-national study has demonstrated that *BRAF* mutation in thyroid cancer is associated with increased mortality [70].

The prevalence of *BRAF* mutation in papillary thyroid carcinoma is approximately 45% [40, 70]. It is worth noting that *BRAF* mutation has been found to have a high prevalence in thyroid cancer in Korea. Lee and colleagues in Korea reported *BRAF* mutation in 50% (n=1 of 2) of cases from DSVPTC, while the conventional type papillary thyroid carcinomas showed slightly higher frequency of BRAF mutation (62%, n=51 of 82) [21]. Similarly, Lim and
colleagues in Korea showed \textit{BRAF} mutation in 61\% DSVPTC (n=62 of 98) and 75\% conventional papillary thyroid carcinomas (n= 2210 of 2947) respectively [71]. In studies outside Korea, a lack of \textit{BRAF} mutation (n=0 of 7) has also been reported in DSVPTC [22]. In addition, Asioli and colleagues reported a lack of \textit{BRAF} mutation (0\%) in DSVPTC whereas conventional papillary thyroid carcinoma and other aggressive variants showed high prevalence of \textit{BRAF} mutation (40-80\%) [72]. Furthermore, using an immunohistochemical study, V600E-mutated BRAF protein was not detected in 7 cases of DSVPTC [73]. Thus, all the evidences suggest that \textit{BRAF} mutation is lower in prevalence in DSVPTC when compared to conventional papillary thyroid carcinoma.

\textit{BRAF} mutations and \textit{RET/PTC} rearrangements play a dominant role in the activation of the RAS-RAF-MAPK pathway and thus in the pathogenesis of papillary thyroid carcinoma [69]. Involvement of \textit{RAS} oncogenes has not been studied to any significant degree in DSVPTC. Santoro and colleagues studied \textit{RAS} mutations in DSVPTC cases that occurred after the Chernobyl nuclear accident in the population of Southern Belarus and Northern Ukraine [60]. In this study, both conventional papillary thyroid carcinoma and DSVPTC (25\%, n=15 of 82) showed no occurrence of \textit{RAS (Ki, Ha or N)} mutations. Overall, these studies signify that occurrence of \textit{BRAF} and \textit{RAS} mutations are uncommon events in DSVPTC and involvement of \textit{RAS-RAF-MAPK} pathway in DSVPTC could be due to the direct activation of \textit{RET/PTC} rearrangements.

Many studies have proven that \textit{BRAF} mutations and \textit{RET/PTC} rearrangements are strictly different pathways in the molecular pathogenesis of papillary thyroid carcinomas [74-76]. This low incidence of \textit{BRAF} mutations implies that \textit{BRAF} mutations act as an initiating genetic event in only a small proportion of this rare entity. On the other hand, the high frequency of
RET/PTC rearrangements in DSVPTC suggests that the biological aggressiveness of DSVPTC may be related to additional genetic changes in a different molecular pathway.

14. Conclusion

Diffuse sclerosing variant of papillary thyroid carcinoma (DSVPTC) is an uncommon variant of papillary thyroid carcinoma and is highly prevalent in paediatric/young patients and in patients affected by irradiation. Compared to conventional papillary thyroid carcinoma, DSVPTC has distinct clinicopathological characteristics such as extensive fibrosis, squamous metaplasia, numerous psammoma bodies and high incidence of lymph node metastases. However, the prognosis of DSVPTC patients was noted to be similar to conventional papillary thyroid carcinoma. In addition, when compared to conventional papillary thyroid carcinoma, DSVPTC showed rare BRAF and RAS mutations and high frequency of activation of RET/PTC rearrangements. Thus, DSVPTC had different clinical, pathological and molecular profiles when compared to conventional papillary thyroid carcinoma.
Figure legends

Figure 1
Histogram showing the distribution of cases of DSVPTC in different age groups, separated into decades of life.
Figure 2A

Histopathology of diffuse sclerosing variant of papillary thyroid carcinoma showing the carcinoma had numerous psammoma bodies, lymphoplasmacytic infiltrates with germinal centre and fibrous stroma. (haematoxylin and eosin x 8)
Figure 2B

Higher magnification showing many tumour cells have squamoid differentiation and nuclear characteristic of papillary thyroid carcinoma. (haematoxylin and eosin x 10)
<table>
<thead>
<tr>
<th>Author / Year/Country</th>
<th>No.</th>
<th>Mean age in years (range)</th>
<th>Male/ Female</th>
<th>Recurrence</th>
<th>Distant metastases</th>
<th>Follow-up in years (range)</th>
<th>Died</th>
<th>Outcome/Remarks</th>
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<tr>
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<td>15</td>
<td>29.3 (9-63)</td>
<td>3/12</td>
<td>8</td>
<td>3 (lung)</td>
<td>7.7 (2 - 13)</td>
<td>0</td>
<td>5 alive with diseases</td>
</tr>
<tr>
<td>Wu /1989/UK</td>
<td>3</td>
<td>38.0 (33-46)</td>
<td>1/2</td>
<td>1</td>
<td>1 (bone)</td>
<td>1 - 5</td>
<td>0</td>
<td>1 alive with disease</td>
</tr>
<tr>
<td>Soares /1989/Portugal</td>
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<td>34.7 (10-67)</td>
<td>1/9</td>
<td>5</td>
<td>5 (lung)</td>
<td>3 - 14</td>
<td>1</td>
<td>5 alive with diseases</td>
</tr>
<tr>
<td>Fujimoto /1990/Japan</td>
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<td>19.6 (10-28)</td>
<td>0/14</td>
<td>3</td>
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<td>15 (1 - 31)</td>
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<td>41.7 (32-60)</td>
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<td>-</td>
<td>1</td>
<td></td>
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<tr>
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<td>19.5 (11-27)</td>
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<td>1 (lung)</td>
<td>-</td>
<td>0</td>
<td>1 alive with disease</td>
</tr>
<tr>
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<td>3 - 9</td>
<td>0</td>
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<td>7.8 (6 -10)</td>
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<td>6.4 (1 - 12)</td>
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<td>11.6 (1.5 -28.5)</td>
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<td>33.3 (14-61)</td>
<td>0/8</td>
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<td>1</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Fukushima /2009/Japan</td>
<td>35</td>
<td>30.4 (13-57)</td>
<td>5/30</td>
<td>9</td>
<td>4</td>
<td>5.8(2-9)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>[Takagi /2013/Japan]</td>
<td></td>
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<tr>
<td>Koo /2010/Korea</td>
<td>49</td>
<td>24.9(6-66)</td>
<td>11/38</td>
<td>8</td>
<td>4 (lung)</td>
<td>34.2(11-130)</td>
<td>-</td>
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<tr>
<td>[Koo /2009/Korea (n=28)]*</td>
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<td>[Kwak /2007/Korea (n=6)]*</td>
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<tr>
<td>Zhang /2010/China</td>
<td>8</td>
<td>30 (14-35)</td>
<td>1/7</td>
<td>0</td>
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<tr>
<td>Kazaure /2012/USA</td>
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<td>48.5(-)</td>
<td>45/216</td>
<td>0</td>
<td>0</td>
<td>4.0 (21)</td>
<td>7</td>
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<td>Regalbuto /2011/Italy</td>
<td>34</td>
<td>43.2 (15-78)</td>
<td>4/30</td>
<td>15</td>
<td>1</td>
<td>4.5(1-10)</td>
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<td>Yun /2011/China</td>
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<td>24.1(8-49)</td>
<td>5/12</td>
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<td>0</td>
<td>5.2(2-9.1)</td>
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<tr>
<td>Chang /2013/Taiwan</td>
<td>14</td>
<td>35.4 (13-61)</td>
<td>3/11</td>
<td>6</td>
<td>3</td>
<td>3.9 (0-13.7)</td>
<td>3</td>
<td>2 alive with disease; 9 alive without disease</td>
</tr>
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</table>

Note - only series with ≥ 3 cases were included; No = number of cases; *= studies from the same population
Conflict of interest statements

The authors have no conflict of interest in publishing this manuscript.

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Vitae of other authors

Ms. Pillai is a PhD candidate currently investigating the mutational burden of neuroendocrine tumours. She is currently developing customised mutation scanning panels using next-generation sequencing to provide a comprehensive analysis of the mutations types present in such cancers.

Dr. Gopalan is a clinician-scientist whose research has encompassed the intersection of cancer pathology and molecular events. His research has included the analysis of the effects of the genetic mutations in cancer development.

Dr. Smith is a research scientist with a focus on the molecular genetics of cancer, both at a population and cellular level. His research has examined the effect of genetic polymorphisms, mutations and gene expression on the risk of cancer initiation and the evolution of cancers as they grow.
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