Quest Journals
Journal of Medical and Dental Science Research
Volume 9~ Issue 6 (2022) pp: 20-26
ISSN(Online) : 2394-076X ISSN (Print):2394-0751
www.questjournals.org

Research Paper

Prognostic impact of Focal poorly differentiated areas in follicular differentiated thyroid cancer: Is it a distinct entity from poorly differentiated thyroid cancer?

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Abstract
Background
Poorly differentiated thyroid cancer (PDC) and especially poorly differentiated areas (PDA) within follicular cell derived differentiated thyroid cancer are ill-defined clinico-pathological entities. We report our experience with special emphasis on their comparative prognostic outcomes
Material and methods
This is a retrospective study of a prospectively accumulated data on 61 patients (PDC = 29; PDA = 32) operated in our Endocrine and Metabolic Surgery department (2009 to 2017). Clinical and follow up details are collected and digitally tabulated from departmental database. Only cases with predominant histopathology of PDC (solid, trabecular and insular variants) and PDA (papillary and follicular cancer with focal areas of poorly differentiation were included. Descriptive statistics and survival analysis were performed with IBM SPSS software.
Results
Gender ratio was M:F = 1:1.3 and 1:1.6. Mean age was 51 ± 12 years (16 – 76); 54 ± 10.5 years (36 – 81) in PDA and PDC respectively. Mean tumour size (4.6 ±0.9 cm; 4.9 ± 1.2 cm), extrathyroidal invasion (59 %; 73 %) and regional lymphadenopathy was 50 %; 55% in PDA and PDC respectively. Total thyroidectomy was possible in 94% of PDA and in only 77% of PDC. Radio-iodine ablation was utilized in 65% (PDA); 29% (PDC).
With mean follow-up of 64 ± 23.5 months (12 – 103) in PDA and 37 ± 22 months (6 – 94) in PDC, nodal recurrence (PDC = 29%; PDA = 22 %) and systemic metastasis was 41% in PDC (synchronous = 24%; metachronous = 17%); 19% in PDA (synchronous = 16%; metachronous = 3%). Five year event free survival (EFS) and overall survival (OS) was 90% and 93% in PDA, 42% and 44% in PDC respectively. Among AMES and TNM variables, only metastases affected EFS (P value = <005) and none affected OS.
Conclusions
PDA was clinic-demographically comparable with PDC. But, PDA has better radio-iodine avidity and survival rates, thus distinguishing it as a separate clinic-pathological entity with significantly positive prognosis compared to PDC.
(***Key words***: *Poorly differentiated thyroid cancer; thyroglobulin; radioiodine; total thryroidectomy; recurrence*)

R*eceived 01 June, 2022;* ***R****evised 11 June, 2022;* ***A****ccepted 13 June, 2022 © The author(s) 2022.*
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I. Background

Ever since, the first description of poorly differentiated thyroid cancer (PDC) by Sakamoto, [1] it has been evolving as a distinct clinicopathological entity. The widely held hypothesis justified by available literature is that the prognosis of PDC is intermediate between follicular differentiated thyroid cancer (DTC) and anaplastic or undifferentiated thyroid cancer . [2-4] Debate over its pathological definition and management continues due to its rarity and lack of prospective clinical trials or studies. [5-7] Adding to this existing conundrum on PDC, is the pathological entity of poorly differentiated areas (PDA) interspersed within papillary thyroid cancer (PTC). Many case series and retrospective studies with varied inclusion criteria of poorly differentiated pathology within thyroid cancer have been reported Worldwide thus far. [8,9] With further evolution of this entity and increasing knowledge, questions about the prognostic significance of PDA within PTC and its placement

under clinicopathological entity of PDC have raised. There were attempts to further categorize PDA as a separate entity from PDC. [10-12] To address this raging issue, we analysed our own experience of PDC versus PDA with specific emphasis on comparative prognosis and characterization as separate clinicopathological entities.

II. Material And Methods

This is a retrospective study of a prospectively entered database spanning a period from 2009 to 2018. Out of 564 cases of thyroid cancer treated in our Endocrine surgery department, this study cohort included 76 cases with poorly differentiated pathology. Inclusion criteria was all thyroid cancer cases with histopathology of partial or florid poorly differentiated thyroid cancer (insular, trabecular, solid variants) either operated or diagnosed on trucut biospsy (in inoperable cases) with minimum follow up of 1 year. Exclusion criteria are medullary thyroid cancer, other biologically aggressive variants of PTC such as tall cell, columnar cell, oncocytic, diffuse sclerosing variants; cases operated elsewhere; those with incomplete records and lost to followup cases. Finally , the study group included 61 cases as 15 were excluded because of incomplete information or lost to followup. This study complied with the international ethical norms of the Helsinki Declaration — Ethical Principles for Medical Research Involving Human Subjects, 2004. [13] Informed consent was obtained from all the included members of the cohort.

Definitions and standards employed for this study

1) TNM staging of AJCC 6th edition was applied to stage all cases. [14]
2) AMES (Age, Metastasis, Extrathyroidal invasion, Tumour size) of Cady's risk grouping was used. [15]
3) WHO classification was used as a guide to define and classify pathological types. WHO definition of poorly differentitated thyroid cancer was employed. [16]
4) Synchronous distant metastases was defined as either clinically detected metastases within 6 months of surgery, confirmed by ultrasonography, computerized tomography or diagnosed on post radio-iodine ablation scan and metachronous metastases as detected after 6 months or at subsequent post radio-iodine scans.
5) Radio-iodine ablation was defined as "the destruction of residual, macroscopically normal thyroid tissue following surgical thyroidectomy.
6) Recurrence free survival was defined as period from day of surgery to earliest date of recurrence either at locoregional or distant sites.
7) Overall survival was defined as period between day of surgery and day of expiry of patient with or without recurrence.
8) Definition of Poorly differentiated areas within Papillary thyroid cancer (PTC) was presence any foci of solid, trabecular or insular (STI) pathology in trucut or postoperative specimen. This subtype was termed as PDA in our study.

Abbreviations used in this study

PDC = Poorly differentiated thyroid cancer; PDA = Poorly differentiated areas with DTC; DTC = follicular cell derived differentitated thyroid cancer; PTC = Papillary thyroid cancer; ETI = Extrathyroidal invasion; STI = Solid/ trabecular/ insular areas; PD areas/ foci = Poorly differentiated foci; EFS = Event free survival; OS = Overall survival

Treatment and follow-up strategy

It is our departmental protocol to subject the patients with thyroid cancer to total or near total thyroidectomy wherever feasible. Central compartment neck dissection is performed routinely and only therapeutic lateral neck dissection for radiological/ clinically detected/ intraoperatively detected/ suspicious but frozen positive nodes. We seek consultation for all patients with nuclear medicine department and diagnostic I-131 scan is done after 4-6 weeks (when serum TSH $\geq$ 30 mIU/L) of thyroxine deprivation postoperatively. If there is significant remnant or nodal uptake or distant metastasis, empirical therapeutic RAI dose is given (30 – 50 mCi for ablation, 90 – 120 for regional nodal uptake and 200 – 250 mCi for metastatic disease followed 4-7 days later by post ablative therapeutic scan. Our policy is to routinely administer first empirical therapeutic RAI dose irrespective of RAI uptake for all PDC/ PDA cases. Patient is started on suppressive thyroxine therapy with target TSH of < 0.3 mIU/L. it is repeated 6-9 months later after thyroxine withdrawal. RAI dose is preceded by serum thyroglobulin off thyroxine at target TSH of > 30 mIU/L. if there is scan detected disease with or without thyroglobulin > 10 ng/mL, radioiodine is administered in aforementioned doses. If no clinically detectable disease, scan is negative and thyroglobulin < 1 ng/mL, radioiodine was not administered. Since 2002, we added Positron emission tomography (PET) scan in to follow-up protocol of PDC as radioiodine uptake rates and sensitivity of thyroglobulin in predicting recurrence are low. PET scan is performed in all RAI negative cases irrespective of thyroglobulin level. We consider PET positive, radioiodine negative, thyroglobulin (low or high)

as recurrence and are considered for adjuvant radiotherapy or biological therapy or palliative chemotherapy. Follow-up is at 3 months, 6 months , `1 year and then yearly if there is no clinically and radiologically evident recurrence.

Treatment and follow up protocol are similar to DTC. No routine adjuvant external beam radiotherapy (EBRT) was administered as per department protocol. Operable/ resectable locoregional recurrences were operated and incompletely resected cases were given adjuvant EBRT. Resectable single or closely clustered distant metastasis were treated with metastatectomy. Palliative EBRT was given only to unresectable gross residual or recurrent disease.

Statistical analysis

Statistical analysis was performed using IBM SPSS software. Clinico-pathological variables, morbidity details were analysed with descriptive statistics, Student's t test. Recurrence free survival and overall survival rates as a outcome of PDC versus PDA were estimated by Kaplan-Meier product limit estimate method, comparisions made by Log rank test. Univariate and multivariate analysis were done using general linear model. P value of < 0.05 was taken as statistically significant probability cutoff.

III. Results

Mean follow up in PDA and PDC was 64 ± 23.5 months (12 – 103) in PDA and 37 ± 22 months (6 – 94) respectively. Mean age and gender ratio was 51 ± 12 years (16 – 76); M:F = 1:1.3 and 54 ± 10.5 years (36 – 81); 1:1.6 in PDA and PDC respectively. Total thyroidectomy was possible in 96% of PDA and in only 80% of PDC. No cases of permanent hypoparathyroidism or recurrent laryngeal nerve palsy were noted in postoperative period. Frequency distribution of various operative procedures is detailed in Table 1. Regional lymphadenopathy was seen was 50 %; 55% in PDA and PDC respectively. The number of subjects according to TNM group staging were 39%, 19%, 23% and 18% in PDA and 10%, 19%, 23% and 48% in PDC respectively. According to AMES risk stratification, 1.7:1 and 2.5:1 ratio of high risk versus low risk in PDA and PDC respectively.

Histopathology was defined by presence of any STI component seen focally in 32 cases of PDA and predominantly (> 10% area) in 29 cases of PDC. Mean tumour size (4.6 ±0.9 cm; 4.9 ± 1.2 cm), extrathyroidal invasion (59 %; 73 %) and Radio-iodine ablation was utilized in 65% (PDA); 29% (PDC). Adjuvant EBRT was used in five cases of PDC and two cases of PDA. One PDC receive chemotherapy. All these 7 cases except one PDA case expired till last follow-up. Table 2 shows Comparision of all clinic- pathological variables and staging parameters between PDA and PDC shows that age, sex ratio, tumour size, lymphadenopathy rate were statistically insignificant suggesting comparable biology and demography. But ETI rate, recurrence and mortality rates were statistically significant difference (< 0.05), suggestive of a aggressive tumour biology in PDC vis-a-vis PDA. Record of genetic analysis was available only in 3 cases. NRAS mutation was positive in two (PDC) and BRAF mutation was positive in one case (PDA).

Details of both recurrence free survival and overall survival based on TNM and AMES risk groups are shown in Table 3.

Nodal recurrence (PDC = 29%; PDA = 22 %) and systemic metastasis was 41% in PDC (synchronous = 24%; metachronous = 17%); 19% in PDA (synchronous = 16%; metachronous = 3%). Five year event free survival (EFS) and overall survival (OS) was 90% and 93% in PDA, 42% and 44% in PDC respectively. Among AMES and TNM variables, only metastases affected EFS (P value = < 0.05) and none affected OS. Univariate analysis and multivariate analysis on influence of various clinico- pathological factors on recurrence rates and cause specific survival rates of PDA versus PDC are detailed in Table 4. As shown, age of patient, presence of distant metastasis and tumour size but not ETI had statistically significant effect on overall survival and recurrence free survival. But on multivariate analysis only presence of metastases had statistically significant adverse effect on overall survival and recurrences. Finally, Table 5 shows the comparision of survival differences between our study and few other studies from literature.

IV. Discussion

PDC and especially PDA are ill defined clinic-pathological entities largely due to diverse definitions and rarity of disease leading to lack of consensus. Available literature and World wide experience establishes PDC as an intermediate prognostic entity between DTC and ATC. [2-4, 17] At one end of spectrum, DTC is a largely indolent disease and ATC is a rapidly fatal disease at other end of spectrum in terms of prognosis. This biology holds true irrespective of extent and modality of treatment given. But, reported prognosis oscillates within wide zone between that of DTC and ATC. This is partly due to wrong inclusion of either few biologically aggressive variants of DTC such as tall cell, columnar cell, oncocytic, diffuse sclerosing variants or undifferentiated ATC, which leads to erroneous prognostic results. Further, PDA within DTC is a more confusing entity due to lack of uniform pathological criteria. In this study, we specifically tried to address the

prognostic difference between PDC and PDA in based on our clinical experience and data. Further, we attempt to provide a stringent definition enroute establishing PDA and PDC as distinct clinic-pathological entities.

Ever since Sakamoto proposed the term poorly differentitated carcinoma for this entity in 1983, [1] there has been intense effort to arrive at consensus on definition, categorization, prognostication and treatment strategies between institutions from diverse geographies. Sakamoto used the definition of presence of solid, trabecular or scirrhous patterns in follicular origin thyroid cancer as PDC with prognosis intermediate between DTC and ATC. This seminal article was followed by other reports with various inclusion criteria and prognostic outcomes. [5-9] But the probable drawback of all these studies was inclusion of other high grade subtypes of DTC. This defining criteria for PDC was difficult to utilize as they were not objective and relatively vague. To obviate this shortcoming, World Health Organisation (WHO) in 2004 came up with a more objective definition of PDC - "follicular neoplasms that show limited evidence of structural follicular cell differentiation and occupy both morphologically and behaviorally an intermediate position between differentiated (follicular and papillary carcinomas) and undifferentiated (anaplastic) carcinomas." This classification was intended to place various definitions of PDC that have been circulating in literature and diagnostic pathology reports with protean overlapping features and interpretations. [16] This was also intended to place all follicular derived thyroid cancers with high grade features, but did not fit in to established high risk categories of DTC (tall cell, columnar cell, hurthle cell etc.,). Still, this definition was too broad and left scope for false inclusion of other subtypes of DTC. To further streamline this entity, a consensus meet was held at Turin in 2006, which gave a multi-tiered diagnostic algorithm for PDC – "any or all of STI features, absence of typical nuclear features of PTC, mitoses (≥3 mitoses per 10 hpf), convoluted nuclei, or necrosis". This stringent Turin criteria proved to be most widely accepted definition inspite of room for errors in case of encapsulated lesions with high grade features and extent of PD areas. [18] Though majority include STI as PD component, Nikiforov study shows that solid component should not be considered as PD pathology, but as a variant of DTC. Their experience suggests that solid pathology occurs primarily in children either as a result of radiation exposure or dietary iodine deficiency. [19] It rarely occurs in adults and appears to have similar prognosis of WDTC. But, this observation was not replicated by other reports. Encapsulated DTC with high grade features is a rarity. Thus, the only apparent chink in the armour of ideal definition of PDC appears to be extent of PD area. There have been attempts to give alternative definitions based on extent of PD areas. General rules for the Description of Thyroid cancer by Japanese society of thyroid surgery (JSTS) defines PDC as "cases having a poorly differentiated component, a lesion showing STI patterns, were separated from PTC and was an independent entity, even if only a slight amount of such a component is detected". [20] There was a comparative outcome study of PDC based on WHO and Sakamoto definitions. They reported that PDC (WHO) independently affected cause specific survival, but PDC (Sakamoto) did not. That study concluded that PDC based on Sakamoto definition cannot be separated as independent histology, but only useful in predicted carcinoma recurrence and thus PDC (Sakamoto) be considered as a subtype of DTC. [21,22] Another study also concluded that PDC (JSTS) should be defined as a subtype of DTC rather than as an independent entity. [20] To address this shortcoming of categorizing PDC based on extent of PD areas, we conceived this comparative outcome study between less than 10% versus more than 10% PD component PDC.

In the earlier studies, PDA was included in PDC with no distinction. [1,5] Very few studies reported that PDA should be considered as separate entity due to better prognosis. [10,12] Various studies have utilized diverse cutoff criteria ranging from presence of a tiny PD component (less than 10%) to more than 50 % PD areas within a thyroid cancer pathology to bifurcate PDC and PDA. [23,25] But, we opine that a large cutoff is a fallacious overestimate, as biologically any significant PD component in DTC may be tantamount to PDC and not PDA. We presume that lesser number of PDA cases versus PDC cases and inclusion of other high grade variants of DTC (tall cell, columnar cell, hurthle cell) might have resulted in statistically insignificant difference in many reports on PDC. We consider that a small focal area of PD within a predominant DTC pathology suffices to define PDA. Thus we used 10% cutoff albeit arbitrary criterion to differentiate between PDA (< 10%/ focal) and PDC (> 10 %/ predominant) it as PDA. First formal attempt of this distinction within PDC was reported by Nishida et al, [10] which used 10% cutoff and showed statistically significant difference in terms of outcome of PDC. This study showed statistically significant difference of 45% versus 30% relapses and 9.15 years versus 19.03 years mean survival period between PDC and PDA respectively. similar observation was replicated in our study results. But, the apparent drawback of Nishida study was inclusion of high risk DTC cases within less than 10% PD component cases. Another recent study using 10% cutoff of PD component showed the disease specific survival, metastasis free survival and relapse free survival rates of PDC was significantly lower than that of patients with WDTC. But, they included those with less than 10% PD component in DTC category. [20] On the contrary, we consider presence of any PD component with 10% cutoff to differentiate PDA from PDC. At the outset, this was the main inclusion criterion to define PDA apart from PDC and we also propose this new term PDA for any focal PD component less than 10% within DTC. As shown in Table 4, comparing prognostic outcomes of various studies with ours, only Nishida study matched closest to our

design and criteria. But, one striking difference between our study results from others except Nishida study is that survival rates in PDA and PDC are significantly different. It is apparent from Table 4, that the OS rate was lowest at 44% in our study compared to 65 – 85% in other reports. The apparent reason behind this wide difference is inclusion of supposedly PDA cases within PDC group leading to erroneously better survival rates in those studies. But, based on our results it is evident that survival rates are significantly better in PDA versus PDC, justifying their separation as distinct entities.

We opine that PDA is a distinct clinicopathological entity between DTC and PDC. Moreover as shown in our data, PDA appears to have intermediate prognosis between DTC and PDC, but having comparable clinicopathological variables with PDC. It is apparent that difference between variables such as age, gender ratio, lymphadenopathy rate was statistically insignificant, justifying congruity and comparability of PDA and PDC subjects on demographic basis. Moreover, significant difference in tumour size, ETI, metastases rate, survival rates between PDA and PDC shows that they are biologically different. Strengthening this speculation is also availability of few genetic studies suggestive of transition from DTC to PDC. They show increasing mutation rates of RAS gene, BRAF gene, RET-PTC, PPAR/PAX 8, WNT/ B catenin and occasional P53 gene. [18, 25-27] The difference in varied results and genetics could also be due to geographical, ethnic differences influencing tumour biology and etiopathogenesis. The marked influence of geography on biology was also seen in few studies, which was not replicated in reports from other countries. Our genetic data is not robust enough to opine on this aspect.

Tsumori showed that PDA at the site of tracheal invasion in ETI in > 50% of DTC. [28] But in our study, pathologically the sites of ETI was not always PD component. Even non PD areas of DTC could lead to ETI of trachea, muscle etc., in more than 16/31 (50%) of cases. Further, extent, depth and vascular invasion were lesser in PDA vis-a-vis PDC, enabling lesser debulking rates and better R_0 resection rates. We deliberately skipped elaborate details of this pathology in results, as it is felt that its outside the scope of this paper as the main focus is on prognosis and categorization of PDA.

Inspite of various surrogate markers such as age, ETI, genetic markers, PET, thyroglobulin and radioiodine avidity, we opine that the ultimate marker of prognostic outcome is tumour biology dictated by rapidity of growth, presence of distant metastasis and response to treatment. We speculate that comprehensive omics study (genomics, trascriptomics, proteomics, metabolomics) of tumour tissue correlated with prognostic outcome may in future help in predicting the phenotypes and tumour biology at clinical level in future.

Thus studying PDA seperately from PDC might help in better inter-institutional comparision of data, auditing, prognostication. Clear diagnosis based on stringent definition can also lead to lesser aggressive surgery, curative adjuvant RAI and follow-up protocols. The strengths of this study are clear distinction between PDA and PDC, comparision of various survival outcomes, first of its kind study from India. Inspite of these benefits, we concede that our data is plagued by usual problem with any thyroid cancer studies i.e., retrospective design, postoperative staging, shorter follow-up, no reliable preoperative prognostic markers necessitating individualized treatment on case to case basis. Thus we need larger studies with longer follow-up from widely different geographical areas.to establish and utilize our findings.

V. Conclusions

PDA has clinically comparable age, gender ratio, aggressive locoregional disease, metastatic rate with PDC. But, PDA has better radio-iodine avidity and survival rates, thus distinguishing it as a separate clinic-pathological entity with significantly positive prognosis compared to PDC.

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Table 1: Operative details

Surgical procedure	In PDA	In PDC
Thyroid surgery -		
Total thyroidectomy	30 (94%)	22 (77%)
Near total thyroidectomy	2 (6%)	3 (10%)
Debulking	-	4 (13%)
Surgery for lymphadenopathy		
CCLND	32 (100%)	25 (86%)
MRND alone	0	0
CCLND + unilateral MRND	4	5
CCLND + bilateral MRND	1	6
Mediastinal dissection *	2	8
None **	0	4
Other surgeries		
Tracheal resection	0	1
Window tracheal resection	0	2
Shave excision	2	6
Metastatectomy	1	3

* Percentage was not calculated for mediastinal level VI as they were found in addition to CCLN/ MRND
** Lymph node dissection was possible in 4 cases (PDC) in which only tumour debulking was done

Table 2: Comparative significance of clinicopathological and survival variables

Variable	**PDA**	**PDC**	**P value**
Age (in years)	51 ± 12	54 ± 10.5	0.114
Sex ratio (M:F)	1:1.3	1:1.6	0.621
Lymphadenopathy	50%	55%	0.807
Tumour size (in cm)	4.6 ±0.9	4.9 ± 1.2	0.09
ETI	59%	73%	0.03
Metastasis	14%	41%	0.009
Recurrence rate	25%	46%	0.02
5 year RFS	90%	42%	0.09
5 year OS	93%	44%	0.008

Table 3*: TNM and AMES wise Survival

Risk group	5 year RFS in PDA	5 year OS in PDA	5 year RFS in PDC	5 year OS in PDC
TNM				
< 55 years				
Stage I	100%	100%		88%
Stage II	96%	97%		42%
➢ 55 years				
Stage I	100%	100%	58%	62%
Stage II	96%	100%	45%	50%
Stage III	85%	89%	38%	45%
Stage IV	82%	90%	28%	34%
AMES				
Low risk	100%	100%	56%	60%
High risk	88%	90%	34%	40%
Overall 5 year survival	90%	93%	42%	44%

*This table shows the Recurrence free survival (RFS) and Overall survival (OS) rates depicted by Kaplan Meier/ Log rank curves in Figures 1

Table 4: Univariate and multivariate analysis of prognostic factors between PDA vs PDC

Variable	UVA	MVA
Age	0.03	0.08
Sex	0.912	0.756
Tumour size	0.01	0.09
ETI	0.07	0.988
Metastases	0.008	0.01
Lymphadenopathy	0.387	0.623

Table 5: Comparision between various studies in literature

Study group	N =	5 yr OS in PDA	5 yr OS in PDC	5 yr RFS in PDA	5 yr RFS in PDC
Our study	61	93%	44%	90%	42%
Nishida *	102	19.03 years	9.15 years	55%	70%
Lai HW**	82	-	72.2%	-	NM
Volante**	183	-	85%	-	NM
Wreesman**	12	-	70%	-	51%
Sakamoto**	35	-	65%	-	NM

OS = overall survival rate; RFS = relapse free survival rate; N = Number of subjects

*OS is mentioned as mean survival period in this study

** PDA statistics are not applicable as it was not mentioned as separate entity in these studies

*** NM = not mentioned in these studies