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REVIEW

Current evidences in poorly differentiated thyroid carcinoma: a systematic review and subsection meta-analysis for clinical decision making

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Abstract

Background Poorly differentiated thyroid carcinoma (PDTC) is a distinct entity with intermediate prognosis between indolent follicular thyroid cancers and anaplastic carcinoma. The management guidelines are not standardized for these cancers due its low prevalence and limited available literature. Therefore, we did this systematic review with emphasis on current evidence on diagnosis, imaging, molecular markers, and management of these carcinomas.

Materials and methods We searched four databases, PubMed, Medline, EMBASE, and Emcare to identify studies published till October 2023. All studies reporting diagnostic tests, imaging, molecular marker expression and management of PDTC were included in the review. The meta-analysis was conducted on expression of molecular markers in these cancers following recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Random-effects meta-analysis was used to calculate pooled estimated prevalence with 95% confidence intervals.

Summary Based on the inclusion criteria, 62 articles were selected to be incorporated for the review. Differences in pathological diagnostic criteria of PDTC was noted in literature which was addressed in WHO 2022 diagnostic terminologies with expansion of the definition. Surgical management is uniformly recommended for early stage PDTC. However, literature is divided and anecdotal for recommendations on radioactive iodine (RAI), extent of neck dissection and adjuvant treatment in PDTC. Evidence for Next Generation Sequencing (NGS), novel theragnostic approaches, immunotherapy targets are evolving. Based on the subset analysis for expression of molecular markers, we found the most common markers expressed were TERT (41%), BRAF (28%) and P 53 (25%).

Conclusion Poorly differentiated thyroid carcinomas have a high case fatality rate (up to 31%). Eighty-five % of the patients who succumb to the disease have distant metastasis. Even though under-represented in literature, evidence-based management of these aggressive tumors can help personalize the treatment for optimal outcomes.

Keywords Poorly differentiated · Thyroid carcinoma · Turin criteria

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Introduction

Poorly differentiated thyroid carcinoma as a separate entity

Before 1980s, the presence of aggressive variants of follicular cell derived thyroid carcinomas, was recognized by the pathologists and terminologies like moderately differentiated, angio-invasive, invasive, and less well differentiated [1–5] were suggested to capture this entity. However, poorly differentiated thyroid carcinoma was suggested as a new clinicopathological entity by Sakamoto et al. [1] in their study of 258 follicular cell derived thyroid

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cancers [1]. Even before the nomenclature, existence of an aggressive subgroup of thyroid cancers was acknowledged by Langhans in 1907 and termed as "Wuchernde Struma" [6, 7]. While using only morphological features (solid, trabecular and/or scirrhous patterns) as a diagnostic criterion, the incidence of PDTC in Sakamoto's cohort of patients was found to be 13.6%, which was much higher compared to subsequent research. Following the same concept, Carcangiu et al. in 1984 described their version of the poorly differentiated thyroid carcinoma. Along with the architectural changes like solid cluster or "insular" growth pattern, "perithelioma" like structures, notably, they also included consistent mitotic rate and necrotic foci in their diagnosis of PDTC [8]. The current nomenclature suggested by WHO classification of thyroid neoplasms includes the criteria of both morphological features as well as mitotic rate [9, 10].

Follicular cell derived thyroid malignancies are known to be a conglomerate of diverse prognostic groups [11]. While comprising mostly of indolent disease, differentiated thyroid malignancies also have sub-groups who die of disease. In a study of prognostic nomograms of risk of recurrence and death in thyroid cancers a case fatality rate of 8.8% for all the thyroid cancers in the cohort was noted. In this study PDTCs comprised only 4% of the patients who died of their disease. However, PDTCs had a case fatality rate of 31.2% on their own [11].

Incidence of PDTC is region specific and dependent on the diagnostic criteria utilized [12, 13]. In a prevalence study of PDTCs in Japan, the incidence varied depending upon the diagnostic criteria used (11.1% in Sakamoto criteria, 0.8% in WHO criteria and 0.3% in Turin criteria) [12]. Hence, management of these rare and aggressive subgroups of malignancies are at times anecdotal and has remained a challenge as no standardized approach exists till date.

Methodology

Search strategy and selection criteria

This systematic review was performed following recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14]. We have searched four databases Pubmed, Medline, Embase and Emcure to identify manuscripts discussing diagnosis, imaging, molecular marker expressions and management of poorly differentiated thyroid cancers. We used the following search terms: poorly differentiated thyroid cancer, anaplastic thyroid cancer, undifferentiated thyroid cancer, diagnostic imaging, molecular markers and management. Boolean operators (NOT, AND, OR) were also used in succession to narrow and broaden the search. The references of all the studies were screened for any possible additional publications. Any duplication was removed. Independent reviewers screened the manuscripts to include relevant information for our review. Any discrepancy was resolved by a third reviewer. In total, 4418 records were identified through database searching and after removal of duplication it was around 3476. In total, 1174 articles met the eligibility criteria for assessment. Studies included for qualitative synthesis were 62 out of which 7 articles were chosen for subset analysis of molecular markers in PDTC (Supplementary information).

Data extraction and analysis

The data extraction was relevant for the analysis of expression of molecular markers in PDTC. This data extraction was done by three independent authors. The manuscripts reporting the expression of molecular markers were selected and data regarding expression of each molecule was extracted.

Statistics

We performed data analyses using Stata version 12. Random-effects meta-analysis was used to calculate pooled estimated prevalence with 95% confidence intervals [15].The percentage of total variation across studies due to heterogeneity was evaluated by the I^2 measure and values of 25%, 50%, and 75% suggested low, moderate, and high heterogeneity, respectively [16].

Results

Pathology

Challenges in diagnosis of PDTC in cytology (FNAC) in pre-operative scenario

Majority of the operable thyroid carcinomas are best addressed at the first attempt at surgery. Hence, accurate pre-operative diagnosis is key to surgical extent planning. However, only 27% of PDTCs are amenable to a correct pre-operative diagnosis in cytology [17]. Considerable cytomorphological overlap with other subtypes of thyroid carcinoma, like solid variants of papillary thyroid carcinoma and medullary thyroid carcinoma is known to exist with PDTCs [17, 18].

Although high-grade features (necrosis, mitosis) of PDTC are identifiable in FNAC, other cytomorphological features like growth patterns (solid, trabecular, insular) are less discernible [13]. The Turin criteria incorporated

Table 1 Studies on fine needle aspiration cytology features of PDTC

Study	FNAC features	Comments
Kane et al. [57]	• Hypercellularity • Small cell size • Insular pattern • Increased nuclear cytoplasmic ratio	Mitosis was observed in 25% and necrosis was observed in 34% patients.
Purkait et al. [18]	• Solid sheets of cells • Three-dimensional clusters of cells with significant nuclear crowding • Peripheral arrangement of tumor cells giving a "garlanded" appearance • Moderate to high cellularity	Notably, most cases lacked necrosis and mitotic activity, key for diagnosis as per Turin criteria.
Bongiovanni et al. [58]	• Solid, trabecular and insular (STI) cytoarchitecture observed in 92.5% cases • Single cells • High nuclear/cytoplasmic (N/C) ratio • Severe crowding	Necrosis was observed in 15% cases and mitosis in 42.5% patients. This was in contrast with the relative lack of these features in other series (around 4.7% demonstrating necrosis and infrequent mitosis).
Barwad et al. [59]	• The most frequent cytologic finding was hypercellular smear • High nuclear/cytoplasmic ratio • Frequent mitotic figures • Monomorphic small follicular cells arranged in solid clusters	Frequent mitotic figures were observed but background necrosis was observed in only 2/10 cases.

high-grade features as well as growth pattern as a part of their proposal for diagnosis of PDTC [9, 18]. However, the criteria were based on analysis of eighty-three thyroid cancer samples of which histopathology slides were prepared and reviewed [9].

Hence, the diagnostic criteria for PDTC in cytology is yet to be standardized and surrogate findings in FNAC have been suggested by different groups of authors.

Similarly, Saglietti et al. reported that PDTC s are often misdiagnosed as follicular neoplasm/suspicious of follicular neoplasm (Bethesda IV) in up to 33% cases and atypia of undetermined significance (Bethesda III) in 2% cases [13]. This has direct implications in treatment planning, since Bethesda III and IV subcategories are often recommended diagnostic lobectomy or observation, which is sub-optimal treatment for aggressive PDTCs (Table 1).

Prognostic relevance of different diagnostic criteria of PDTC in histopathology

PDTCs have been described by either high risk features (mitosis and necrosis) [19] or architectural pattern (solid/trabecular/insular) [1, 10]. In 2007, the Turin Criteria for diagnosis of PDTC was suggested by a group of pathologists at a congregation at Turin, Italy and was as follows:

(1) solid/trabecular/insular pattern of growth,
(2) absence of conventional nuclear features of papillary carcinoma, and
(3) at least one of the following features: convoluted nuclei, mitotic activity >3/10 high power microscopic fields, and tumor necrosis [9].

Simultaneously, pathologists at Memorial Sloan Kettering Cancer Center (MSK), described high-grade features, i.e.: mitosis of >5/10 high power field and/or necrosis in thyroid carcinomas showing definite follicular cell differentiation (denoted by routine microscopy or thyroglobulin positivity) as the defining criteria of PDTC [10].

Differences in the diagnostic criteria change prognostication, as highlighted in the study by Ghossein et al. [20]. The authors noted that of non-anaplastic follicular cell derived neoplasms, 1.5% of them had fatal disease. Of this aggressive subgroup, 57% were PDTC while using MSKCC-PDTC criteria. However only 27% were diagnosed as PDTC while using Turin criteria. It was noted that only 45% of the patients met both the MSKCC and the Turin diagnostic criteria for PDTC. Hence, Turin criteria under-diagnosed some patients as lesser aggressive variants. Since 9% of the PDTCs diagnosed by MSKCC criteria lacked the solid/trabecular/insular growth pattern, they were missed in Turin criteria. Conversely, none of the cases diagnosed by Turin criteria were missed in MSKCC criteria (Table 2).

Gnemmi et al. analyzed a series of 82 follicular origin carcinomas. Their results showed a concordance rate of 75% between the two diagnostic criteria and that both were able to successfully capture the disease prognosis (The 5-year cause specific survival rates were 73.3% and 71.9% for Turin criteria and MSK criteria, respectively) [21]. Also,

Table 2 Comparative chart: MSK criteria and Turin criteria of PDTC

MSK criteria [10]	Turin criteria [9]
In thyroid carcinomas showing definite follicular cell differentiation (denoted by routine microscopy or thyroglobulin positivity)- • Mitosis of >5/10 high power field • And/or necrosis	• Solid/trabecular/insular pattern of growth • Absence of conventional nuclear features of papillary carcinoma • At least one of the following features: ◦ Convoluted nuclei ◦ Mitotic activity >3/10 high power microscopic fields ◦ Tumor necrosis

Table 3 Comparative chart of PDTC and DHGTC (WHO)

Poorly differentiated thyroid carcinoma (PDTC)	Differentiated high-grade thyroid carcinoma (DHGTC)
• Has poor differentiation histologically (combination of solid, trabecular and insular patterns). • As a part of diagnostic criteria, along with tumor necrosis and convoluted nuclei, required mitotic rate is >3/10 hpf RAS as driver mutation commoner compared to DHGTC.	• Retain their distinctive cytological and architectural properties like papillary thyroid carcinoma, hence differentiated. • As a part of diagnostic criteria, along with tumor necrosis, required mitotic rate is >5/10 hpf. Majority of the driver mutation is BRAF V600E.

the same study noted Ki67 proliferative index >4 as an independent prognostic factor for cause specific survival in PDTC.

WHO classification of thyroid neoplasms formally denoted PDTC as a separate entity in 2004 [22]. Current WHO classifies PDTC under invasive high-grade follicular cell derived neoplasm having intermediate prognosis [23]. Interestingly, the Turin criteria is endorsed by WHO in 2017 as well as 2022 for diagnosis of PDTC whereas the MSK [10] criteria now is utilized to define differentiated high-grade thyroid carcinoma (DHGTC) in 2022 classification of endocrine neoplasms [23]. WHO denotes both entities may have similar clinico-epidemiological nature of while DHGTC may still not have the classical solid, trabecular, insular pattern and may retain certain nuclear features of papillary carcinoma. The diffuse sclerosing, follicular, and classic forms of PTC showed the least incidence of high-grade characteristics, whereas a higher percentage of solid trabecular and histologically aggressive PTC cases could be categorized as DHGTC [24]. DHGTC has a higher $BRAF^{V600E}$ mutation rate (42% vs. 3%; $p = 0.003$), a trend toward more gene fusions (25% vs. 3%; $p = 0.052$), than PDTC [25] (Table 3).

In recent research of 41 such cases, an attempt was made to differentiate between PDTCs and DHGTCs using a reproducible Ki-67 based labeling index cut-off. PDTCs presented at younger age, with larger tumors, multifocal and lesser metastasis compared to DHGTC. However, no differences in the cut-off criteria between the groups were noted [26].

Another area of ongoing debate has been the percentage of poorly differentiated component in well differentiated thyroid cancers and its prognostic implication. Dettemer et al. noted that even as low as 10% of poorly differentiated component in differentiated thyroid carcinomas resulted in a poorer survival outcome compared to control groups [27]. Bichoo et al. studied three groups of patients, PDTCs ($n = 27$), papillary thyroid carcinoma with PDTC component ($n = 27$) and follicular thyroid carcinoma with PDTC component ($n = 88$). Their results revealed 75% of poorly differentiated component in well differentiated cancers to be associated with poor overall survival [28]. Hence, it is imperative that reporting of even a small percentage of poorly differentiated component in the background of well differentiated thyroid carcinomas is prognostically essential.

Role of immunohistochemistry to differentiate PDTC from other differential diagnosis

PDTCs at times can be confused with medullary thyroid cancers or anaplastic thyroid carcinomas [29]. Differentiating from medullary thyroid cancer can be done by positivity for thyroglobulin and PAX8 and negativity for calcitonin, chromogranin and synaptophysin in PDTCs. PDTCs are positive for thyroglobulin and TTF-1, whereas anaplastic thyroid cancers lack that immunostaining or are focally positive.

Significance of molecular markers of PDTC in immunotherapy and survival

Study of molecular mechanisms of tumorigenesis in thyroid cancers (also in PDTC) has gained recent attention to find targetable mutations and biomarkers for effective therapy [30].

Table 4 Incidence of expression of various molecular markers in PDTC

Molecular markers	Pooled prevalence	Number of studies	I2	*p* value
P53	0.25 (0.09–0.44)	6	76.54%	0.00
FLT3	0.16 (0.04–0.33)	2		0.00
ATM	0.10 (0.02–0.23)	3	45.25%	0.16
RB1	0.01 (0.00–0.05)	2	–	0.12
GNAS	0.09 (0.01–0.22)	2	–	0.01
AKT1	0.10 (0.02–0.23)	2	–	0.00
EIK	0.09 (0.04–0.16)	2	–	0.00
paxparg	0.03 (0.01–0.07)	2	–	0.00
PTEN	0.02 (0.00–0.07)	4	4.16%	0.37
STK	0.01 (0.00–0.05)	2	–	0.12
ALK	0.03 (0.01–0.07)	3	0.00%	0.89
NRAS	0.12 (0.04–0.23)	5	57.46%	0.05
HRAS	0.04 (0.01–0.09)	3	0.00%	0.98
KRAS	0.01 (0.00–0.05)	4	5.49%	0.37
PIK	0.08 (0.01–0.20)	5	71.95%	0.01
RET	0.07 (0.03–0.12)	4	0.00%	0.45
TERT	0.41 (0.32–0.49)	3	0.00%	0.87
BRAF	0.28 (0.21–0.35)	5	0.00%	0.43

Also, knowing the mutational burden in PDTC can be a potential indicator of its location in the spectrum of aggressiveness between differentiated thyroid cancers and anaplastic thyroid cancers. It has been noted that in PDTCs, the mutation burden lies in between papillary thyroid cancers (PTC) and anaplastic thyroid cancers (ATC), with 1 ± 1 for PTCs, 2 ± 3 for PDTCs and 6 ± 5 for ATCs [31]).

Most common driver mutations of PDTC are $BRAF^{V600E}$, NRAS, TERT, EIF1AX, ATM, and ERBB4 [7, 32]. Based on the meta-analysis we performed, the table demonstrates the incidence of expression of various molecular markers in PDTC (Table 4 and Figs. 1 and 2).

We found that the most common markers expressed were TERT (41%), BRAF (28%) and P 53 (25%). It has been postulated that in a stepwise transition from well differentiated to undifferentiated (ATCs) tumors, the thyroid malignancies accumulate genetic mutations. This is demonstrated particularly by BRAF and RAS mutations being more common in ATC than PDTCs [32]. Also, TERT mutation, a known aggressive factor and indicator of RAI refractoriness, is found in an increasing manner in PTCs, PDTCs and ATCs (9%, 40% and 73% respectively) [31, 33].

A lucrative concept is to therapeutically exploit the main driver mutation in PDTC. But there have been limitations to the practical applicability of the same, for example for common mutations like BRAF in thyroid carcinomas. Unlike BRAF mutation in melanomas and hairy cell leukemias, the BRAF mutated thyroid cancers are less responsive to vemurafenib, probably due to activation of epidermal growth factor receptor signaling [30, 34]. Also, patients with genomic mutations of RET or NTRK1, RAS (N, H, K), and BRAF are known to have activation of mitogen-activated protein kinase (MAPK) signaling pathway, which inhibits expression of thyroid hormone biosynthesis genes including sodium iodine symporter. Selumetinib, a MAPK kinase inhibitor demonstrated benefit in reversing refractoriness to radio-iodine in radio-iodine refractory patients in a pilot clinical trial [35]. However, the same drug failed to maintain its benefit in phase III trials [36]. Amongst other possible causes, one suggested cause of the failure was toxicity due to high dose requirements to maintain sustained MAPK inhibition. Hence, successful drug development against a potentially actionable mutation has many limiting steps and is a complex process.

BRAF mutations were found to be less common in PDTC (22%) compared to anaplastic thyroid cancers (56%) and were also a prominent marker of PDTCs with anaplastic components by Duan et al. [32]. Majority of the driver mutations are seen more commonly in ATCs compared to PDTCs, e.g. TP53 (73% vs. 8% respectively) and is attributed to the aggressive nature of ATC [31] (Table 5).

Management

Optimal imaging strategy for suspected/diagnosed PDTCs

PDTCs can present clinically as well circumscribed small tumors or ones with gross extrathyroidal extension [23]. Evaluation of complete disease extent is of utmost importance with help of imaging and pre-operative evaluation of vocal cord function. The first imaging to delineate the extent

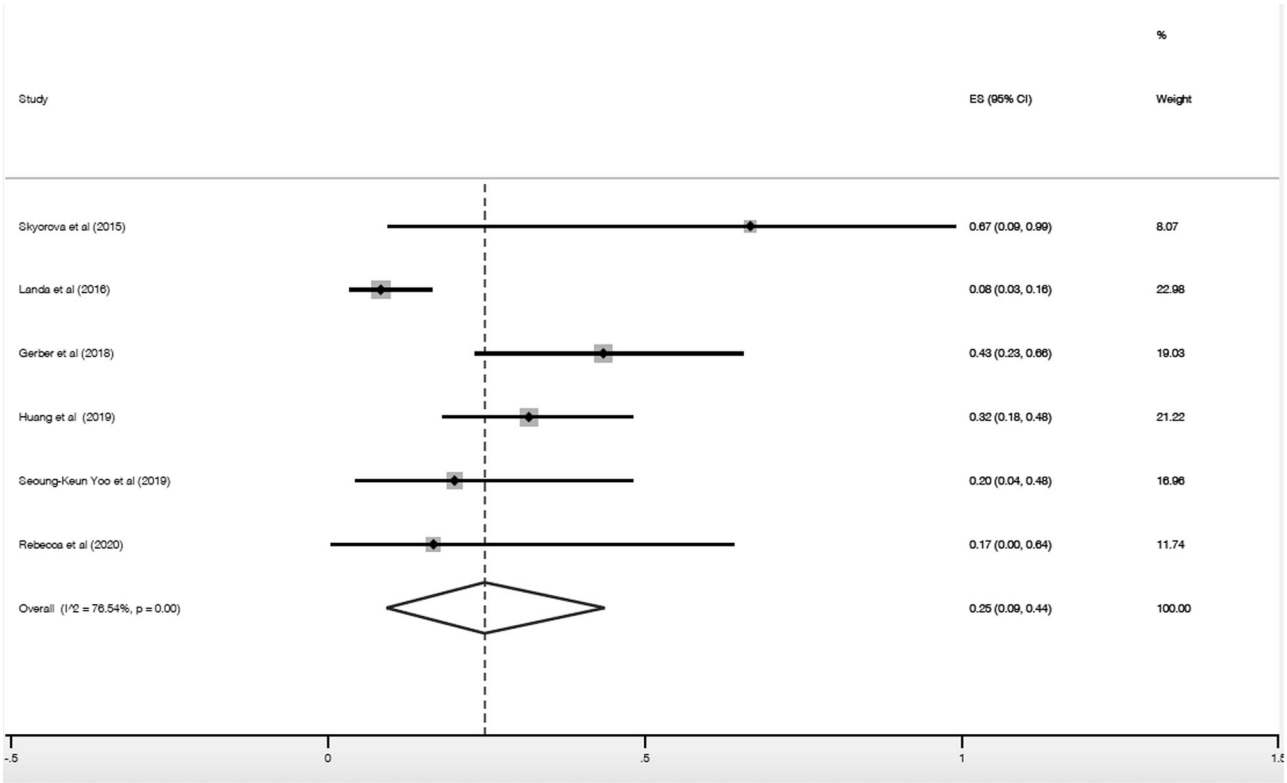

Fig. 1 Forest plot demonstrating pooled prevalence of P53 mutation in PDTC

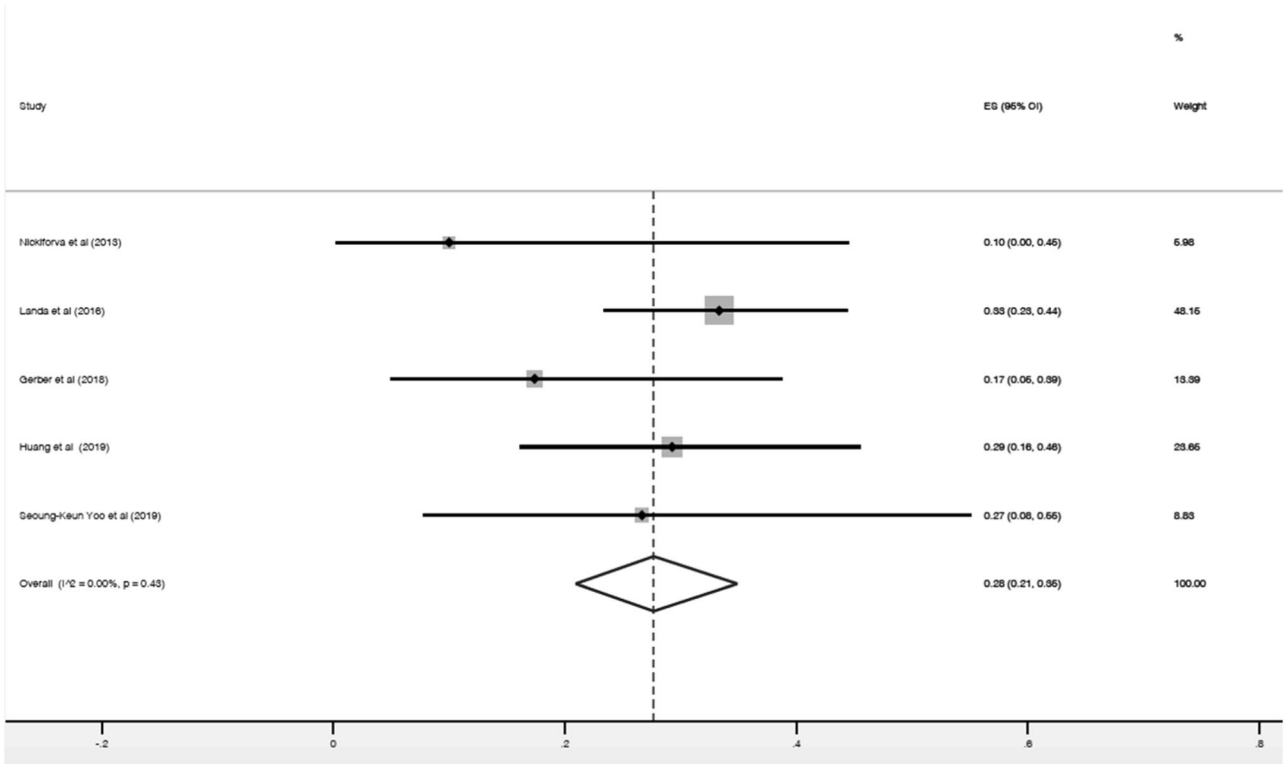

Fig. 2 Forest plot demonstrating pooled prevalence of BRAF mutation in PDTC

Table 5 Common genetic mutations in PDTC and their clinical relevance

Study	No of PDTC cases	Most common mutations	Clinical relevance
Duan et al. [32]	41	BRAF 22% RAS 10% TP53 27% TERT 22%	• WDTC components were observed in 53% of PDTCs. • Concurrent TERT and PIK3CA mutations were associated with poor overall survival. • PDTC with PTC components commonly demonstrated RET fusion. • On multivariate analysis, only TERT mutation was the independent predictor of poor overall survival.
Chernock [60]	6	DICER1 83%	• Association with childhood and adolescence poorly differentiated thyroid carcinoma. • Absence of other common mutations like BRAF, RAS, TERT
Landa [31]	84	BRAF 33% RAS 28% TERT 40% EIF1AX 11% TP53 8%	• BRAF mutated PDTCs were smaller and had higher nodal metastasis. • RAS mutated PDTCs were larger and had higher distant metastatic rate. • *EIF1AX* mutations were associated with larger tumors and poor survival. • 92% of RAS mutated (hence more aggressive) diseases were captured by using Turin-PDTC criteria, but that dropped to 81% while using MSKCC-PDTC criteria.
Nickiforova [61]	10	BRAF NRAS PIK3CA GNAS 30%	• 9% thyroid cancers which are mutation positive contained more than one mutation. • ThyroSeq (12 gene panel), which notably was used in both histopathology and FNAC samples, was able to detect mutation in 30% of the PDTCs.
Sykorova [62]	3	TP53 66% (two out of three cases) CHEK2 FANCD2 CDH 1 33% (one case each)	• Targeted NGS analysis aimed at exclusively screening the mutational status of cancer-associated genes in PDTC and ATC. • TruSight Cancer panel was utilized.
Gerber [63]	25	TP53 43% *APC* ERBB4 FLT3 KIT SMAD4 BRAF 17% each ATM EGFR FBXW7 13% each	• ThyroSeq cancer panel was utilized. • Even though 43% of the PDTCs had TP53 positivity, notably there was no significant difference regarding the clinical course, extrathyroidal extension or vascular invasion between *TP53*-positive tumors and the other tumors. • Two potential genetic targets, EGFR (ERBB1) and ERBB4, were identified in this study.
Yoo [64]	15 PDTC And 3 focal ATC/PDTC	$BRAF^{V600E}$ *RAS* 26.67% RET fusion TERT 47.39%	• Focal ATC/PDTCs had higher $BRAF^{V600E}$ mutation (82.14%) compared to PDTCs, resulting in a more aggressive nature.

of involvement for PDTC is an Ultrasonography (USG). In a first of its kind comparative study by Hahn et al., USG findings of PDTC and anaplastic thyroid carcinomas were compared. Dominant findings in PDTCs were heterogeneous echogenicity, solitary nodules, and hypo echogenicity. Almost 2/3rd (63.3%) of the PDTCs retained circumscribed margin [37]. This contrasted with anaplastic carcinomas, where only one third was well circumscribed.

Also, the incidence of lymph node metastasis in PDTC is 30–59%, extrathyroidal extensions is 50%–75% [38] and distant metastasis is 13–33% [13, 39]. If a suspicion of advanced disease in ultrasound is raised, axial imaging (CT/ MRI) and distant metastatic screening may be useful. With suspicion of extrathyroidal extension, esophagoscopy and trans esophageal ultrasound may be required as well [40].

Functional molecular imaging like PET CT scan can play a dual role of screening distant metastasis and providing information of the disease biology in cases of PDTC. Theoretically, the more thyroid tumors de-differentiate, the less is the expression of sodium iodine symporter and more is gain of FDG avidity [38].

Optimal management strategy for non-metastatic PDTC—role and extent of surgery

Resectable PDTCs have better survival outcomes compared to unresectable PDTCs, despite multimodality treatment [41]. Complete resection of the primary disease with therapeutic neck dissection is advisable in PDTC since the lymph node metastasis rate is high (30–59%) [13, 39].

However, the role of elective neck dissection in these sub-groups of tumors is not known. It is of note that in a clinicopathological trend analysis of PDTCs and ATCs, despite adequate imaging, the positive resection margin at surgery was 19.7% [41]. Hence, the surgeons should be adept with management of partial carotid encasement, trachea-esophageal invasion and thorough nodal clearance while managing PDTCs.

Optimal management strategy for advanced/metastatic/un-resectable PDTC—role of non surgical treatments

Resection of locoregionally advanced thyroid cancer with involvement of adjacent structures (larynx, esophagus, trachea, carotid vessels) is extensive, technically challenging, and morbid. Shaving the disease off the vital structures with gross residual disease (R2 resection) is known to have poor survival outcome in thyroid disease compared to resection without any residue or with microscopic residual tumor R0/R1 resection [42]. Hence, novel approaches of neoadjuvant targeted therapy (elaborated in future directions section) followed by surgical resection are in development.

Current evidence for radiotherapy in the treatment of PDTC is extrapolated from differentiated thyroid cancers. Differentiated thyroid cancers had demonstrated benefit with addition of radiotherapy in gross residual or unresectable disease [43]. Adjuvant treatment after surgery for locoregionally advanced PDTC showed increased disease specific survival compared to surgery alone [41]. However, addition of radiotherapy to gross residual disease or T4b disease did not demonstrate exponential benefit in PDTC [44]. Also, surgery followed by radiotherapy vs. surgery followed by RAI did not show any survival difference between themselves [41].

Radio-iodine avidity in PDTC is a complex interplay of multiple factors. It is difficult to predict the percentage of well differentiated components in PDTCs which is the main driver of RAI avidity since PDTCs can arise de novo or can de-differentiate from well differentiated thyroid carcinomas. Studies have revealed that almost half (53%) of the PDTC patients can harbor well differentiated components [32] and hence, may theoretically benefit from RAI. Moreover, mutations like TERT, can play a role in radio-iodine refractoriness [33]. In an ex vivo study of pre-therapeutic RAI avidity in PDTC, Nilsson et al. found that tumoral Thyroglobulin expression and Ki-67 index were correlated with avidity [45]. Same findings were corroborated at a clinical level [46] in a series of thyroglobulin "non-secretor" PDTCs who were refractory to RAI. In the Nilsson study, a tracer amount of I-131 was given to PDTCs and RAI avidity was checked at histopathology. The PDTC cases ($n = 6$, 16%) in this study demonstrated a nature akin to "unfavorable" subgroup of study by Ho et al. [47], showing 10 times lower RAI avidity than "favorable" group of thyroid cancers. Overall, PDTCs are known to be RAI avid in up to 40–80% cases [48, 49].

In a SEER database analysis in 2022, of PDTC patients who received radioactive iodine (RAI) treatment vs. who did not receive RAI, it was revealed that RAI radioiodine therapy was an independent favorable factor for overall survival (OS) in PDTC patients (hazard ratio = 0.57; 95% CI, 0.44–0.75, $p < 0.001$) [50].

Future directions in management of PDTCs

Prostate-specific membrane antigen (PSMA) is expressed in the micro-vasculature of thyroid and experimental studies have explored the feasibility of Ga 68 PSMA scans in detecting disease burden in PDTC and as a potential theranostic option for radiolabeled lutetium (177Lu)-PSMA [51, 52]. As a diagnostic modality however FDG-PET/CT scan is found to be superior to Ga 68-PSMA scan (89% vs. 11% Sabine et al. [51], 100% vs. 72.7% Heath et al. [52]).

Neoadjuvant approach of targeted therapy for locoregionally advanced thyroid cancers is a concept in evolution [53]. Differentiated thyroid cancers are known to have a better overall response rate and subsequent R0/R1 resection compared to their PDTC counterparts with this approach (overall response rate 83.3% vs. 0%) [53].

In a recent (2021) study of six patients of ATC and two patients of PDTC, a systemic approach to treat high tumor burden disease was studied with 4–24 mg Lenvatinib daily with pembrolizumab at a fixed dose of 200 mg every 3 weeks [54]. Both the patients of PDTC showed partial response as best overall response (BOR) in this group, whereas complete response was noted in 66% of ATCs ($n = 4/6$). All these patients were extensively pre-treated (surgery, radiotherapy, RAI, systemic therapy with carboplatin/cisplatin—paclitaxel) and expressed PD-L1 between 1–90%, with the majority expressing PD-L1 > 50%. Even though currently experimental, Lenvatinib-pembrolizumab may hold a role in future for treatment refractory metastatic PDTCs expressing PD-L1.

Summary and outcome

Five year overall survival of PDTC has been reported around 50–60% [41, 55, 56]. Almost 85% of the patients of

PDTC who die of their disease succumb to distant metastasis [55].

Conclusion

PDTC is an aggressive thyroid cancer. A consensus guideline in the management of PDTC might be imperative. Surgery with neck dissection is an acceptable form of treatment for these cancers but administration of adjuvant treatment in terms of radiotherapy and RAI still is a matter of debate. We found TERT (41%), BRAF (28%) and P 53 (25%) as the commonly expressed markers in these cancers and future studies looking into targeted therapy for these molecules might play an important role in improving the outcomes of these aggressive cancers.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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