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Short Report

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Association of hypothyroidism with survival in pancreatic cancer: retrospective cohort study

Ingrid Garajová[1], Annalisa Comandatore[2,3], Lenka Boyd[3], Mahsoem Ali[3], Fabio Gelsomino[4], Stefania de Lorenzo[5], Giuseppe Pedrazzi[6], Andrea Spallanzani[4], Giulio Martinelli[4], Rita Balsano[1], Francesco Leonardi[1], Matteo Palmeri[2], Geert Kazemier[7], Gregorio Di Franco[2], Simone Guadagni[2], Niccolò Furbetta[2], Manuel Gentiluomo[8], Niccolò Ramacciotti[2], Giulio Di Candio[2], Elisa Giovannetti[3,9] and Luca Morelli[2,*]

[1]Medical Oncology Unit, University Hospital of Parma, Parma, Italy
[2]General Surgery Unit, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy
[3]Department of Medical Oncology, Lab of Medical Oncology, Cancer Center Amsterdam, Amsterdam UMC, VU University Medical Center (VUmc), Amsterdam, The Netherlands
[4]Department of Oncology and Hematology, University Hospital of Modena, Modena, Italy
[5]Oncology Unit, Azienda USL Bologna, Bologna, Italy
[6]Department of Medicine and Surgery, University of Parma, Parma, Italy
[7]Department of Surgery, Amsterdam UMC, VU University Medical Center, Amsterdam, The Netherlands
[8]Department of Biology, University of Pisa, Pisa, Italy
[9]Cancer Pharmacology Lab, AIRC Start-Up Unit, Fondazione Pisana per la Scienza, San Giuliano Terme, PI, Pisa, Italy

Correspondence to: Luca Morelli, General Surgery Unit, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Via Paradisa 2, Pisa 56124, Italy (e-mail: luca.morelli@unipi.it)

Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most aggressive tumours, with a 5-year survival rate of approximately 8 per cent[1]. This is mostly due to the delay in early diagnosis and to tumour resistance against treatments, despite considerable recent effort in both preclinical and clinical research[2–5]. New studies are needed to identify potential risk factors of progression and incidence of PDAC.

Thyroid disorders are a common public health problem worldwide. The most common type of thyroid disorder is hypothyroidism[6], which is characterized by insufficient levels of thyroxine (T4), along with elevated levels of thyroid-stimulating hormone (TSH)[7]. Levothyroxine replacement therapy is the first-line treatment for hypothyroidism[6,8]. Thyroid hormones influence the growth and homeostasis of gastrointestinal organs through the binding to receptors in the epithelium. They regulate some cellular processes such as proliferation, differentiation, apoptosis and metabolism, and some studies suggest their role in cancer progression[7,9,10].

Several clinical studies have demonstrated that hypothyroidism could inhibit cancer cell proliferation, but data on the potential association between hypothyroidism and survival of PDAC patients are lacking[11,12]. The aim of this study was to examine the prevalence of hypothyroidism among patients with PDAC and assess its association with overall survival.

Methods

Consecutive patients with any stage of PDAC according to the National Comprehensive Cancer Network (NCCN) classification[13] between 2012 and 2021 at the University Hospitals of Parma, Modena and Pisa, were retrospectively reviewed using electronic medical records. The presence of hypothyroidism and treatment with levothyroxine was recorded. Cut-off values of FT4, FT3 and TSH were defined according to each laboratory protocol. Hypothyroidism was defined as low levels of FT4 (normal value 10–23 pmol/l). Normal values for TSH and FT3 were respectively, 0.4–4.0 mU/I and 5.4–12.3 pmol/l. Follow-up phone calls were used to assess the survival status of patients.

Patients aged 18 years or more with cytologically or histologically confirmed diagnosis of PDAC were included, while patients with a diagnosis of concomitant malignancy were excluded. The study protocol (344/2021/OSS/AOUPR, 8 July 2021) was approved by the local Ethics Committees, in accordance with the Declaration of Helsinki.

Continuous variables were reported as median and interquartile range (i.q.r.), and were compared using the Mann–Whitney *U* test. Categorical variables were reported as numbers and percentages, and were compared using chi-square or Fisher exact tests, as appropriate. Confidence intervals (c.i.) for prevalence estimates were obtained using the modified Wilson method. Overall survival (OS) was estimated using the Kaplan–Meier method.

Cox proportional hazards regression was used to assess the association between hypothyroidism and OS, after correcting for confounders. The following, prespecified confounders were adjusted in the Cox regression model: age, sex, T stage, N stage, adjuvant therapy use, log-transformed carbohydrate antigen 19-9(CA19-9) and log-transformed carcinoembryonic antigen (CEA). Missing covariate data were handled using multiple imputation with additive regression, predictive mean matching and bootstrapping under the missing at random

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Table 1 Baseline demographics of the hypothyroidism and euthyroidism groups

Variables	Hypothyroidism (*n* = 75)	Euthyroidism (*n* = 418)	*P*
Age (years), median (i.q.r.)	73 (68–79)	71 (63–78)	0.045
Sex			<0.001
Female	57 (76)	184 (44)	
Male	18 (24)	234 (56)	
Setting			0.78
(Borderline) resectable	49 (65)	271 (65)	
Locally advanced	3 (4)	11 (3)	
Metastatic	23 (31)	136 (33)	
Adjuvant therapy after surgery	23/36 (64)	120/244 (49)	0.14
Resection margin			0.82
R0	19 (83)	84 (78)	
R1	4 (17)	23 (21)	
R2	0 (0)	1 (1)	
T stage			0.57
T1	1 (1)	20 (5)	
T2	22 (32)	105 (28)	
T3	32 (46)	171 (45)	
T4	14 (20)	84 (22)	
N stage			0.81
N0	15 (23)	96 (27)	
N1	33 (51)	169 (47)	
N2	17 (26)	94 (26)	
(CEA μg/l), median (i.q.r.)	6 (2–16)	5 (2–9)	0.33
CA19-9 (U/ml), median (i.q.r.)	233 (19–1001)	255 (34–1351)	0.39

Categorical variables are reported as *n* (%) unless indicated otherwise. CEA, carcinoembryonic antigen; i.q.r., interquartile range.

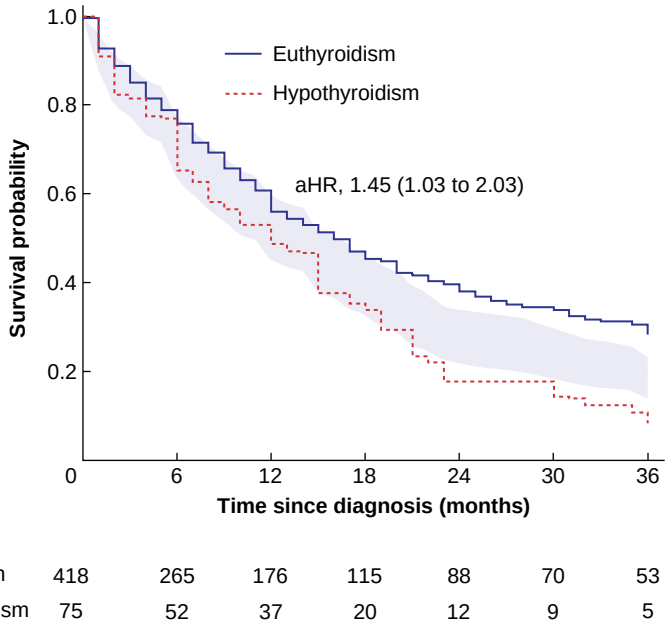

Fig. 1 Covariate-adjusted Kaplan–Meier curve

The grey shaded region indicates the 'null zone'. If, at a certain timepoint, both Kaplan–Meier curves fall outside the null zone, then the difference in overall survival between the two curves at that timepoint is statistically significant. aHR, adjusted hazard ratio. The Kaplan–Meier curve and number at risk for the euthyroidism and hypothyroidism groups are shown in black and orange respectively.

assumption[14]. Resection margin was not imputed, as this variable was likely to be missing not at random.

Three sensitivity analyses were performed: Firth's correction was used to assess sensitivity to sparse data bias; Royston–Parmar flexible parametric survival models were fitted instead of Cox regression models; missing data were handled with an alternative imputation procedure (that is, multivariate imputation by chained equations).

A *P* value <0.05 was considered statistically significant. All statistical analyses were performed in R, version 4.2.1 (R Foundation for Statistical Computing), as described in the *Supplementary Material*. The authors have read the STROBE

Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items. The study protocol was approved by the Ethics Committee (344/2021/OSS/AOUPR, 8 July 2021) which was in accordance with the Declaration of Helsinki. All patients signed an informed consent to authorize the scientific use of the collected data.

Results

Baseline clinicopathological characteristics of the 493 patients included in this study are detailed in *Table 1*. In total, 75 patients had hypothyroidism. Patients with hypothyroidism were more frequently female (76 per cent (57/75) *versus* 44 per cent (184/418), $P < 0.0001$) and were older (73 (68–79) years *versus* 71 (63–78) years; $P = 0.045$). The prevalence of hypothyroidism was 15.0 per cent (26/173) in locally advanced/metastatic patients and 15.3 per cent (49/320) in patients with resected PDAC ($P = 0.78$). Adjuvant therapy was more frequently used in the hypothyroidism group (23 *versus* 120, $P = 0.14$).

During the follow-up (median follow-up time, 11 months; i.q.r. 5–22 months), 48 patients with hypothyroidism died (70 per cent; 570 per 1000 person-years) *versus* 232 patients without hypothyroidism (63 per cent; 425 per 1000 person-years).

Hypothyroidism was associated with worse OS, after adjusting for demographic and clinicopathological variables (HR 1.45; 95 per cent c.i. 1.03 to 2.03; $P = 0.032$) as shown in *Fig. 1* and *Table S1*. The adjusted difference in 1–, 2- and 3-year survival probability between patients with and without hypothyroidism was 8.0 per cent (–6.6 per cent to 22.6 per cent), 20.5 per cent (8.2 per cent to 32.7 per cent) and 20.2 per cent (10.8 per cent to 29.5 per cent) respectively. This association was similar between men and women (interaction test, $P = 0.13$), between resected PDAC and locally advanced/metastatic PDAC (interaction test, $P = 0.59$), and remained consistent in several sensitivity analyses (*Table S2*).

Discussion

Hypothyroidism might be associated with worse OS in PDAC patients regardless of sex and cancer stage; this association remained consistent across several sensitivity analyses. A relatively high prevalence of hypothyroidism was observed in PDAC patients, compared with the prevalence of hypothyroidism in the general population (15 per cent in PDAC patients *versus* 4–8 per cent in the general population)[15–17]. These findings might be explained by the increase in TSH levels associated with hypothyroidism. Recent preclinical studies showed that high TSH levels stimulated glioma proliferation and limited T cell killing[18], and induced oxidative stress and genomic instability in mammary cells[19].

The current study suggested an association between hypothyroidism and a higher mortality risk in PDAC patients. The higher mortality risk in hypothyroidism patients could potentially be associated with an increased risk of perineural invasion and nodal invasion in patients with hypothyroidism[20], as Vascular Endothelial Growth Factor (VEGF) secretion is stimulated by TSH[21]; thus, TSH might promote metastasis by stimulating VEGF secretion and angiogenesis. Sarosiek *et al.* reported a 14 per cent prevalence of hypothyroidism in a retrospective analysis of 504 PDAC patients[22], in line with the current findings.

The strengths of this study include a patient cohort of consecutive patients instead of a case-control design, correction for confounders that are important prognostic factors, a robust multiple imputation approach and consistent results across sensitivity analyses. Limitations include the retrospective nature of the study, a high prevalence of missing data for several prognostically important variables (for example, resection margin and use of neoadjuvant therapy), and the possibility of residual confounding due to baseline differences in clinicopathological variables and co-morbidities that were not determined in our study.

Further studies are needed to consider other factors such as neoadjuvant therapy use, performance status, co-morbidities and patient frailty. Additional studies should assess whether hypothyroidism is associated with disease-specific survival in PDAC. Furthermore, future studies should aim to develop optimal management strategies of patients with both PDAC and hypothyroidism.

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Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

Data supporting the findings of this study are available from the authors upon request.

Author contributions

Ingrid Garajová (Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft, Writing—review & editing), Annalisa Comandatore (Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft, Writing—review & editing), Lenka Boyd (Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft), Mahsoem Ali (Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft), Fabio Gelsomino (Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft), Stefania de Lorenzo (Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft), Giuseppe Pedrazzi (Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft), Andrea Spallanzani (Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft), Giulio Martinelli (Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft), Rita Balsano (Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft), Francesco Leonardi (Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft), Matteo Palmeri

(Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft), Geert Kazemier (Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft), Gregorio Di Franco (Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft), Simone Guadagni (Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft), Niccolò Furbetta (Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft), Manuel Gentiluomo (Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft), Niccolò Ramacciotti (Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft), Giulio Di Candio (Conceptualization, Data curation, Formal analysis, Validation, Writing—original draft), Elisa Giovannetti (Conceptualization, Data curation, Formal analysis, Project administration, Supervision, Validation, Writing—original draft, Writing—review & editing) and Luca Morelli (Conceptualization, Data curation, Formal analysis, Project administration, Supervision, Validation, Writing—original draft, Writing—review & editing)

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