Cancer Epidemiology 60 (2019) 46–50

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Incidental and Non-incidental Papillary Thyroid Microcarcinoma in Denmark 1996–2015: A national study on incidence, outcome and thoughts on active surveillance

Rasmus Reinke[a,*], Jes Sloth Mathiesen[a], Stine Rosenkilde Larsen[b], Christoffer Holst Hahn[c], Henrik Baymler Pedersen[d], Jens Bentzen[e], Sten Schytte[f], Christian Godballe[a], Stefano Christian Londero[f], A study from The Danish Thyroid Cancer Group – DATHYRCA (part of the DAHANCA organization)

[a] Department of ORL Head & Neck Surgery and Audiology, Odense University Hospital, University of Southern Denmark, Denmark
[b] Department of Pathology, Odense University Hospital, Denmark
[c] Department of ENT Head & Neck Surgery, Copenhagen University Hospital, Denmark
[d] Department of ENT Head & Neck Surgery, Aalborg University Hospital, Denmark
[e] Department of Oncology, Herlev Hospital, Denmark
[f] Department of ENT Head & Neck Surgery, Aarhus University Hospital, Denmark

ARTICLE INFO

Keywords:
Thyroid cancer
Microcarcinoma
Papillary thyroid carcinoma
Incidental
Non-incidental
Active surveillance

ABSTRACT

Background: Incidental and non-incidental papillary microcarcinomas (PMC) are associated with different outcomes and treatment options may vary. The least favourable outcome is typically seen when carcinoma is suspected prior to surgery. Only a few studies have addressed the prognosis based on the way of detection for PMC, and they have been limited to retrospective single-center studies. We hypothesize that the "way of detection" may predict prognosis.

The aim was to calculate the incidence and outcome of PMC based on the way of detection and to identify patients that may be suitable for active surveillance.

Method: This national cohort study consists of 803 patients diagnosed with PMC in Denmark from 1996 to 2015. Patients were identified from the DATHYRCA database and allocated into groups according to the way of detection leading to surgery: Incidental at surgery (n = 527), non-incidental with symptoms suspected from the index tumor (n = 134) and non-incidental with symptoms suspected from a metastasis (n = 142).

Results: Age-standardized incidence rates increased from 0.35 per 100,000 per year in 1996 to 1.19 per 100,000 per year in 2015. A significant rise in incidence was found for both the incidental group and non-incidental group with symptoms suspected from a metastasis. Recurrence free survival was significantly worse for patients with suspicion of metastasis prior to surgery than patient groups without. No difference in mortality was found between groups.

Conclusion: PMC patients without suspicion of metastasis have the same low risk of recurrence as incidental cases and may be candidates for active surveillance.

1. Introduction

The incidence of thyroid cancer has increased globally over the past 40 years [1,2], with a substantial rise in the papillary subtype and in Denmark alone more than 300 patients are diagnosed each year [3,4].

When tumors of papillary thyroid carcinomas (PTC) are ≤1.0 cm in largest dimension, they are defined as papillary microcarcinomas (PMC) [5]. While PMC can be a fatal disease, the prognosis is generally favorable [6,7]. According to autopsy studies 11–36% of the population has PMC [8,9]. Despite increasing incidence, the ability to predict

* Corresponding author at: Department of ORL Head and Neck Surgery, Odense University Hospital, University of Southern Denmark, Sdr. Boulevard 29, 5000 Odense C., Denmark.

E-mail addresses: reinke91@icloud.com (R. Reinke), Jes_Mathiesen@yahoo.dk (J.S. Mathiesen), Stine.rosenkilde.larsen@rsyd.dk (S.R. Larsen), christoffer.holst.hahn.01@regionh.dk (C.H. Hahn), hebp@rn.dk (H.B. Pedersen), jens.bentzen@regionh.dk (J. Bentzen), sten.schytte@aarhus.rm.dk (S. Schytte), christian.godballe@rsyd.dk (C. Godballe), stelon@rm.dk (S.C. Londero).

https://doi.org/10.1016/j.canep.2019.03.011
Received 9 January 2019; Received in revised form 17 March 2019; Accepted 18 March 2019
Available online 23 March 2019

tumors with metastatic potential is unchanged, since diagnostic tools are dependent on post-surgical evaluation [10]. Point scores are used to predict outcome and determine treatment options, and researchers have investigated whether way of detection could predict outcome [10,11]. Currently there is no clear definition for incidental PMC. As a consequence, the proportion varies from 0% to 100% in published series [12,13]. It is generally recognized that incidental PMC has a significantly better prognosis than non-incidental [11]. The authors of a recent systematic review proposed to increase the number of groups by differentiating between whether metastasis is suspected or not [11]. Another treatment option for non-incidental PMC currently in practice in Japan and USA is active surveillance [14,15]. This option delays treatment until the cancer shows signs of significant progression to avoid overtreatment and complications associated with surgical treatment, such as recurrent laryngeal nerve paralysis or hypoparathyroidism [16,17]. This should only be considered in properly selected patients, without suspicion of metastatic disease [14].

The purpose of this study was to investigate the incidence and outcome of PMC based on the way of detection and to identify patients suitable for active surveillance.

2. Materials and methods

The study design is a national cohort study. Since 1996 thyroid cancer patients in Denmark, have been prospectively registered in the validated Danish Thyroid Cancer (DATHYRCA) database [18].

The database consists of systematically registered clinical, surgical, histopathological and follow-up data on a national scale. Every citizen in Denmark is given a 10-digit personal indication number (CPR-number), making it possible to trace everyone throughout governmental registries.

The study was based on data available from the DATHYRCA database on March 14, 2017.

Patients diagnosed with PMC were found using the DATHYRCA database with the following inclusion criteria:

- Histologically verified papillary thyroid carcinoma.
- Diagnosed between January 1, 1996, and December 31, 2015.
- Largest dimension ≤ 1.0 cm.
- No prior history of thyroid cancer.
- Alive at the time of diagnosis.

Medical records were reviewed, and each patient was assigned to either an incidental (IPMC), non-incidental (NIPMC) or non-incidental with metastasis (NIMPMC) group according to the following criteria:

Incidental [19]:

- The PMC must not be the index tumor (the tumor for which surgical treatment was performed).
- A metastasis from thyroid cancer must not be the reason for the thyroid surgery resulting in detection of PMC.
- The histology of the surrounding specimen had to be benign (no malignancy except for the PMC must be found by histological examination of the thyroid specimen).

Moreover, multifocal PMC were considered incidental if they fulfilled the mentioned criteria.

Non-incidental tumors were divided to either:

- Non-incidental tumors with symptoms and/or radiological findings leading to discovery of the intrathyroidal index tumor prior to surgery.
- Non-incidental tumors with symptoms and/or radiological findings leading to discovery of a metastasis from thyroid cancer prior to surgery.

To determine outcome, follow-up data from the validated DATHYRCA database [18] was used and supplied with information regarding recurrence status from the Danish Pathology Register [20].

Wilcoxon rank sum and chi-square test were adopted to examine the relationship between variables, and Cuzick's test for trend was used to explore changes in incidence [21]. P-values of < 0.05 were considered significant. All tests were two-sided. The Kaplan–Meier method was used to estimate survival. Age-adjusted incidences were calculated for the years from 1996 to 2015 according to the WHO World Standard Population (W) 2000–2025 [22]. Data of the Danish population were retrieved from StatBank Denmark (www.statbank.dk). STATA 14 (StataCorp LP, College Station, TX, USA) was used for statistical analyses. The project was approved by the Regional Ethics Committee (**S-20160178**) and by the National Danish Data Protection Agency (**17/6146**).

3. Results

A total of 803 patients met the inclusion criteria. The crude incidence rate for PMC in the period 1996–2015 was 0.73 cases per 100,000 per year. A rise in age-adjusted incidence rate was seen from 0.35 per 100,000 per year [95% confidence interval (CI) 0.27–0.43] in 1996 to 1.19 per 100,000 per year [CI 1.06–1.32] in 2015, and this was significant for Cuzick's test for trend ($p < 0.01$). Crude and age-adjusted incidence rates are shown in Fig. 1.

Characteristics for patients with PMC according to way of detection are shown in Table 1.

527 cases (66%) were categorized as incidental (IPMC), 134 as non-incidental (NIPMC) (17%) and 142 as non-incidental with symptoms from a metastasis (NIMPMC) (18%). Younger median age, larger tumor size, higher frequency for extra thyroid extension and metastasis, both nodal and distant, were found for the NIMPMC group. Both NIPMC and NIMPMC showed significant larger tumors than the IPMC group.

The annual cases of IPMC, NIPMC and NIMPMC is shown in Fig. 2, where an increased incidence of IPMC and NIMPMC seems to be present. Cuzick's test for trend proved significant for both the IPMC and the NIMPMC cases ($p < 0.05$) whereas no significant trend could be found for NIPMC ($p = 0.083$).

The median follow-up time was 7.1 years (range 0.06–20.99): for the IPMC group 6.95 years (range 0.06–20.88), for the NIPMC group 7.4 years (range 0.6–20.9) and for the NIMPMC group 7.7 years (range 0.7–20.99).

During this period 26 cases of recurrences occurred; 10 in the IPMC group, three in the NIPMC group and 13 in the NIMPMC group. Crude and recurrence free survival was equal for the IPMC and NIPMP as shown in Table 2.

Fig. 3 shows a Kaplan-Meier plot of recurrence-free survival for all groups.

During follow-up, two patients died from PMC, one in IPMC group and one in the NIMPMC group. 45 patients died of other causes. Among these, 18 died from another cancer, 22 died from other diseases, two

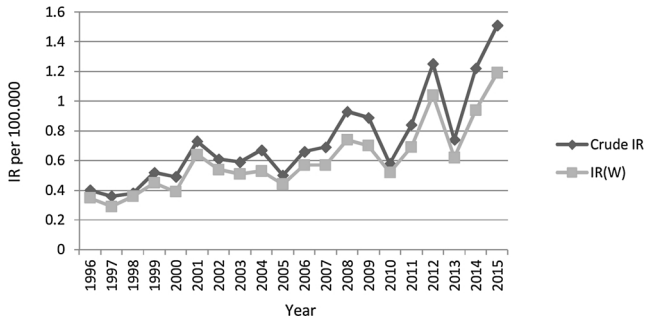

Fig. 1. Crude and age-adjusted [IR(W)] incidence rates for papillary microcarcinoma in Denmark 1996–2015.

Table 1
Characteristics for Patients with Papillary Microcarcinomas According to Mode of Detection in Denmark from 1996 to 2015.

	Incidental (N = 527)	Non-incidental (N = 134)	Non-incidental with metastasis (N = 142)	Whole series (N = 803)	Group* 1-2 (P)	Group* 1-3 (P)	Group* 2-3 (P)
Median age (years)	49 (range 13-84)	48.5 (range 22-80)	42 (range 11-86)	47.5 (range 11-86)	0.37	< 0.05	< 0.05
Median diameter (mm)	4 (range 1-10)	6.5 (range 1-10)	7 (range 1-10)	5 (range 1-10)	< 0.05	< 0.05	0.60
Male/female	90/437	22/112	67/75	179/624	0.86	< 0.05	< 0.05
Multifocality[a]	109 (21%)	35 (26%)	78 (55%)	222 (28%)	0.17	< 0.05	< 0.05
Nodal metastasis[a]	17 (3%)	7 (5%)	137 (96%)	161 (20%)	0.27	< 0.05	< 0.05
Distant metastasis	0 (0%)	1 (0.7%)	5 (4%)	6 (0.7%)	< 0.05	< 0.05	0.11
Extrathyroidal extension	18 (3%)	6 (4%)	29 (20%)	53 (7%)	0.56	< 0.05	< 0.05

[a] Histologically confirmed.
* Group numbers corresponds to when they appear in the table i.e. Group 1 = Incidental.

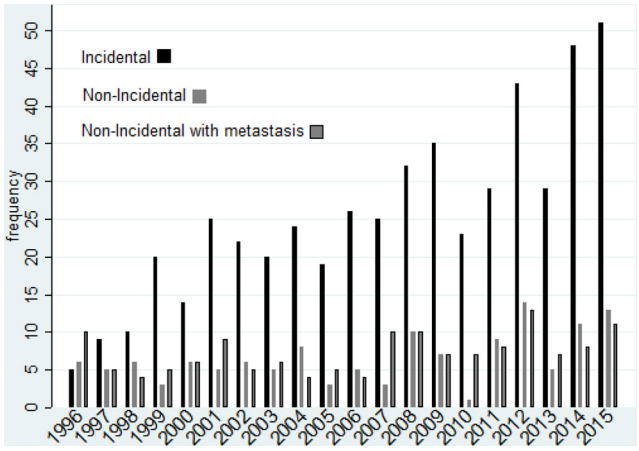

Fig. 2. Annual number of patients with papillary microcarcinoma diagnosed in Denmark 1996–2015 according to way of detection.

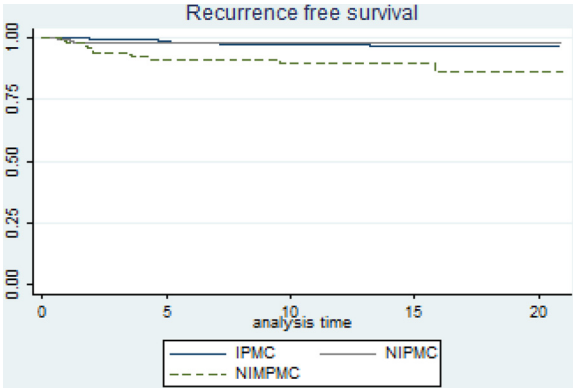

Fig. 3. Plot of recurrence free survival in 527 patients with incidental papillary microcarcinoma (IPMC), 134 patients with non-incidental papillary microcarcinoma (NIPMC) and 144 patients with non-incidental papillary microcarcinoma with metastasis (NIMPMC) in Denmark 1996–2015.

committed suicide, and in three cases, the cause of death could not be determined. No patients in the NIPMC group died of their thyroid cancer. The crude and cause-specific survival is shown in Fig. 4.

4. Discussion

This is the first national study to examine papillary microcarcinomas over a 20-year period to estimate the risk of recurrence based on way of detection. When divided into groups based on way of detection, we showed that risk of recurrence is equal in incidental cases and non-incidental cases when metastasis is not suspected prior to surgery. This suggests that patients in the NIPMC group may be candidates for active surveillance.

4.1. Strengths and limitations

Our study has some limitations and the results reported here must be interpreted considering known weaknesses of an observational study. This national registry study is based on data collected prospectively; therefore, missing or incorrect data entries could impact our results, however each patient had their medical history reviewed by the authors and missing or erroneous data were corrected. Another topic that is debatable is patient outcomes; since different treatment modalities have been used within and between groups. A randomized controlled design as the pioneering work from Kuma Hospital [23] would have been preferable to identify patients suitable for active surveillance. All patients in our series received treatment and some might argue that no knowledge exists regarding the natural history of the disease. However, the ATA guidelines acknowledges that nodules ≤ 1 cm requires no further investigation [24]. Our finding, that risk of recurrence is equal in incidental cases and non-incidental cases when local or distant metastasis is not suspected prior to surgery, underlines that active surveillance is possible for selected patients. This has previously been shown in randomised studies from Japan [23], and our study whilst not randomised contribute with data from a national unselected cohort with long-term follow-up. We used two databases in this study, the DATHYRCA database with a very high degree of completeness [18] that is routinely checked for completeness and missing cases in correlation with the governmental registries. The second registry used was the Danish Pathology Register. Since September 1968 the diagnosis of most pathological specimens have been registered. Registration became mandatory in 1997, containing all histological and cytological reports [20]. Using two national databases selection bias is reduced, and this study is also unbiased by social class as Denmark's a

Table 2
Five and 10-year crude and recurrence-free survival for patients with papillary microcarcinomas in Denmark 1996–2015 according to way of detection.

	Incidental (N = 527)	Non-incidental (N = 134)	Non-incidental with metastasis (N = 142)	Whole series (N = 803)
Crude 5 years	95.4% [CI 92.8–97.0]	96.8% [CI 91.8–98.8]	95.3% [CI 89.9–97.9]	96.7% [CI 95.3–98.0]
Crude 10 years	94.6% [CI 91.8 – 96.5]	92.8% [CI 85.1–96.6]	88.5% [CI 80.3 – 93.4]	95.9% [CI 93.9–97.3]
RFS* 5 years	98.4% [CI 96.5–99.3]	97.7% [CI 93.0–99.6]	91.1% [CI 84.5–95.0]	97.0 % [CI 95.4–98.0]
RFS* 10 years	97.3% [CI 94.9–98.6]	97.7% [CI 93.0–99.6]	89.3% [CI 81.4–94.0]	96.0 % [CI 94.0–97.3]

* Recurrence free survival.

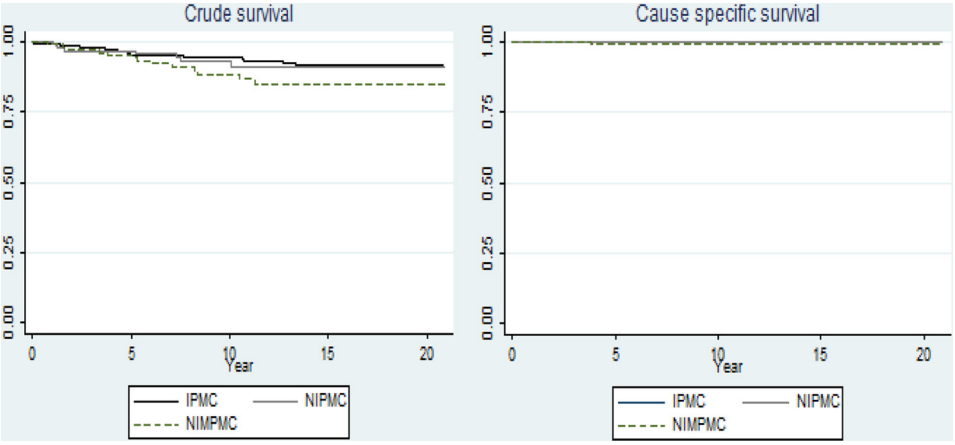

Fig. 4. Plot of crude and cause-specific survival in 527 patients with incidental papillary microcarcinoma (IPMC), 134 patients with non-incidental papillary microcarcinoma (NIPMC) and 144 patients with non-incidental papillary microcarcinoma with metastasis (NIMPMC) in Denmark 1996–2015.

public health care system is tax financed. Conversely the Danish population is primarily of Caucasian decent; therefore, our results may not be representative for populations with a diversity of ethnicity.

The DATHYRCA database does not contain variables describing whether the cancer was found incidentally or non-incidentally. However, we reviewed the medical records of each patient to determine how the cancer was discovered. And thereby assign the patient to the correct groups.

4.2. Groups

Studies have previously examined patient outcomes for both the incidental and non-incidental groups [11,19,25,26]. One systematic review suggests at least two distinct entities of PMC exist, with reference to the incidental and non-incidental group [11]. In contrast to these findings our data suggest that tumors with symptoms and/or radiological findings leading to discovery of the intrathyroidal index tumor prior to surgery behave identical to those found incidentally after surgery when looking at survival and risk of recurrence. Only patients where metastases lead to the diagnosis of thyroid carcinoma have a significant higher risk of recurrence.

In line with our findings, Jen-Der Lin et al. report that the prognosis of incidental PMC is excellent and they propose aggressive surgery and postoperative adjuvant treatment for non-incidental cases presenting with distant metastases or local/regional invasion [25]. Our findings suggest that treating patients according to way of detection is more complex than dividing into two groups, as the non-incidental tumors without suspicion prior to surgery for metastases have the same prognosis as incidental tumors, where the only observed difference was significantly larger tumors.

4.3. Incidence

Thyroid cancer incidence is increasing in developed countries worldwide [26]. Our data provides further evidence that PMC is more frequently detected. The causes of this “thyroid cancer epidemic” is still debated [27]. The rise in PMC incidence rate may represent either a true increase in the occurrence of the disease or an increasing number of diagnoses due to increased surveillance. Our findings demonstrate that the increased incidence rate on a national scale is mainly contributed by incidental cases. However, our study also showed a significant increase in NIMPMC cases.

4.4. Outcome

The outcome for patients with PMC in this series is excellent and comparable to findings elsewhere [6,7]. 10-year recurrence-free survival was 96% for all patients included in this study. For this reason, large cohorts with extended follow-up periods are needed to show events. Even with long-term follow-up events cannot be guaranteed, as the tumor tend to be indolent in most cases as evidenced by autopsy studies [8,9]. This has led some researchers to consider alternative treatment options, such as active surveillance. Since 1993 and 1995 two hospitals in Japan have initiated an active surveillance trial [23] and a study from USA concluded that active surveillance could be used as a first-line management for low risk PMC [14]. Another argument for active surveillance came with a recent study from the Kuma hospital in Japan [14,15] that concluded that the medical costs for immediate surgery with 10-year postoperative management were 4.1 times the medical costs of active surveillance.

With excellent survival rates and minimal risk of recurrence, as shown in this study, the disease seems indolent in most cases and active surveillance could be used as first line management for the NIPMC group. Researchers in Japan have already used this management strategy for a similar patient group [28].

5. Conclusion

PMC patients without suspicion of metastasis have the same low risk of recurrence as incidental cases and may be candidates for active surveillance, as the disease seems indolent in most cases and to reduce unnecessary surgery related complications.

Author contributions

The ICMJE recommends that authorship be based on the following 4 criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors in the study: “Incidental and Non-incidental Papillary Thyroid Microcarcinoma in Denmark 1996–2015: A national study on incidence, outcome and thoughts on active surveillance.” Have been part of the ICMJE recommendations included above.

Author disclosure

No competing commercial interests exist.

Acknowledgments

We thank the Odense University Hospital, University of Southern Denmark, DAHANCA, Ørelæge Hans Skouby's og hustru Emma Skouby's fond, and Kong Christian den Tiendes Fond.

References

[1] L. Davies, H.G. Welch, Increasing incidence of thyroid cancer in the United States, 1973–2002, JAMA 295 (2006) 2164–2167.
[2] S.C. Londero, A. Krogdahl, L. Bastholt, J. Overgaard, H.B. Pedersen, T. Frisch, J. Bentzen, P.U. Pedersen, P. Christiansen, C. Godballe, Papillary thyroid carcinoma in Denmark 1996–2008: an investigation of changes in incidence, Cancer Epidemiol. 37 (2013) e1–e6.
[3] Danish Head and Neck Cancer Group, Årsrapport 2015 for den kliniske kvalitetsdatabase DAHANCA, (2019) (Last accessed on 12.10, 2016), https://www.sundhed.dk/sundhedsfaglig/kvalitet/kliniske-kvalitetsdatabaser/kraeft/hoved-halskraeft/.
[4] C.K. Jung, M.P. Little, J.H. Lubin, A.V. Brenner, S.A. Wells Jr., A.J. Sigurdson, Y.E. Nikiforov, The increase in thyroid cancer incidence during the last four decades is accompanied by a high frequency of BRAF mutations and a sharp increase in RAS mutations, J. Clin. Endocrinol. Metab. 99 (2014) E276–285.
[5] C.W.E. Hedinger, L.H. Sobin, Histological typ- ing of thyroid tumours, WHO International Histological Classification of Tumors, second edition, Springer Verlag, Berlin, 1988, pp. 9–11.
[6] I.D. Hay, M.E. Hutchinson, T. Gonzalez-Losada, B. McIver, M.E. Reinalda, C.S. Grant, G.B. Thompson, T.J. Sebo, J.R. Goellner, Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period, Surgery 144 (2008) 980–987 discussion 987–988.
[7] S. Noguchi, H. Yamashita, S. Uchino, S. Watanabe, Papillary microcarcinoma, World J. Surg. 32 (2008) 747–753.
[8] H.R. Harach, K.O. Franssila, V.M. Wasenius, Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study, Cancer 56 (1985) 531–538.
[9] Y. Yamamoto, T. Maeda, K. Izumi, H. Otsuka, Occult papillary carcinoma of the thyroid. A study of 408 autopsy cases, Cancer 65 (1990) 1173–1179.
[10] S.C. Londero, M.L. Jespersen, A. Krogdahl, L. Bastholt, J. Overgaard, S. Schytte, C. Godballe, J. Alsner, Gene-expression classifier in papillary thyroid carcinoma: validation and application of a classifier for prognostication, Anticancer Res. 36 (2016) 749–756.
[11] H. Mehanna, T. Al-maqbili, B. Carter, E. Martin, N. Campain, J. Watkinson, C. McCabe, K. Boelaert, J.A. Franklyn, Differences in the recurrence and mortality outcomes rates of incidental and nonincidental papillary thyroid microcarcinoma: A systematic review and meta-analysis of 21 329 person-years of follow-up, J. Clin. Endocrinol. Metab. 99 (2014) 2834–2843.
[12] Y. Ito, A. Miyauchi, H. Inoue, M. Fukushima, M. Kihara, T. Higashiyama, C. Tomoda, Y. Takamura, K. Kobayashi, A. Miya, An observational trial for papillary thyroid microcarcinoma in Japanese patients, World J. Surg. 34 (2010) 28–35.
[13] K. Gulben, U. Berberoglu, O. Celen, H.H. Mersin, Incidental papillary microcarcinoma of the thyroid–factors affecting lymph node metastasis, Langenbecks Arch. Surg. 393 (2008) 25–29.
[14] S. Leboulleux, R.M. Tuttle, F. Pacini, M. Schlumberger, Papillary thyroid microcarcinoma: time to shift from surgery to active surveillance? Lancet Diabetes Endocrinol. 4 (2016) 933–942.
[15] A. Miyauchi, Y. Ito, H. Oda, Insights into the management of papillary microcarcinoma of the thyroid, Thyroid (2017).
[16] F. Frattini, A. Mangano, L. Boni, S. Rausei, A. Biondi, G. Dionigi, Intraoperative neuromonitoring for thyroid malignancy surgery: technical notes and results from a retrospective series, Updates Surg. 62 (2010) 183–187.
[17] M. Testini, A. Gurrado, N. Avenia, R. Bellantone, A. Biondi, P. Brazzarola, F. Calzolari, G. Cavallaro, G. De Toma, P. Guida, G. Lissidini, M. Loizzi, C.P. Lombardi, G. Piccinni, P. Portincasa, L. Rosato, N. Sartori, C. Zugni, F. Basile, Does mediastinal extension of the goiter increase morbidity of total thyroidectomy? A multicenter study of 19,662 patients, Ann. Surg. Oncol. 18 (2011) 2251–2259.
[18] S.C. Londero, J.S. Mathiesen, A. Krogdahl, L. Bastholt, J. Overgaard, J. Bentsen, C.H. Hahn, S. Schytte, H.B. Pedersen, P. Christiansen, C. Godballe, study from the Danish Thyroid Cancer G, Completeness and validity in a national clinical thyroid cancer database: DATHYRCA, Cancer Epidemiol. 38 (2014) 633–637.
[19] S.C. Londero, A. Krogdahl, L. Bastholt, J. Overgaard, W. Trolle, H.B. Pedersen, J. Bentzen, S. Schytte, P. Christiansen, C. Godballe, Danish Thyroid Cancer G, Papillary thyroid microcarcinoma in Denmark 1996–2008: a national study of epidemiology and clinical significance, Thyroid 23 (2013) 1159–1164.
[20] B. Bjerregaard, O.B. Larsen, The Danish pathology register, Scand. J. Public Health 39 (2011) 72–74.
[21] J. Cuzick, A wilcoxon-type test for trend, Stat. Med. 4 (1985) 87–90.
[22] O.B. Ahmad, C. Boschi-Pinto, A.D. Lopez, C.J.L. Murray, R. Lozano, M. Inoue, Age Standardization of Rates: a New WHO Standard, World Health Organization, Geneva, 2001, pp. 1–14 31.
[23] Y. Ito, A. Miyauchi, H. Oda, Low-risk papillary microcarcinoma of the thyroid: A review of active surveillance trials, Eur. J. Surg. Oncol. (2017).
[24] B.R. Haugen, E.K. Alexander, K.C. Bible, G.M. Doherty, S.J. Mandel, Y.E. Nikiforov, F. Pacini, G.W. Randolph, A.M. Sawka, M. Schlumberger, K.G. Schuff, S.I. Sherman, J.A. Sosa, D.L. Steward, R.M. Tuttle, L. Wartofsky, 2015 american thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the american thyroid association guidelines task force on thyroid nodules and differentiated thyroid Cancer, Thyroid 26 (2015) 1–133.
[25] J.-D. Lin, S.-F. Kuo, T.-C. Chao, C. Hsueh, Incidental and Nonincidental Papillary Thyroid Microcarcinoma, Ann. Surg. Oncol. 15 (2008) 2287–2292.
[26] A. Pisanu, I. Reccia, O. Nardello, A. Uccheddu, Risk factors for nodal metastasis and recurrence among patients with papillary thyroid microcarcinoma: differences in clinical relevance between nonincidental and incidental tumors, World J. Surg. 33 (2009) 460–468.
[27] L.G.T. Morris, A.G. Sikora, T.D. Tosteson, L. Davies, The increasing incidence of thyroid cancer: the influence of access to care, Thyroid 23 (2013) 885–891.
[28] Y. Ito, A. Miyauchi, Nonoperative management of low-risk differentiated thyroid carcinoma, Curr. Opin. Oncol. 27 (2015) 15–20.