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RESEARCH

Risk characteristics of papillary thyroid cancer > 1–4 cm is associated with increased tumour size

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Abstract

Recent guidelines recommend total thyroidectomy for papillary thyroid cancers (PTC) larger than 4 cm. For papillary macrocarcinoma with a diameter >1–4 cm, less intensive surgery can be managed, but this is still a matter for debate. The aim of our study was to assess the prevalence of risk factors such as vascular invasion, positive margin, extrathyroidal extension, aggressive histology, lymph nodes and distant metastases associated with a primary PTC tumour with a diameter >1–4 cm, and the association between tumour size and the risk of having one or more of these factors. A retrospective analysis of the medical records of 857 patients who underwent total thyroidectomy between 2000 and 2020, with a final post-operative diagnosis of a PTC >1–4 cm. Overall, less than a half (47.0%) of tumours were associated with at least one risk factor. The prevalence of analysed risk factors, except aggressive histology and a positive margin status, was significantly associated with larger tumour size (>2–4 cm). The optimal cut-off value for a cumulative risk of having one or more risk factors was estimated as 2.0 cm. Patients with a primary tumour < 2.0 cm had almost double less risk (p-value < 0.0001; OR 1.95; 95% CI 1.47–2.58) of having one or more risk factors than patients with PTC ≥ 2.0 cm. In an era of de-escalation, the cut-off value of 2 cm can be helpful in identifying patients with PTC >1–4 cm and lower risk of having aggressive disease providing less extensive treatment approach.

Keywords Papillary thyroid cancer · Risk features · Tumour size > 1–4 cm · Diameter cut-off

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Introduction

The incidence of thyroid cancer (TC) has risen markedly worldwide. Indeed, this trend has been reported in many cancer registers, including the WHO International Agency for Research on Cancer as well as the Polish National Cancer Registry [1–3]. As the number of patients with TC has increased steadily in the last decade, recommendations regarding the most optimal management strategies have evolved [4].Given the fact that papillary thyroid cancer (PTC) is the most common type of TC, accounting for up to 80–90% of all cases, the main focus is on appropriate treatment for PTC [4, 5].In general, PTC has a favourable prognosis, despite having a well-known risk of recurrence [6]. Thus, in 2015, the American Thyroid Association (ATA) categorised factors that increase the risk of PTC recurrence as intermediate-high (I-H), with the aim of clarifying the extent of initial surgery required [5]. For very low risk unifocal PTC with a diameter up to 1 cm and with no clinical evidence of aggressive disease (i.e., papillary microcarcinoma; MPTC), less intensive surgery, such as unilateral thyroid lobectomy (TL) or an active surveillance are recommended [4, 5, 7]. Likewise, in the past, total thyroidectomy (TT) was preferred for PTCs measuring > 1 cm [8, 9]. However, recent revised clinical guidelines issued by the ATA, as well as the National Comprehensive Cancer Network (NCCN) and the British Thyroid Association (BTA), recommend less invasive surgery (TL) as the initial option for PTC primary tumours between 1 and 4 cm and lacking I-H risk factors [5, 10, 11].The main reason for this is to avoid overtreatment and to reduce the risks associated with over-extensive surgery with a recent trend toward de-escalation of the treatment. Patients who undergo TT are at higher risk of surgical complications than those who undergo less intensive surgery such as TL. Risks include laryngeal nerve injury, chronic hypoparathyroidism, wound complications (i.e., hematoma), and a lifelong need for thyroid hormone replacement and a reduced quality of life. However, the majority of I-H risk factors (i.e., aggressive histology, vascular invasion, a positive margin, extrathyroidal extension [ETE] and clinically inapparent lymph node [LN] metastases) are diagnosed after surgery [12–14]. In addition, distant metastases (DM) are often identified only on whole body scans (WBS) taken during radioiodine (RAI) therapy, which is only administered after TT.

Most studies of the risk characteristics of PTC measuring ≤ 4 cm in size usually include primary tumours of 1 cm in the group of tumours measuring 1–4 cm, despite the fact that a diameter of 1 cm defines MPTC, for which a less invasive surgical approach is needed [5, 11–13, 15]. By contrast, other studies aimed to assess a prevalence of I-H risk factors that are undetectable before surgery to estimate the risk of reoperation after initial eligibility for TL [12, 13, 15, 16]. However, it is not clear whether the risk of having a particular I-H characteristics, or the cumulative risk of having more than one risk feature, is dependent on a tumour size in PTC of ≤ 4 cm (excluding MPTC measuring ≤ 1 cm). It is thought that a tumour size of approximately 2 cm can be considered as a cut-off for low and higher risk PTC; however, hypothetically, TL can be usually a more cost-effective surgical option for PTC of ≥ 2.5 cm [15–18].

Therefore, the aim of the present study was to evaluate the relationship between tumour size and the risk of having I-H risk factors in patients who underwent TT for a confirmed PTC measuring > 1–4 cm.

Material and methods

Study group

Between January 1, 2000, and December 31, 2020, a database of 2918 consecutive patients with differentiated TC treated at a single oncological centre was compiled. Patients with a TC type other than PTC [249 patients, (pts); → 2669 PTC], PTC measuring ≤ 1 cm (1666 pts; → 1003 pts) or > 4 cm (91 pts; → 912 pts) after TL (3 pts; → 909 pts), or pre-operatively identified apparent aggressive disease (52 pts; → 857 pts) were excluded. Therefore, 857 patients who underwent TT and had a pathologically confirmed PTC > 1–4 cm were included (Fig. 1). Thus, patients with no pre-operative evidence of nodal or DM, or no evidence of ETE, could be recommended for less extensive surgery, e.g., TL. Next, a retrospective analysis of medical records was performed, focusing on the risk factors for PTC listed in surgical reports, as well as post-operative data regarding the presence of DM. In accordance with 2015 ATA guidelines, post-surgical pathology assessed the prevalence of the following I-H risk factors for PTC > 1–4 cm: aggressive histology (tall cells/columnar cells, and diffuse sclerosing, solid, and hobnail subtypes); any involved resection margin; ETE (microscopic or gross); vascular invasion; or positive LNs.[5] Finally, to determine post-operative DM status, WBS after RAI-therapy was analysed to detect RAI-avid DM. All included patients underwent TT and central LN dissection (CND). Cases with pre-operatively apparent LN metastases were excluded; therefore, CND was performed prophylactically in patients with clinically uninvolved central neck lymph nodes (cN0). All encapsulated follicular variants of PTC were reviewed, and non-invasive follicular thyroid neoplasms were excluded before completion of the PTC database [19].

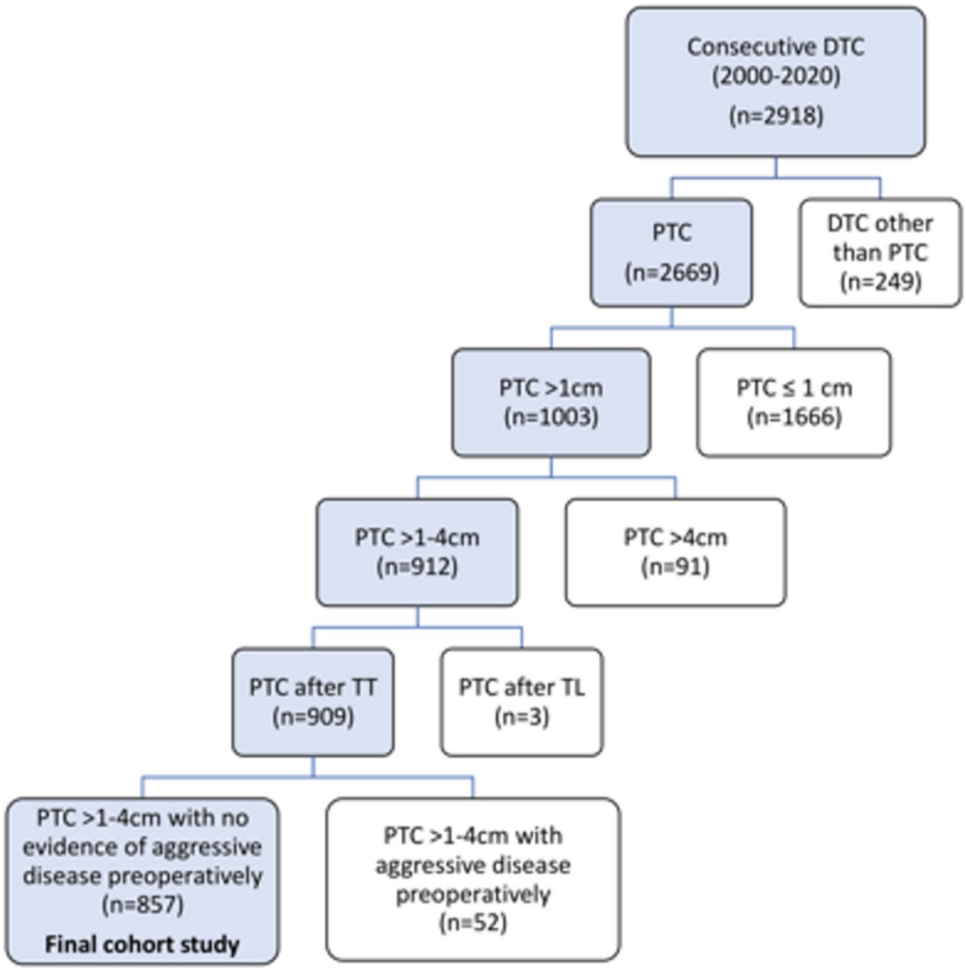

Fig. 1 Flow chart of patients selection resulting in the final study group of 857 PTC with tumour size > 1–4 cm and no evidence of aggressive disease preoperatively. *DTC* differentiated thyroid cancer; *PTC* papillary thyroid cancer; *TT* total thyroidectomy; *TL* thyroid lobectomy

The prevalence of each I-H risk factor, and at least one or more risk factors for PTC > 1–4 cm, was analysed in all the 857 patients. The patients were then divided into two subgroups based on the size of the primary tumour: > 1–2 cm and > 2–4 cm. These subgroups were compared by analysing differences in the prevalence of each individual I-H factor, and in the prevalence of at least one or more risk factors. The effect of an increase in tumour diameter on the risk of having more than one risk factor was also assessed. Finally, the entire group, and both subgroups, were assessed regarding the risk of having a particular I-H risk factor, as well as the cumulative risk of having one or more risk factors. This was done to establish an optimal cut-off diameter for single and cumulative risk.

All data collection and analysis were performed according to the institutional guidelines and ethical standards of the Helsinki Declaration, and all the study procedures were approved by the Institutional Review Board of Jan Kochanowski University in Kielce (No. 42/2023).

Statistical analysis

Categorical data are described by absolute numbers and percentages. Continuous variables are presented as the mean and standard deviation or as the median (quartiles and minimum and maximum quartile ranges). Group comparisons were performed using the Chi-square or Fisher's exact test for categorical variables, a t-test for quantitative, normally distributed variables, or the Mann–Whitney test for quantitative, non-normally distributed variables. Normality of distribution was checked by the Shapiro–Wilk test. A series of univariable logistic regression models was created to examine the association between tumour size and risk factors of interest (vascular invasion, positive margin, ETE, aggressive histology, positive LN, and DM). Odds ratios (OR) accompanied by 95% confidence intervals (95% CI) were calculated to assess the strength and significance of these associations. For a more comprehensive view of the analysed relationship, the explanatory variable (tumour size) in the mentioned logistic regression

models was treated in three ways: as a continuous variable, as a dichotomous variable with a cut-off = 2 cm, or as a dichotomous variable with a cut-off determined by maximising the Youden's index. A two-tailed p-value < 0.05 was considered statistically significant. All statistical analyses were performed using R software package version 4.0.3.

Results

The study cohort comprised 738 females (86.1%) and 119 males (13.9%). The detailed analysis of final pathology revealed that the most common I-H risk factor was ETE (26.7%), followed by positive LN (21.0%) and positive margin status (15.4%). Of 229 ETE-positive PTCs, the majority (85.2%) had microscopic feature; 34 cases (14.8%) were

Table 1 Clinicopathological characteristics of the 857 PTC cases with a tumour > 1–4 cm, and comparison of the prevalence of post-operatively determined risk features in each subgroup (cut-off value = 2 cm)

Feature	Total (N = 857)	> 1–2 cm (N = 603)	> 2–4 cm (N = 254)	*P*-value
Age at diagnosis (years)				**0.2321**
Mean (SD)	49.6 (15.1)	49.1 (14.8)	50.5 (15.8)	
Median (Q1, Q3)	51.0 (39.0, 61.0)	51.0 (39.0, 62.0)	52.0 (39.0, 62.0)	
Range	13.0–85.0	15.0–85.0	13.0–85.0	
Gender				**0.0001**
Female (%)	738 (86.1)	537 (89.1)	201 (79.1)	
Male (%)	119 (13.9)	66 (10.9)	53 (20.9)	
Primary tumour size (mm)				
Mean (SD)	18.7 (7.6)	14.5 (2.9)	28.6 (5.9)	
Median (Q1,Q3)	16.0 (12.0, 22.0)	14.0 (12.0, 17.0)	27.0 (24.0, 35.0)	
Range	10.4–40.0	10.4–20.0	21.0–40.0	
PTC aggressive subtype (%)	12 (1.4)	**9 (1.5)**	**3 (1.2)**	**0.0966**
Columnar cell variant	1 (0.1)	1 (0.2)	0 (0.0)	
Tall cell variant	3 (0.4)	2 (0.3)	1 (0.4)	
Diffuse sclerosing	5 (0.6)	3 (0.5)	2 (0.8)	
Solid	3 (0.4)	3 (0.5)	0 (0.0)	
Non-aggressive subtype				
CPTC	617 (72.0)	422 (70.0)	195 (76.8)	
FVPTC	171 (20.0)	132 (21.9)	39 (15.4)	
Other non-aggressive	57 (6.6)	40 (6.6)	17 (6.7)	
Vascular invasion (%)	83 (9.7)	**47 (7.8)**	**36 (14.2)**	**0.0039**
Margin status (%)	132 (15.4)	**87 (14.2)**	**45 (17.7)**	**0.5376**
Microscopic (R1)	127 (14.8)	84 (13.9)	43 (16.9)	
Macroscopic (R2)	5 (0.6)	3 (0.5)	2 (0.8)	
ETE (%)	229 (26.7)	**144 (23.9)**	**85 (33.5)**	**0.0038**
Microscopic	195 (22.8)	133 (22.1)	62 (24.4)	
Gross	34 (4.0)	11 (1.8)	23 (9.1)	
Lymph nodes (%)	180 (21.0)	**104 (17.2)**	**76 (29.9)**	**< 0.0001**
Negative	677 (79.0)	499 (82.8)	178 (70.1)	
pN0	535 (62.4)	403 (66.8)	132 (52.0)	
pNx (cN0)	142 (16.6)	96 (15.9)	46 (18.1)	
Distant metastases (%)	16 (1.9)	**4 (0.7)**	**12 (4.7)**	**0.0002**
At least one risk factor (%)	403 (47.0)	**261 (43.3)**	**142 (55.9)**	**0.0007**
At least two risk factors (%)	180 (21.0)	**102 (16.9)**	**78 (30.7)**	**< 0.0001**
At least three risk factors (%)	55 (6.4)	**27 (4.5)**	**28 (11.0)**	**0.0004**
At least four risk factors (%)	14 (1.6)	**5 (0.8)**	**9 (3.5)**	**0.0072**

Bold values indicate variables included in statistical comparisons with corresponding *P*-values

PTC papillary thyroid cancer; *CPTC* conventional papillary thyroid cancer; *FVPTC* follicular variant of papillary thyroid cancer; *ETE* extrathyroidal extension; *pNx* no LN on pathology; *cN0* clinically LN-negative status

identified as having gross ETE. Since we excluded patients with apparent LN metastases pre-operatively, all 180 LN-positive cases were identified by pathological examination post-surgery. All M1 cases were identified by post-RAI WBS, and defined as RAI-avid DM (16/857; 1.9%) (Table 1).

When patients were subdivided into groups according to tumour size [> 1–2 cm (n = 603; 70.4%) and > 2–4 cm (n = 254; 29.6%)], the three most common I-H risk factors were the same for each subgroup: ETE (23.95% and 33.5%, respectively), positive LN (17.2% and 29.9%, respectively) and incomplete resection (14.3% and 16.9%, respectively); however, the percentage of patients with these features was higher in the > 2–4 cm subgroup than in the entire cohort. When comparing both subgroups, we found that vascular invasion, presence of ETE, positive LN, and DM type were significantly more prevalent in the > 2–4 cm group with p-values 0.0039, 0.0038, < 0.0001, and 0.0002, respectively. Tumours > 2–4 cm were also significantly more common in males (p-value: 0.0001), although age at diagnosis did not differ significantly between PTC of > 1–2 cm and > 2–4 cm (Table 1). In addition, we compared cases with gross ETE with all remaining cases with microscopic or no ETE. The result showed that gross ETE was also significantly more common in tumours > 2–4 cm (p < 0.0001).

In general, of the 857 patients with PTC > 1–4 cm with no pre-operative evidence of aggressive disease, less than a half (403/857; 47.0%) cases had at least one risk factor identified post-operatively. The prevalence of at least one, or more, I-H risk factors was also significantly higher in those with larger tumours > 2–4 cm than in > 1–2 cm (55.9% *vs.*43.3%; p-value: 0.0007) (Table 1).

Analysis of the relationship between increased tumour size and the risk of having one or more risk factors revealed a "risk continuum". An increase in tumour diameter by 1 mm in those with PTC > 1–4 cm was associated with a significant increase in the risk of having of all I-H risk features, except an aggressive histology. Regarding cumulative risk, an increase of 1 mm increased the risk of having more than one factor by 3% (p-value: 0.0002). The highest association was observed for DM; an increase in 1 mm resulted in a risk of having of DM measuring as 10% (Table 2).

Univariate analysis of the two subgroups revealed that the risk of having any of the analysed risk factors, except aggressive histology and positive margin, was significantly higher for patients with PTC > 2–4 cm. In these patients, the risk of vascular invasion, LN and DM was almost twice, twice, and seven times higher, respectively, that in patients with smaller tumours. Thus, patients with PTC > 2–4 cm had more than one and half times the cumulative risk of having one or more aggressive risk factors than patients with PTC > 1–2 cm (Table 3). Finally, we found that for a risk of having an incomplete resection, vascular invasion, ETE, positive LN, and DM, the optimal cut-off value for tumour size was 1.4, 1.7, 1.8, 2.0, and 2.1 cm, respectively. With respect to the cumulative risk of having one or more risk factors, the optimal cut-off value was 2.0 cm. Patients with a primary tumour ≥ 2.0 cm in diameter had almost double the risk of having more than one aggressive risk factor than those with PTC < 2.0 cm (Table 4).

Table 2 An increase in tumour size of 1 mm in those with PTC > 1–4 cm increases the risk of having more than one risk factor

Feature	Univariable OR*	95% CI	*P*-value
Vascular invasion	1.07	1.04–1.09	< 0.0001
Aggressive histology	0.96	0.88–1.05	0.4285
Extrathyroidal extension	1.03	1.01–1.05	0.0008
Positive margin	1.03	1–1.05	0.023
Metastatic lymph node	1.04	1.02–1.06	0.0001
Distant metastases	1.1	1.04–1.16	0.0004
Cumulative risk of at least 1 of the above	1.03	1.02–1.05	0.0002

*Association between an increase of tumour diameter by 1 mm and the risk of having any of the analysed risk factors

Table 3 Relationship between tumour size and the risk of having a single risk factor, and the cumulative risk of having ≥ 1 risk factor, in the two subgroups (cut-off = 2 cm)

Feature	Univariable OR	95% CI	*P*-value
Vascular invasion			
> 1–2 cm	Ref. level		
> 2–4 cm	1.95	1.23–3.1	0.0045
Aggressive histology			
> 1–2 cm	Ref. level		
> 2–4 cm	0.79	0.21–2.94	0.7237
Extrathyroidal extension			
> 1–2 cm	Ref. level		
> 2–4 cm	1.6	1.16–2.21	0.0039
Positive margin			
> 1–2 cm	Ref. level		
> 2–4 cm	1.28	0.86–1.89	0.224
Metastatic lymph node			
> 1–2 cm	Ref. level		
> 2–4 cm	2.05	1.46–2.88	< 0.0001
Distant metastases			
> 1–2 cm	Ref. level		
> 2–4 cm	7.43	2.37–23.25	0.0006
Cumulative risk of at least 1 of the above			
> 1–2 cm	Ref. level		
> 2–4 cm	1.66	1.24–2.23	0.0008

Table 4 Optimal cut-off value for tumour size associated with having a single factor, and the cumulative risk of having more than one risk factor, in those with PTC > 1–4 cm

Feature	Univariable OR	95% CI	*P*-value
Vascular invasion			
< 1.7 cm	Ref. level		
≥ 1.7 cm	2.98	1.82–4.89	< 0.0001
Aggressive histology			
< 1.6 cm	Ref. level		
≥ 1.6 cm	1.29	0.41–4.11	0.6613
Extrathyroidal extension			
< 1.8 cm	Ref. level		
≥ 1.8 cm	1.79	1.32–2.43	0.0002
Positive margin			
< 1.4 cm	Ref. level		
≥ 1.4 cm	1.61	1.04–2.49	0.0322
Metastatic lymph node			
< 2.0 cm	Ref. level		
≥ 2.0 cm	2.0	1.44–2.8	< 0.0001
Distant metastases			
< 2.1 cm	Ref. level		
≥ 2.1 cm	7.43	2.37–23.25	0.0006
Cumulative risk of at least 1 of the above			
< 2 cm	Ref. level		
≥ 2 cm	1.95	1.47–2.58	< 0.0001

Discussion

Total thyroidectomy with or without CND was the recommended/preferred treatment for PTC > 1 cm [8, 9]. However, in 2014, Adam et al. asked a question: should tumour size be an absolute indication for TT? This question arose from an analysis of 61,775 PTC with tumours 1–4 cm in diameter with no clinically high risk features (i.e., ETE, metastases, or aggressive histology), which suggested that the overall survival between patients who underwent TT was no different from that of those who underwent TL [20]. Thus, the ATA (2015) and European Society for Medical Oncology (ESMO; 2019) revised their guidelines with respect to initial management of patients; the recent guideline state that TL is equivalent to TT with respect to PTC > 1–4 cm with no apparent clinically aggressive factors on pre-operative evaluation [5, 21]. Management should also take into account patient preference [4].

It must be acknowledged that the entire risk landscape of PTC is determined after surgery and is based on the final pathology report. Post-operative findings are crucial for patients who would have been eligible for initial TL. Thus, the prevalence of high risk features in those with PTC > 1–4 cm has become an important area of interest; however, several studies included PTC of 1 cm (MPTC) or follicular TC within the analysed groups [12–17]. These studies indicated that 30% to nearly 50% of patients have unrecognised pre-operative high risk factors, even though the PTC was identified as low risk initially [12–14, 16]. Additionally, the majority of studies showed that the prevalence of I-H risk factors was higher in those with tumours ≥ 2–4 cm [12, 13, 16, 17]. Our findings are in line with these results. Here, we found that risk factors such as vascular invasion, ETE, and LN and DM were significantly more common in those with larger tumours than in those with PTC > 1–2 cm. It is worth noting that we analysed patients with no apparent pre-operative LN metastases who underwent TT with CND. This selection of patients might have impacted our results, which are close to the upper reported frequency of at least one risk factor (i.e., 47%); however, they are concordant with the knowledge that CND identifies more positive LN, and the prevalence of occult central LN metastases rises with increased tumour size [22]. Our study also showed that patients with PTC of > 2–4 cm had almost double the risk of vascular invasion, a well-known risk factor for further metastases, and double and seven times the risk of having LN and DM, than those with smaller tumours of > 1–2 cm.

With respect to tumours of > 1–4 cm, a diameter of 2 cm is thought to be the most useful cut-off value for distinguishing between less and more advanced PTC; this is reflected in the maintenance of a 2 cm cut-off between pT1 and pT2 tumours during pT staging using the recent tumour-node-metastases (TNM) classification [23]. However, according to the ATA or ESMO guidelines, low risk PTC larger than 1 cm but no larger than 4 cm are recommended for TL, as the outcome is not worse than that of TT [5, 21]. Nevertheless, the above studies show that higher risk features are more common in those with PTC 2–4 cm; our results are consistent with these findings. This leads to an interesting question: is a cut-off value of 2.0 cm really associated with a lower/higher risk of having one or more risk factor in those with PTC > 1–4 cm. The answer to this question could be essential when making the decision between the two surgical approaches, and should facilitate the choice between more appropriate treatment based on the risk of having aggressive disease that will require a second surgery after TL.

As expected, the cut-off value of 2 cm for pre-operatively low risk PTC is most likely the optimal value for identifying PTC patients in the > 1–4 cm group as having post-operatively 'lower' or 'higher' risk. Our data suggest that patients with PTC ≥ 2 cm in diameter had almost double the cumulative risk of having one or more aggressive risk factors such as vascular invasion, ETE, involved margin status, LN-positivity and DM compared with those with a smaller tumour of < 2.0 cm. The highest optimal cut-off value of 2.1 cm was established for the risk of DM. Our data may (in part) explain why patients with tumours > 2 cm showed higher

mortality after TL in the recent meta-analysis by Zhang et al. [24]. On the other hand, Choi et al. reported that TL is sufficient and does not affect the long-term or oncological outcome of patients with low risk PTC of 1–4 cm, a finding supported by the recent study by Bosset et al. [25, 26].

This study has some limitations. First, although it used consecutive data from a single-centre, it was retrospective in nature, and analysis of medical records was limited only to available data from the past. Second, although prophylactic CND was performed in all studied patients, nearly 17% had an undetermined pathological LN-status (pNx), and the size of LN metastases was not reported in most final pathology reports covering LN-positive specimens. Thus, we included overall LN-positivity as a risk factor without excluding LN micro-metastases. Third, the relatively small number of patients with an aggressive subtype on final pathology potentially underpowers their importance in our analyses of the relationship between tumour size and the risk of having an aggressive histology. Finally, we examined the risk characteristics of those with PTC > 1–4 cm, as well as the relationship between tumour size and the risk of having a single, or the cumulative risk of having one or more risk factors, with the aim of establishing an optimal cut-off value for the tumour diameter associated with either of these. We did not assess the impact on long-term outcome, including overall survival or disease recurrence. The present study was intended to provide information that will be clinically useful and enable clinicians to make a risk–benefit analysis regarding selection of patients with PTC of 2 cm or less in > 1–4 cm tumours who are eligible for less intensive surgical management at the time of diagnosis with a current trend toward de-escalation of treatment.

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Availability of data and materials Data is provided within the manuscript.

Code availability No custom code or software was used in the preparation of this article.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All the study procedures were approved by the Institutional Review Board of Jan Kochanowski University in Kielce (No. 42/2023). For this type of study formal consent is not required.

Consent to participate This study has obtained IRB approval from of Jan Kochanowski University in Kielce and the need for informed consent was waived.

Consent for publication For this type of study consent for publication is not required.

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