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Prognosis of Poorly Differentiated Thyroid Carcinoma: A Systematic Review and Meta-Analysis

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Background: Poorly differentiated thyroid carcinoma (PDTC) accounts for a small portion of thyroid carcinomas but contributes to a significant proportion of thyroid carcinoma-associated deaths. The clinicopathological prognostic factors and clinical outcomes of PDTC remain unclear. We aimed to evaluate the clinical outcomes of patients with PDTC after curative treatment.

Methods: A comprehensive search was performed up to September 2023. We included studies investigating treatment outcomes in patients with PDTC who underwent initial surgery. The 5-year disease-free survival (DFS) and overall survival (OS) were extracted. In this meta-analysis, the enrolled PDTC histological criteria included 3rd, 4th, and 5th World Health Organization (WHO) and Memorial Sloan Kettering Cancer Center (MSKCC) classification. A random-effects model was used for the pooled proportion analysis. Meta-regression analysis was conducted to evaluate the prognostic factors.

Results: Twenty retrospective studies published between 2007 and 2023, including 1,294 patients, met all inclusion criteria. Studies that diagnosed PDTC based on various histological criteria including 3rd WHO (n=5), 4th WHO (n=12), 5th WHO (n=2), and MSKCC (n=1) were included. Overall, 5-year DFS and 5-year OS were 49.4% (95% confidence interval [CI], 42.3 to 56.4) and 73.8% (95% CI, 66.5 to 79.9), with moderate heterogeneity of 58% and 55%, respectively. In meta-regression analysis, extrathyroidal extension (ETE) was a prognostic factor for OS.

Conclusion: The meta-analysis of DFS and OS in patients with PDTC show the moderate heterogeneity with a variety of histological criteria. ETE appears to have a significant impact on OS, regardless of histological criteria.

Keywords: Thyroid neoplasms; Carcinoma; Meta-analysis; Prognosis; Survival; Pathology

INTRODUCTION

Thyroid cancer is the most common tumor of the endocrine system, and its incidence is gradually increasing [1]. Poorly differentiated thyroid carcinoma (PDTC) is a rare cancer reported in only 2% to 15% of all thyroid cancers [2]. It was first proposed by Sakamoto et al. [3] in 1983 as a new clinicopathological entity. In 2004, it was categorized in the 3rd World Health Organization (WHO) classification as a specific entity, characterized by solid, trabecular, or insular architecture, infiltrative growth, necrosis, and vascular invasion of follicular cell origin, with morphological and biological attributes intermediate between well differentiated and anaplastic carcinoma of the thyroid [4]. In 2006, Memorial Sloan Kettering Cancer Center (MSKCC)

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histologic criteria based solely on mitotic index ≥5/10 high-power fields (HPFs) and/or tumor necrosis was proposed to define PDTC [5].

In 2007, the Turin histological criteria for diagnosis were proposed [6] and were adopted in the 4th WHO classification published in 2017 [7]. These criteria included: (1) the presence of a solid/trabecular/insular growth pattern; (2) the absence of the conventional nuclear features of papillary carcinoma; and (3) at least one of the following three features: convoluted nuclei, mitotic activity of ≥3 per 10 HPFs, and tumor necrosis [6]. Recently, PDTC has been newly classified as a subtype of one of the high-grade follicular cell-derived non-anaplastic thyroid carcinoma (ATC) categories in the 2022 WHO classification [8].

Another subtype, the differentiated high-grade thyroid carcinoma (DHGTC) was included in the 5th WHO (2022 WHO classification), reflecting the histology of increased mitoses or tumor necrosis of MSKCC criteria. PDTC accounts for a small portion of thyroid carcinomas but contributes to a significant proportion of thyroid carcinoma-associated deaths [9]. Reports on PDTC are rare, owing to its rare occurrence [2]. Moreover, the pathological criteria used in these studies were heterogeneous, and the clinical outcomes and prognoses are inconsistent. Therefore, the established clinical presentations, clinicopathological prognostic factors, and clinical outcomes of PDTC remain unclear. This knowledge can help in establishing a treatment strategy and improving the survival of the patients.

Herein, we performed a comprehensive systematic review and meta-analysis of published studies to clarify the treatment outcomes, 5-year disease-free survival (DFS), and overall survival (OS) of patients with PDTC after curative treatment.

METHODS

This systematic review was performed using structured search terms, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplemental Table S1) [10]. This review has been registered in the International Prospective Register of Systematic Reviews (CRD42022342531).

Search strategy

On September 4, 2023 a comprehensive computerized literature search of three databases (Embase, PubMed, and the Cochrane Library) was performed to identify relevant studies without time period limitations. Literature searches were conducted by an expert librarian. The following search terms were used: ('thyroid cancer' or 'thyroid carcinoma') AND ('poorly differentiated', 'insular', 'high-grade', 'high grade', 'non-anaplastic' or 'non anaplastic'), AND ('thyroidectomy' or 'surgery' or 'operation') AND ('outcome', 'prognoses', 'recurrence', 'progression', 'relapse', 'progression', 'mortality' or 'survival'). An additional manual search of the reference lists of the related articles was performed (Supplemental Table S2).

Inclusion and exclusion criteria

Studies were included only if they met the following criteria: (1) patients with newly diagnosed and histologically confirmed PDTC; (2) patients who underwent thyroidectomy; (3) reported 5-year DFS or OS; and (4) definite PDTC histological criteria of 3rd WHO, MSKCC, Turin histological criteria/4th WHO and 5th WHO classification. Searches included English language publications with all types of articles including grey literature and human studies. Non-electronic sources were not searched.

The exclusion criteria were as follows: (1) studies irrelevant to our research questions; (2) studies from which data for analysis (DFS or OS) could not be extracted; (3) studies with a short follow-up period (median follow-up <3 years); (4) studies such as review articles, conference papers, or letters that did not contain original data; (5) patients aged <18 years; (6) studies with <10 patients; (7) studies with no definite histological criteria to diagnosis; (8) old criteria including PDTC diagnostic criteria prior to the 3rd WHO criteria; and (9) studies from Surveillance, Epidemiology, and End Results (SEER) Program or National Cancer Database (NCDB).

In this study, old criteria of PDTC included 2nd WHO classification, criteria of Carcangiu et al. [11], criteria of Sakamoto et al. [3], a solid, trabecular or insular growth pattern, insular carcinoma, well-differentiated thyroid carcinoma (DTC) with component of poorly differentiated or insular carcinoma etc. Studies obtained from SEER or NCDB were excluded to avoid data overlap from individual hospital studies. If a patient group was diagnosed by multiple histological criteria in the same publication, patients diagnosed by the most recent diagnostic criteria were included to avoid duplication of patients. In studies using the same patient population enrolled at the overlapped time, only a representative study was included in the meta-analysis to avoid data duplication. Even if patients with recurrent disease or those untreated were included, the study was only included if the number of patients was small enough (approximately 10%).

Data extraction

Three authors (J.Y.K., S.K., and S.J.L.) independently performed

full-text assessments to determine the eligibility of the articles and independently extracted data from each article and recorded the data in a standard form. Subsequently, all eligible and extracted data were discussed and disagreements were resolved with a pathologist author (J.K.M.). The following data were extracted: (1) first author name, country, publication year, research design (prospective or retrospective), and study period; (2) number of included patients, patient age, sex, cancer stage, and cancer staging system (American Joint Committee on Cancer [AJCC] or Union for International Cancer Control [UICC]) at the time of diagnosis; (3) pathological criteria, tumor size, extrathyroidal extension (ETE), distant metastasis, and radioactive iodine therapy (RAI); (4) outcomes (DFS, recurrence-free survival [RFS], distant RFS [DRFS], distant metastasis-free survival [DMFS], progression-free survival [PFS], OS, cause-specific survival [CSS], and disease-specific survival [DSS]); and (5) prognostic factors for each outcome.

If the data were shown as Kaplan-Meier curve only, we extracted the data using the Engauge Digitizer software version 10.4 (http://markummitchell.github.io/engauge-digitizer/).

Risk of bias and quality assessments

Funnel plots were created to assess possible publication bias for the proportions of DFS and OS. The trim-and-fill method was used to correct funnel plot asymmetry due to publication bias. Quality assessment was performed by two authors (J.Y.K. and S.J.L.) using the Quality in Prognostic Studies (QUIPS) tool for prognostic studies [12], which considers the following domains: (1) study participation; (2) study attrition; (3) prognostic factor measurement; (4) outcome measurement; (5) study confounding; and (6) statistical analysis and reporting. The risk of bias was categorized as low, moderate, or high for each domain. Discrepancies were resolved by consensus (Supplemental Table S3).

Statistical analysis

The primary endpoints were DFS and OS. DFS was defined as the time of remission until relapse, disease progression, death, or last follow-up. OS was defined from the time of treatment start until death or last follow-up. We included DFS, RFS, DRFS, and PFS in the definition of the overall 5-year DFS. We included OS, DSS, and CSS in the definition of the overall 5-year OS.

All analyses were performed using the R software version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). The packages used for the analysis were 'meta,' 'metafor,' and 'tidyverse' [13-15]. A random-effects model was used to estimate the proportion changes in DFS and OS in patients with PDTC. Heterogeneity between studies was assessed using the I^2 statistic, which describes the percentage of overall variance due to inter-study heterogeneity. Heterogeneity was considered to be low when I^2 <40%, moderate when 40≤ I^2 <60% and high when I^2 ≥60%. In cases of high heterogeneity, sensitivity tests or subgroup analyses were conducted to determine whether the heterogeneity could be attributed to individual studies and to assess the consistency of the results. Forest plots were generated using the clinical outcomes of 5-year DFS and 5-year OS. Meta-regression analysis was used to understand the high heterogeneity of meta-analysis of survival outcomes and evaluate the prognostic factors. If any prognostic factor is discussed in more than 10 studies, meta-regression was performed.

RESULTS

Study selection and characteristics

In all, 681 studies from 1973 to 2023 were screened after removing duplicates (Fig. 1). Based on the titles and abstracts, 129 studies were considered potentially relevant and evaluated further. When the full-text review was completed, 40 studies remained, and 89 studies were excluded based on the eligibility criteria. Of the 40 studies, fourteen were excluded because of duplication of patients, and six studies had a short-term median follow-up of less than 3 years (Supplemental Table S4). The remaining 20 studies with 1,294 patients with PDTC were included in this meta-analysis. The characteristics of the included studies are summarized in Table 1 [16-35].

All included studies were retrospective observational studies. PDTC was diagnosed according to various histological criteria, summarized in Table 2. Twelve studies diagnosed PDTC based on the Turin histological criteria/4th WHO, five based on the 3rd WHO criteria, one based on the MSKCC, and two based on the 5th WHO criteria.

The median size of the tumor ranged from 3.0 to 7.1 cm, and distant metastases ranged from 0% to 76.7%. One study [27] involved patients without distant metastases. The patients underwent surgical resection and were treated from 29% to 100% with postoperative RAI therapy. Bichoo et al. [28] included two cases of recurrent disease among 27 patients. Lee et al. [22] included four patients without any treatment among 38 patients. Ito et al. [26] reported 10-year outcomes without 5-year outcomes; therefore, 5-year data was extracted from the Kaplan-Meier curve.

Qualitative analysis using the QUIPS tool shows that not all

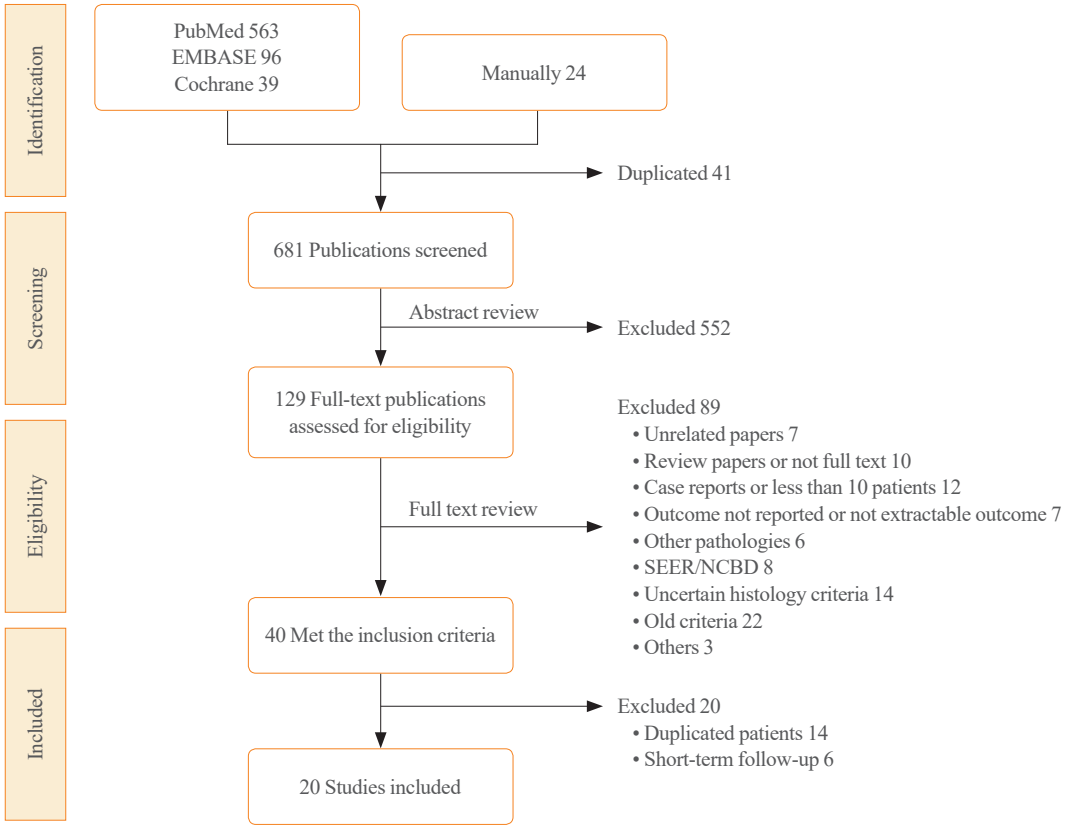

Fig. 1. Flow diagram of study selection. SEER, Surveillance, Epidemiology, and End Results; NCDB, National Cancer Database.

studies have been conducted strictly. The domains showing the greatest potential risk of bias were study attribution and study confounding.

Meta-analysis results

Twenty studies with 1,294 patients reported OS and 11 studies with 758 patients reported DFS. The 5-year DFS and OS of patients with PDTC were 49.4% (95% confidence interval [CI], 42.3 to 56.4) and 73.8% (95% CI, 66.5 to 79.9), respectively (Fig. 2). There were substantial levels of heterogeneity, I^2=58% and I^2=55%, respectively.

DFS and OS were determined using subgroup analysis according to PDTC histological criteria (Fig. 3). DFS was analyzed by classifying the studies into three groups, 3rd WHO (n=2), Turin (n=9) and DHGTC of 5th WHO (n=2). The DFS was 34.0% (95% CI, 1.3 to 95.3) for 3rd WHO, 49.8% (95% CI, 41.5 to 58.0) for Turin, and 53.9% (95% CI, 14.8 to 88.8) for DHGTC groups (Fig. 3A).

For OS, subgroup analysis was conducted by classifying the studies into 3rd WHO (n=5), MSKCC (n=1), Turin (n=14), and DHGTC of 5th WHO (n=2). Each OS was 63.0% (95% CI, 47.8 to 76.0) for 3rd WHO, 76.1% (95% CI, 66.6 to 83.6) for Turin, and 91.0% (95% CI, 0.0 to 1.00) for DHGTC groups.

In DFS and OS meta-analysis, sensitivity analysis was carried out with the successive omission of each study. The leaving-one-out study revealed that no study altered the pooled results significantly (Supplemental Table S5). For OS, the exclusion of the study by Bichoo et al. [28] resulted in reduced heterogeneity without significant change of OS (overall OS, 73.8% [95% CI, 66.5% to 79.9%; I^2=55%] to OS, 74.6% [95% CI, 68.2% to 0.1%; I^2=42%]).

Supplemental Fig. S1 shows the funnel plots of the meta-analysis in Fig. 2 after applying the trim-and-fill method. The plot of DFS was roughly symmetrical, but that of OS was asymmetrical indicating publication bias. When the trim-and-fill method was applied, five missing studies were added for OS, reducing OS from 73.8% (95% CI, 66.5% to 79.9%) to 68.0% (95% CI, 60.5% to 74.6%).

Table 3 shows the included studies' prognostic factors. Age, sex, tumor size, ETE, distant metastasis, and RAI therapy are well known to be associated with poor prognosis in patients with differentiated thyroid cancer. Including these factors, 41

Table 1. Characteristics of Included Studies for Poorly Differentiated Thyroid Carcinomas Diagnosed according to Turin Histological Criteria

Study characteristic			Patient characteristics				Pathology						Outcome	
Study	Country	Year	Study period, yr	No. of patients (men %)	Median age, yr	Stage (*n*)	AJCC/ UICC	Pathology criteria	Median size of tumor, cm	ETE, *n* (%)	Distant metastasis, *n* (%)	RAI, *n* (%)	Median follow-up, mo	5-Year outcome
Lin et al. [16]	Taiwan	2007	1978–2005	67 (35.8)	50.3	Stage I/II–IV (21/46)	UICC 6th	3rd WHO	4.2	NA	NA	45 (67.2)	70.8	OS 67%
Jung et al. [17]	South Korea	2007	1990–2004	49 (26.5)	49.3	Stage I/II/III/IV (16/3/15/15)	TNM[a]	3rd WHO	4.7	29 (59)	16 (33)	38 (78)	46	OS 68%
Asioli et al. [18]	USA, Italy	2010	1955–2008	152 (38.2)	61.4	NA	NA	Turin	5.9	NA	38.2	48.7	NA	OS 71.6%
Bhargav et al. [19]	India	2010	1989–2002	24 (41.7)	54	Tx/T1/T2/T3/T4 (%) (8.3/0/25/25/41.7)	AJCC 6th	3rd WHO	5.0	17 (71)	6 (25)	NA	43	DFS 25% OS 50%
Hod et al. [20]	Israel	2013	1992–2009	17 (58.8)	63	NA	NA	3rd WHO	3.7	9 (52.9)	4 (23.5)	17 (100)	84	OS 83%
Gnemmi et al. [21]	France	2014	2000–2010	46 (43)	55.5	I/II/III/IV (7/10/17/12)	AJCC	Turin	5.0	NA	NA	NA	68	DRFS 59.24% CSS 73.3%
Lee et al. [22]	South Korea	2016	1985–2013	38 (31.6)	51.7	Resectable tumor (32); T4b (5); M1 (3)	TNM	Turin	3.5	NA	3 (7.9)	14 (36.8)	51.5	DSS 65.8%
Skansing et al. [23]	Denmark	2017	1970–1992	66 (NA)	NA	NA	UICC 4th	MSKCC	NA	NA	NA	NA	28 years	DSS 71%
Yu et al. [24]	Philippines	2017	2006–2015	18 (27.8)	62	Stage I/II/III/IVa/IVb/ IVc (1/1/5/6/1/4)	TNM	Turin	5.8	8 (44.4)	5 (27.8)	8 (44.4)	60	DFS 50.0% OS 83.3%
de la Fouchardiere et al. [25]	France	2018	2000–2010	104 (38.5)	62	pT1/T2/T3/T4/Tx (3/27/58/13/3); pN0/ N1/Nx (27/22/55)	AJCC 7th	Turin	NA	40 (40.0)	28 (26.9)	99 (95.2)	59.3	RFS 45.3% OS 72.8%
Ito et al. [26]	Japan	2018	1984–2004	31 (NA)	NA	Stage I/II/III/IV (12/7/16/8)	AJCC 7th	Turin	NA	NA	NA	NA	167	CSS 77.1%[b]
Nunes da Silva et al. [27]	Portugal	2018	1986–2010	38 (36.8)	NA	T1–T3/T4 (20/18); N0/ N1 (22/16); All M0	AJCC 7th	Turin	NA	24 (63.2)	0	38 (100)	88.2	RFS 63.2% DSS 76.3%
Bichoo et al. [28]	India	2019	1989–2016	27 (18.5)	50.1	Stage I/II/ III/IVb (11/ 10/4/2)	AJCC 8th	Turin	7.1	16 (59.0)	10 (37.0)	20 (74.0)	47.5	RFS 34% OS 36%
Akaishi et al. [29]	Japan	2019	2006–2017	30 (33.3)	62	NA	AJCC 8th	Turin	5.3	10 (33.3)	23 (76.7)	25 (89.0)	63	DFS 44% CSS 97%
Wong et al. [30]	USA	2019	2005–2018	47 (40.0)	57	pT1a/T1b/T2/T3a/T3b/ T4a/T4b (1/2/16/21/1/4/2)	AJCC 8th	Turin	4.3	16 (34.0)	8 (19.0)	62	76.8	DFS 50% DSS 89%
Kersting et al. [31]	Germany	2021	2007–2020	51 (45.1)	58.5	Stage I/II/III/IV (12/3/8/28)	AJCC 7th	Turin	NA	28 (54.9)	22 (43.1)	47 (92.2)	61.1	OS 58.8%
Panchangam et al. [32]	India	2022	2009–2018	29 (37.9)	54	Stage I/II/III/IV (%) (10/19/23/48)	AJCC 6th	3rd WHO	4.9	21 (73.0)	12 (41.0)	8 (29.0)	37	RFS 42% OS 44%
Xu et al. [33]	USA	2022	1981–2020	200 (47.5)	59	pT1/T2/T3/T4 (22/51/102/24); pN0-pNx/pN1a-pN1b (164/36)	AJCC 8th	5th WHO (Turin)	4.7	150 (79.8)	53 (27.9)	150 (78.5)	61.2	DMFS 40%, DSS 68%

(Continued to the next page)

Table 1. Continued

Study characteristic			Patient characteristics				Pathology						Outcome	
Study	Country	Year	Study period, yr	No. of patients (men %)	Median age, yr	Stage (*n*)	AJCC/ UICC	Pathology criteria	Median size of tumor, cm	ETE, *n* (%)	Distant metastasis, *n* (%)	RAI, *n* (%)	Median follow-up, mo	5-Year outcome
				164 (37.2)	55	pT1/T2/T3/T4 (37/49/53/24); pN0-pNx/pN1a-pN1b (82/82)	AJCC 8th	5th WHO (DHGTC)	3.0	114 (75.0)	31 (19.9)	121 (77.6)	64.8	DMFS 52%, DSS 70%
Gubbiotti et al. [34]	USA	2023	2007–2022	65 (44.6)	55.8	NA	AJCC	Turin	5.2	31 (47.7)	19 (29.2)	33 (50.8)	96	CSS 81.5%
Jeong et al. [35]	South Korea	2023	~2021	22 (54.5)	NA	Stage I/II–IV (11/11)	AJCC 8th	5th WHO (Turin)	NA	3 (13.6)	6 (27.3)	NA	NA	DFS 68.2% CSS 100%
				14 (28.6)	NA	Stage I/II–IV (8/6)	AJCC 8th	5th WHO (DHGTC)	3.3	8 (57.1)	2 (14.3)	NA	NA	DFS 78.6% CSS 100%

AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; ETE, extrathyroidal extension; RAI, radioactive iodine; WHO, World Health Organization; NA, not applicable; OS, overall survival; TNM, tumor, node, metastasis; DFS, disease free survival; DRFS, distant recurrence-free survival; CSS, cause specific survival; DSS, disease specific survival; MSKCC, Memorial Sloan Kettering Cancer Center; RFS, recurrence free survival; DMFS, distant metastasis-free survival; DHGTC, high-grade thyroid carcinomas.
[a]TNM classification of malignant tumors at the time of diagnosis; [b]Extraction from the Kaplan-Meier curve.

Table 2. Histological Criteria of Poorly Differentiated Thyroid Carcinoma

Classification (published year)	Definition
3rd WHO (2004) [6]	Identification of solid, trabecular or insular patterns with an infiltrative pattern of growth, necrosis, and obvious vascular invasion
MSKCC (2006) [7]	Presence of ≥5 mitoses per 10 high-power microscopic fields (×400) and/or fresh tumor necrosis in thyroid carcinoma
Turin (2007) [8], 4th WHO (2017) [9]	(1) A solid, trabecular or insular pattern of growth (2) Absence of conventional nuclear features of papillary carcinoma (3) presence of at least one of the following features: conventional nuclei, mitotic activity (≥3×10 HPF), necrosis
5th WHO (2022) [10]	Differentiated high-grade thyroid carcinoma (1) A papillary, follicular or solid[a] of growth (2) One of the following two features: mitotic count ≥5/2 mm^2 or tumor necrosis Poorly differentiated thyroid carcinoma Diagnostic criteria of 4th WHO

WHO, World Health Organization; MSKCC, Memorial Sloan Kettering Cancer Center; HPF, high-power field.
[a]Tumors with solid growth and papillary thyroid carcinoma nuclear features are classified as differentiated high-grade thyroid carcinoma.

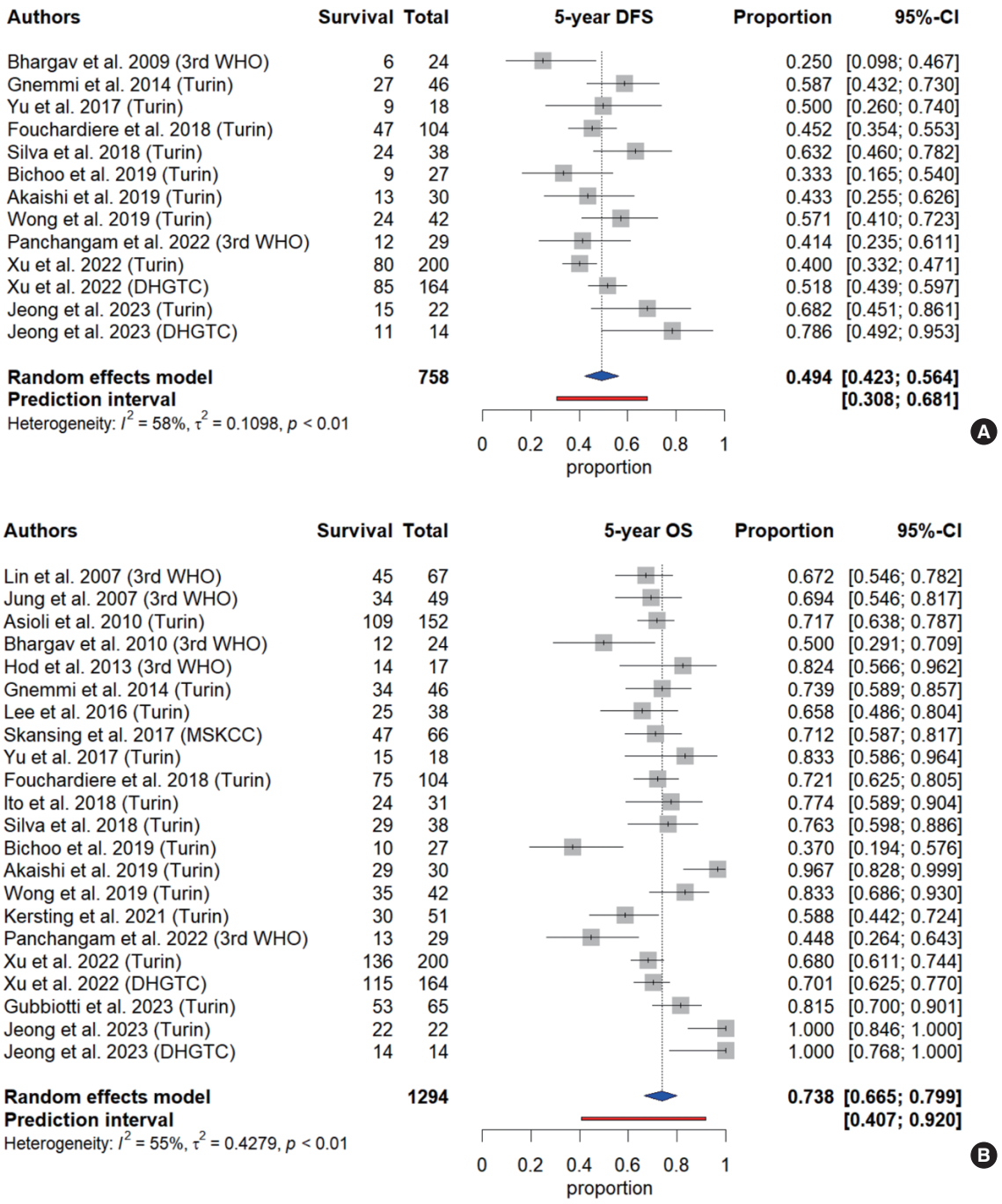

Fig. 2. Forest plots of the proportion for treatment outcomes in patients with poorly differentiated thyroid carcinoma: (A) 5-year disease-free survival (DFS) and (B) 5-year overall survival (OS). The squares represent the proportion of each study and their size represents the weight of the study in the meta-analysis. The horizontal lines crossing the squares represent the 95% confidence interval (CI). WHO, World Health Organization; MSKCC, Memorial Sloan Kettering Cancer Center; DHGTC, differentiated high-grade thyroid carcinoma.

factors were discussed for OS and 35 factors were discussed for DFS (Supplemental Table S6).

Age (seven out of seven), tumor size (four out of seven), ETE (three out of four), nodal status (three out of four), cancer stage (three out of four), resection margin (two out of three), and RAI therapy (two out of three) were frequently analyzed in the included studies and were suggested as potential predictive factors for OS in over 50% of analyzed studies. Age (two out of

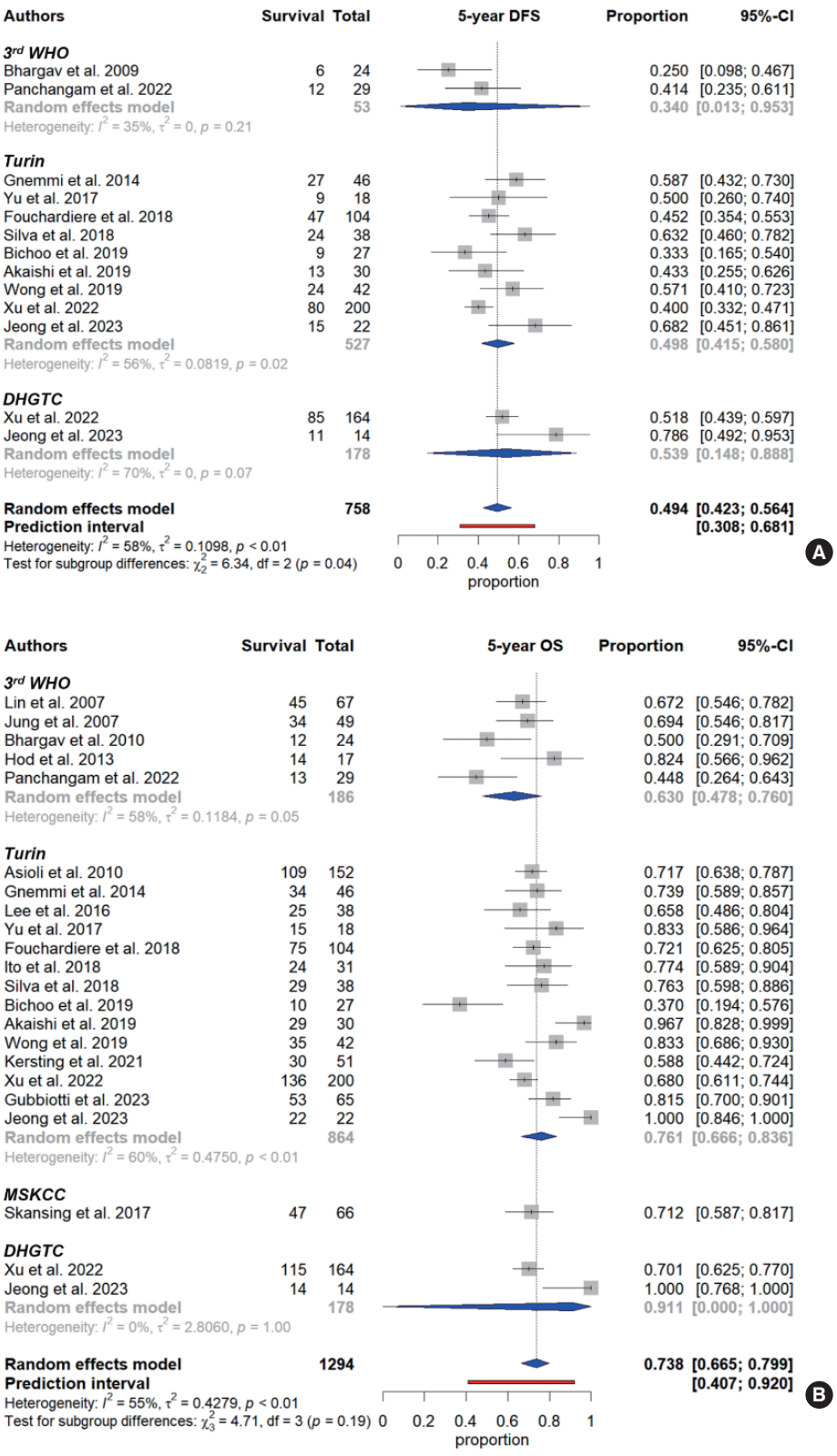

Fig. 3. Forest plots of the subgroup analysis for treatment outcomes in patients with poorly differentiated thyroid carcinoma (PDTC) according to PDTC histology criteria: (A) 5-year disease-free survival (DFS) and (B) 5-year overall survival (OS). CI, confidence interval; WHO, World Health Organization; DHGTC, differentiated high-grade thyroid carcinoma; MSKCC, Memorial Sloan Kettering Cancer Center.

four), tumor size (two out of four), ETE (two out of three), and vascular invasion (three out of four) were prognostic factors for DFS in several studies. Sex was the most frequently studied factor in both OS and DFS; however, it had a poor correlation with prognosis.

Meta-regression analyses were conducted in both DFS and OS to assess the potential prognostic factors. In Table 4, age, sex, tumor size, ETE, distant metastasis, and RAI therapy were tested. Of these, ETE and age had a statistically significant effect on OS. There was no significant prognostic factors affecting DFS.

DISCUSSION

In this meta-analysis, the 5-year DFS and OS in PDTC patients were 49.4% and 73.8%, respectively. According to the 2022 WHO classification (5th edition) [8], PDTC exhibits morphological as well as biological characteristics that lie between well-DTC and undifferentiated ATC [8,36], for instance, the 5-year DSS in patients with PDTC (51%) was between that in patients with DTC (91%) and those with ATC (0%) [33].

Although PDTC is relatively rare, its incidence in thyroid cancer varies. Yu et al. [24] reported an incidence of 0.23% to 2.6% in the Philippines while up to 15% of thyroid cancer patients have been reported in Northern Italy [2]. One of the included studies [18] reported different prevalence of 1.8% (56/3,128) and 6.7% (96/1,442) in the USA and Italy, respectively, when applying Turin histological criteria. This might be attributed to differences in environmental factors and histopathological interpretations. Most studies have reported a female predominance among the patients. In the studies included in this meta-analysis, the median age at PDTC diagnosis was 50s to 60s.

PDTC has been diagnosed using different pathological criteria, leading to inconsistent treatment strategies and a broad spectrum of prognoses. In this study, meta-regression analysis showed that age and ETE were significant factors affecting OS regardless of histological criteria (Table 4).

ETE was the significant factor in two out of three studies of DFS and three out of four studies of OS (Table 3). It cannot be distinguished whether gross or microscopic ETE is associated with prognosis, as most of the included studies did not differentiate between gross and micro ETE. Ibrahimpasic et al. [37] showed that the removal of all diseases in patients with PDTC presenting gross ETE (pT4) minimizes the risk of local recurrence.

Among the multiple prognostic factors, patient age at diagnosis was a potential predictor of OS (Table 3). Seven of seven studies reported that patient age was significantly associated with poor OS at ≥45 or ≥55 years, i.e., relatively older ages at diagnosis. Contrary to expectations, the meta-regression analysis of Table 4 actually showed that older age was a good prognostic factor with a weak positive correlation coefficient of 0.047. We

Table 3. Prognostic Factors Used in Meta-Regression Analysis

Prognostic factors	Number[a]/significant[b]	
	OS	DFS
Age	7/7	4/2
Sex	7/1	4/1
Tumor size	7/4	4/2
Extrathyroidal extension	4/3	3/2
Distant metastasis	2/1	1/0
RAI therapy	3/2	1/1

OS, overall survival; DFS, disease free survival; RAI, radioactive iodine.
[a]The total number of enrolled studies discussing prognostic factors; [b]The number of studies evaluated as significant prognostic factors among enrolled studies.

Table 4. Meta-Regression Analysis for Survival in Patients with Poorly Differentiated Thyroid Carcinoma

Moderators	DFS			OS		
	Coefficient	*P* value	95% CI	Coefficient	*P* value	95% CI
Age	0.012	0.742	–0.067 to 0.090	0.047	0.018[a]	0.009 to 0.085
Sex	0.011	0.479	–0.023 to 0.045	0.032	0.139	–0.011 to 0.076
Tumor size	–0.221	0.092	–0.487 to 0.045	–0.241	0.221	–0.645 to 0.162
ETE	–0.010	0.155	–0.024 to 0.004	–0.042	0.006[a]	–0.070 to –0.014
Distant metastasis	–0.014	0.082	–0.029 to 0.002	0.004	0.815	–0.028 to 0.034
RAI therapy	0.005	0.467	–0.009 to 0.018	0.006	0.395	–0.009 to 0.022

DFS, disease-free survival; OS, overall survival; CI, confidence interval; ETE, extrathyroidal extension; RAI, radioactive iodine.
[a]Statistically significant results.

considered that this result may be an error caused by using the median age instead of the ratio of older age and younger age as input data.

In this study, the median tumor size ranged from 3.0 to 7.1 cm (Table 1). The OS and DFS of patients with the smallest median tumor size of 3.0 cm were 52% and 70%, respectively, and those with the largest median tumor size of 7.1 cm were 36% and 34%, respectively [28,33]. Among studies involving Turin histology criteria, the group with the largest median tumor size of 7.1 cm had the worst OS prognosis.

In 16 of 20 studies, the rate of distant metastasis in patients with PDTC varied from 0% to 76.7%. The remaining four studies did not describe distant metastases in detail (Table 1). Nunes da Silva et al. [27] included patients with PDTC without distant metastases. The most common site of distant metastasis is the bone and lungs [19,38].

In this meta-analysis, many other factors have been proposed as potential prognostic factors for OS and DFS; however, they were insufficient to assess their meaning since these were studied only in a few studies. These results could be attributed to the diversity in the histological classification of PDTC and the lack of established treatment guidelines for PDTC, resulting in the use of various treatments.

Recently, a new entity, "high-grade follicular cell-derived non-anaplastic thyroid carcinoma" was introduced in the 2022 WHO classification [8]. This entity has two histological subtypes, PDTC and DHGTC. The histologic criteria to diagnose PDTC and DHGTC differently depends on the presence of the distinctive architectural and/or cytologic properties of well-differentiated histotypes of well-differentiated carcinomas of follicular cell derivation. MSKCC histologic criteria (2006) in Table 2 include these two histologic subtypes. In this meta-analysis, one study with MSKCC diagnostic criteria by Skansing et al. [23] was included. Xu et al. [33] and Jeong et al. [35] reported each survival in patients with DHGTC and PDTC Turin histology criteria, therefore we included patients with two subtypes for meta-analysis.

We analyzed differences in outcomes according to histological criteria. The patients with PDTC Turin criteria obtained from nine studies was 49.8% for DFS. It has limitation to compare with DFS of other histological criteria of 3rd WHO or DHGTC (only two studies each). The OS of patients with PDTC Turin criteria of 14 studies was 76.1% (95% CI, 66.6% to 83.6%) and the OS of patients with 3rd WHO criteria of five studies was 63.3% (95% CI, 47.8% to 76.0%). There was no difference OS between two histological types. In OS analysis, the MSKCC and DHGTC criteria could not be compared with the other two criteria due to one and two studies, respectively. The DHGTC defined in the 5th edition of the WHO is considerably similar to the MSKCC diagnostic criteria (Table 2). If OS is evaluated for patients diagnosed with DHGTC criteria or with MSKCC criteria, the 5-year OS of 244 patients in the three studies is 72.1% (95% CI, 66.2% to 77.4%).

The treatment strategies for PDTC have not yet been standardized. Patients underwent surgery, followed by various therapies, including RAI therapy, external beam radiotherapy, chemotherapy, and tyrosine kinase inhibitors. Surgical resection is the mainstay treatment for PDTC [39]; however, postoperative RAI therapy and radiotherapy are debatable.

Additional RAI or external beam radiotherapy was performed postoperatively, and sometimes both. Lee et al. [22] reported that adjuvant treatment, radiotherapy, or RAI therapy postoperatively increased DSS, although this was not statistically significant. In this study, postoperative adjuvant therapy was administered based on each patient's status and decision, without guidelines for selecting radiotherapy or RAI therapy. The authors considered the results to be inconclusive considering the small number of patients [40].

In a study by Ibrahimpasic et al. [41], postoperative radiotherapy was administered alone or in combination with RAI in patients with gross residual disease and positive microscopic margins. This limits the ability to completely assess the impact of RAI on prognosis.

In one of the included studies, de la Fouchardiere et al. [25] reported that the tumor genotype of the telomerase reverse transcriptase promoter mutation was correlated with RAI resistance, although it was not an independent prognostic factor. Moreover, the use of postoperative external beam radiation and the role of chemotherapy in PDTCs remains controversial. BRAF and TP53 are associated with the dedifferentiation progress to ATC, and gene variants of TP53 have been observed in some PDTCs. However, there was no difference in clinical features according to these genetic alterations [42].

Serum thyroglobulin (Tg) levels may have a prognostic role after initial surgical resection and subsequent RAI therapy in PDTC. Tg levels in PDTC without distant metastasis after the initial treatment had a predictive value similar to that in patients with differentiated thyroid cancer [27,43]. Detectable Tg levels showed a more aggressive disease with a higher nodal and metastatic recurrence rate, leading to a reduced OS.

Our study had several limitations. First, only a few studies were included owing to the rarity and heterogeneity of PDTC.

Second, it has a retrospective nature of initial primary data extraction. Third, the pathological heterogeneity and treatment diversity make comparing studies challenging. Thus, there was substantial heterogeneity in the assessment of 5-year DFS and OS in patients with PDTC. Unlike in DTC, patients are treated with various therapies, including surgery, RAI therapy, external beam radiotherapy, chemotherapy, and tyrosine kinase inhibitors. Therefore, it was difficult to evaluate surgery- or RAI therapy-related prognoses in this analysis. Moreover, it is not possible to assess survival outcomes according to the cohort time. The effect of cohort time should be evaluated under the same histological criteria. Subgroup analysis of OS included five studies by 3rd WHO, and 14 studies by Turin criteria. The range of publication years for each study is as follows, 2007 to 2022 for 3rd WHO, and 2010 to 2023 for Turin criteria. Within studies with the same histological criterion, there was no significant difference across cohort time as shown in Fig 3B. Finally, only two studies of new entity of DHGTC were enrolled in this meta-analysis for prognosis. More studies need to be accumulated to evaluate the survival of DHGTC criteria.

In conclusion, the meta-analysis of DFS and OS in patients with PDTC show the moderate degree of heterogeneity despite enrolling studies with a variety of histological criteria from 3rd WHO, 4th WHO, 5th WHO, and MSKCC. Subgroup analysis and sensitivity analysis showed relatively stable outcomes. ETE was a prognostic factor for OS from meta-regression analysis.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: S.J.L. Acquisition, analysis, or interpretation of data: J.K.M., S.K., Y.Y.C., S.J.L. Drafting the work or revising: J.Y.K., J.K.M., S.K., K.T., Y.Y.C., S.J.L. Final approval of the manuscript: J.Y.K., S.J.L.

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