Acta Biomed 2022; Vol. 93, N. 6: e2022268 DOI: 10.23750/abm.v93i6.13366

Original article

Should patients on levothyroxine therapy be screened for pancreatic cancer?

Ingrid Garajová[1], Rita Balsano[1], Matilde Coriano'[1], Fabio Gelsomino[2], Francesco Tovoli[3], Stefania De Lorenzo[4], Paolo Del Rio[5], Raffaele Dalla Valle[5], Matteo Ravaioli[6], Francesco Leonardi[1]

[1]Medical Oncology Unit, University Hospital of Parma, Parma, Italy; [2]Department of Oncology and Hematology, University Hospital of Modena, Modena, Italy; [3]Division of Internal Medicine, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [4]Oncology Unit, Azienda USL Bologna, Bologna, Italy; [5]Department of Medicine and Surgery, University of Parma, Parma, Italy; [6]Department of General Surgery and Transplantation, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

Abstract *Background:* Pancreatic ductal adenocarcinoma is an aggressive disease with increasing incidence. Thyroid hormones play different roles in development and physiological processes of the entire digestive system, including pancreas. Therefore, many have hypothesized that thyroid hormone supplementation for hypothyroidism disorders might increase the risk of malignancy. *Patients and methods:* We conducted retrospective observational mono-centre study. The aim was to examine the prevalence of thyroid disorders among patients with pancreatic cancer. Moreover, we investigated the impact of thyroid hormone supplementation in pancreatic cancer patients' outcome and the correlation with various clinicopathologic parameters. *Results:* A total of 92 consecutive pancreatic cancer patients were retrospectively reviewed: 18.5% patients had a history of hypothyroidism and all received a replacement hormone therapy with levothyroxine, in particular 20% in metastatic group and 11% in radically resected PDAC patients' group. Nor in radically resected neither in metastatic group, we did not observe any statistically significant difference in outcome between the group with or without thyroid disorders. On multivariate analyses, cox proportional hazards model analysis showed that only the presence of perineural invasion was associated with a significantly higher hazard ratio for overall survival in metastatic PDAC patients (HR=2.7; 95%CI=1.029-6.925; p=0.009). *Conclusions:* We observed higher prevalence of thyroid disorders in PDAC patients. Further studies are warranted to explore the impact of levothyroxine therapy on outcome in PDAC patients. (www.actabiomedica.it)

Key words: pancreatic cancer, levothyroxine, hypothyroidism

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the solid tumor with the worst prognosis at all (1,2). Despite ongoing research, PDAC remains one of the most aggressive tumors to contrast with five-year survival rate less than 10%. Radical surgery is the only potentially curative treatment, though, even in this group of radically resected patients, the five-year survival rate is only 20% (3,4)

Thyroid hormones play different roles in development and physiological processes of the entire digestive system (5). The thyroid hormones stimulate different targets, such as TGF-β, hyperphosphorylation of Rb, and MAP kinase pathways (6–8), and, have also been shown to promote angiogenesis in cancer cells

by upregulating HIF-1α (7). Due to the established effect of thyroid hormone on growth and development, many have hypothesized a correlation between hypothyroidism and malignancy. Levothyroxine is a first-line treatment for the hypothyroidism. Levothyroxine therapy is provided to inactivate abnormal thyroid tissue growth or function and to restore the clinical and biochemical euthyroid state in the thyroid gland (9,10). Some evidence exists for hypothyroidism as a possible risk factor for respiratory, colon, breast, liver cancer and also PDAC (11–13).

Based on these considerations, the aim of this retrospective observational study was to examine the prevalence of hypothyroidism and thyroid hormone supplementation (THS) among patients with pancreatic cancer and to correlate THS with patients' outcome and various clinicopathologic parameters.

Materials and methods

Patients and follow-up

A total of 92 consecutive PDAC patients treated between 2015 and 2020 at University Hospital of Parma were retrospectively reviewed using electronic medical records. The presence of hypothyroidism and the treatment with levothyroxine as hormone replacement treatment has been recorded.

Only patients age 18 or more with cytologic or histologic confirmed diagnosis of pancreatic cancer were included. Patients with a diagnosis of concomitant malignancy were excluded. We collected basal clinical and pathological characteristics of our patients: age, ECOG PS, date of surgical resection for pancreatic cancer, histology/cytology, TNM, presence of lymphatic/vascular/perineural invasion, tumour grading, resection margins and tumour biomarkers (CEA and CA19.9 at diagnosis) in patients who underwent surgery or biopsy for PDAC. Moreover, date of relapse after surgery, date of progression after chemotherapy (adjuvant or palliative), type of chemotherapy, date of last follow-up or date of death was collected. The study protocol was approved by the ethics comittee (344/2021/OSS/AOUPR, 8 July 2021) which was in accordance with the Declaration of Helsinki and Good Clinical Practice.

Statistical analysis

The patients were divided into two groups: PDAC patients with or without hypothyroidism and the treatment with levothyroxine as hormone replacement treatment. Clinicopathologic and long-term survival data were collected and reviewed to explore the prognostic implication of hypothyroidism. Overall survival (OS) was calculated from the date of pancreatic cancer diagnosis to the date of death or date of the last follow-up. Relapse-free survival (RFS) was calculated from the date of pancreatic surgery to the date of disease recurrence. Progression-free survival (PFS) was defined as the time of therapy initiation to disease progression or death. OS, RFS and PFS curves were constructed using Kaplan-Meier method, and differences were analyzed using log-rank (Mantel-Cox) test. A Cox proportional hazards model analysis was performed to determine the joint association of several clinical factors investigated (hypothyroidism, CEA, CA 19-9, perineural invasion). The p value was bilaterally tested, and values less than 0.05 were regarded as statistically significant.

Results

Population characteristics

Of 92 PDAC patients included in our study, 45 were male (49%) and 47 were female (51%). The median age at diagnosis was 72 years (range 33-89 years). 41 PDAC patients (44.5%) were metastatic at diagnosis. Out of 27 PDAC patients (29%) who underwent surgery, 14 patients (51.8%) had a relapse of disease after surgery. PDAC patients who had a history of hypothyroidism in THS was 18.5% and they all received a replacement hormone therapy with levothyroxine. We noticed more THS-PDAC in metastatic group (20%) then in radically resected PDAC patients' group (11%).

Basic clinico- pathological characteristics of the 92 patients are detailed in Table 1.

Overall survival in patients affected by metastatic pancreatic cancer

Median OS was not significantly different between the two groups of metastatic PDAC patients

Table 1. Clinico-pathological characteristics of the patients.

Characteristics of 92 PDAC patients		**n (%)**
Sex	Male	45 (49%)
	Female	47 (51%)
Age (years)		72 (33-89)
THS in all PDAC pts	Yes	17 (18.5%) - Female: 15 (88%) - Male: 2 (12%)
	No	75 (81.5%)
Pts who underwent radical surgery for PDAC	Yes	27 (29%)
	No	54 (71%)
THS in radically resected PDAC pts	Yes	3 (11%)
	No	24 (89%)
Relapse after surgery		14 (51.8%)
Relapse after surgery	pts with euthyroidism	10 (71%)
	pts with THS	4 (29%)
Presence of perineural invasion (in resected pts)	Yes	19 (79%)
	No	5 (11%)
Metastatic PDAC pts at diagnosis	Yes	41 (44.5%)
	No	51 (55.5%)
THS in metastatic PDAC pts	Yes	8 (20%)
	No	33 (80%)

with hypothyroidism treated with THS (8 PDAC patients) and euthyroidism (33 PDAC patients), as demonstrated in Fig. 1. Median OS for the whole group was 11.8 months (95% CI 10.2 – 14.3 months). PDAC-THS patients showed a shorter median OS of 10.6 months (95% CI 6.7 – 15.6 months) in comparison to euthyroidism PDAC patients with median OS of 11.8 months (95% CI 10.2 – 14.7 months), though, not statistically significant (p=0.721). The majority of PDAC- THS patients were females (88%).

Progression-free survival and first-line chemotherapy for metastatic PDAC

Out of 41 metastatic PDAC patients who underwent the first-line chemotherapy, 33 (80%) did not present any thyroid disorders. The resting 8 patients (20%) were affected by hypothyroidism on THS, as demonstrated in Fig. 2. Median PFS for the whole group was 6 months (95% CI 4.6 – 7.7 months), not statistically significant between the two groups (p=0.817).

Overall survival in patients in radically resected pancreatic cancer

Median OS was not significantly different between the two groups of radically resected PDAC patients with hypothyroidism treated with THS (3 PDAC patients) and the group of patients without any thyroid disorder (24 PDAC patients). Median OS for the whole group was 16.2 months (95% CI 12.1 – 16.4 months). Any statistically significant difference had been seen between the two groups (p=0.839).

Relapse after surgery

Out of 27 PDAC patients who underwent radical surgery, 14 had disease recurrence (51.8%). From 14 PDAC patients with recurrence after radical

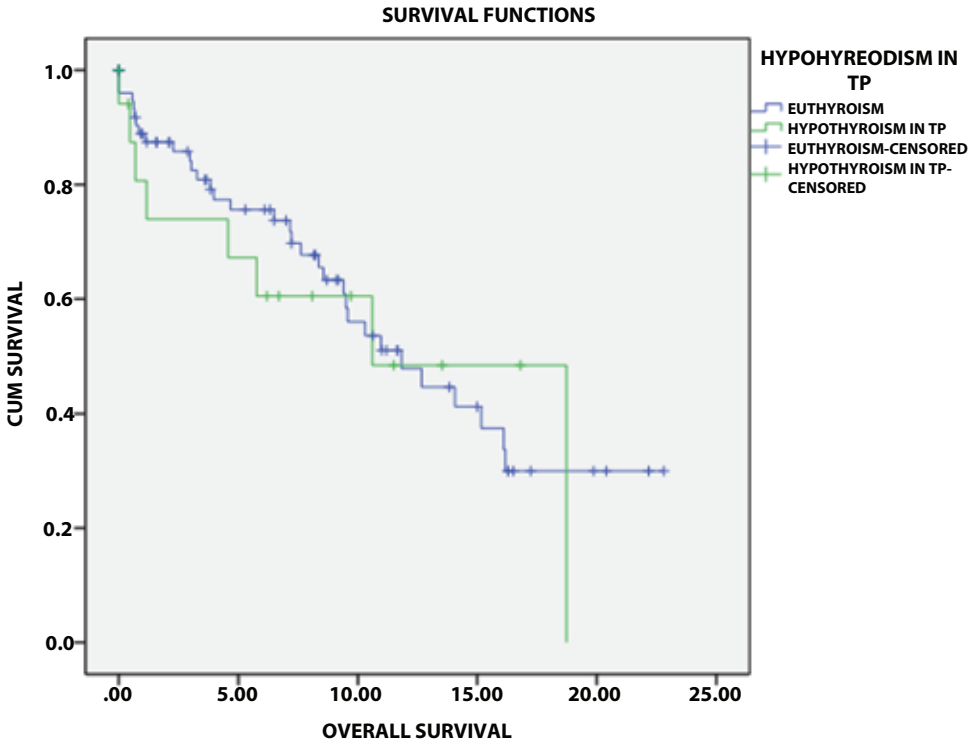

Figure 1. Overall survival in patients affected by metastatic pancreatic cancer with or without thyroid disorders. OS was not significantly different between the two groups of patients with hypothyroidism and euthyroidism (p=0.721).

surgery, 4 (29%) were PDAC-TSH patients and 10 euthyroidism PDAC patients (71%). Median OS was not significantly different between the two groups of recurred PDAC (p=0.352), as demonstrated in Figure 3.

Prognostic factors of overall survival

On multivariate analyses, cox proportional hazards model analysis showed that only the presence of perineural invasion was associated with a significantly higher hazard ratio (HR) for OS in metastatic PDAC patients (HR=2.7; 95%CI=1.029-6.925; p=0.009).

Discussion

In our study, we observed high prevalence of thyroid disorders among patients with pancreatic cancer. In particular, 18.5% of our PDAC patients had a history of hypothyroidism and all received a replacement hormone therapy with levothyroxine. The prevalence was higher in metastatic group of PDAC patients, around 20%. In our study, nor in radically resected neither in metastatic group, we did not observe any influence of thyroid disorders on patients' outcome.

Generally, the prevalence of thyroid disorders increases with age and it account up to 4.4% after 60 years of age, with higher prevalence in females (14–16). Higher prevalence of PDAC patients with thyroid disorders in females was confirmed also in our study. Wu *et al.* (9) conducted a large retrospective control-case study of 601.733 patients and 2 406 932 controls. Patients on THS with levothyroxine showed a 50% higher risk of cancer at any site compared to non-users. In particular, significant increased risks were observed for brain cancer, skin cancer, PDAC and female breast cancer (9). Though, the above-mentioned study described associations and not causal relationships between levothyroxine and cancer risks. In another

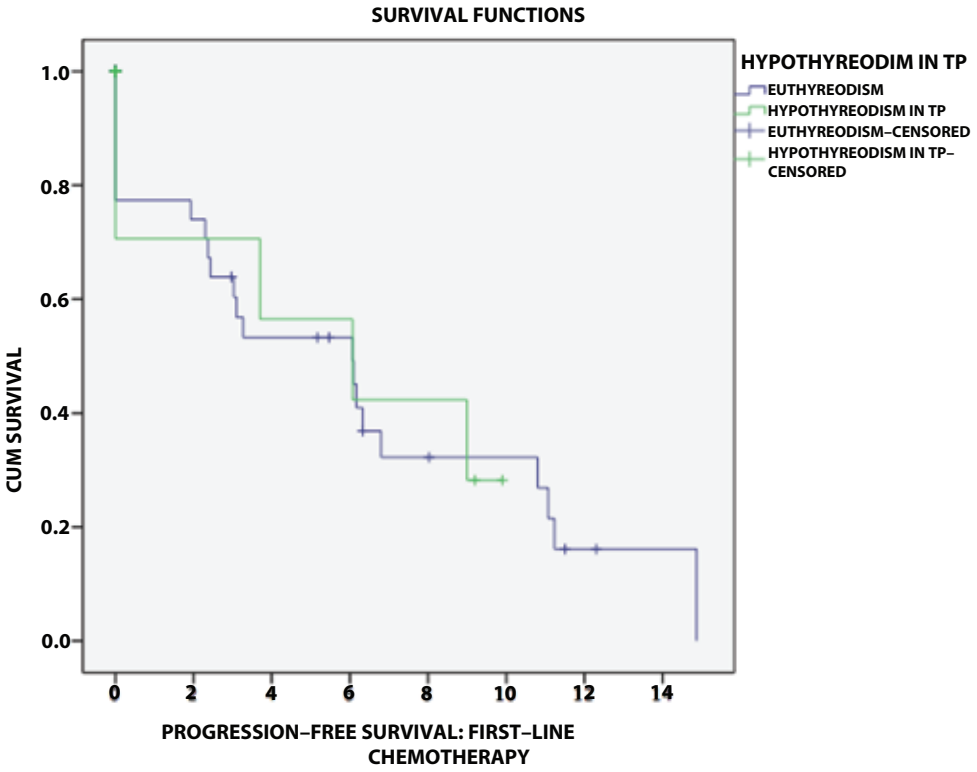

Figure 2. Progression-free survival after first-line chemotherapy in metastatic PDAC, with or without thyroid disorders. PFS was not significantly different between the two groups of patients with hypothyroidism and euthyroidism (p=0.817).

study with 5.000 female patients, it was calculated that the rate of breast cancer in patients taking thyroid supplements for hypothyroidism was 12.1% versus 6.2% in a control group (17). Cornelli *et al.* (18) reported correlation between levothyroxine and an increased risk of lung cancer; however, long-term use of levothyroxine was associated with a reduction in risk of colorectal cancer (11). The higher prevalence of thyroid disorders in PDAC patients have been reported by Sarosiek *et al.* (8) comparable to our study (14.1%). Interestingly, Strzalka *et al.* (19) measured the concentration of D-dimers and thyroid hormones in blood samples from portal and peripheral vein intraoperatively. The peripheral FT3 level showed statistically significant negative correlation with portal D-dimer concentration level and therefore, the authors suggested that FT3 or its receptors can influence PDAC progression (19).

Some studies even suggest that a diagnosis of hypothyroidism may result in poor response to therapy in cancer patients (8,20). In our study, we did not observe any statistically significant difference in PDAC patients' outcome with or without thyroid disorders, in the terms of OS, PFS and RFS. Sarosiek *et al.* (8) found that hypothyroid patients taking exogenous thyroid hormone were more than three times likely to have perineural invasion, and about twice as likely to have higher T stage, nodal spread, and overall poorer prognostic stage. In accordance with our study, and despite these poor prognostic factors, there was no significant difference in OS between patients taking thyroid hormone supplementation compared to patients who were not on medication. Interestingly, the authors evaborate an original hypothesis that spontaneous hypothyroidism might develop in cancer patients as a protection mechanism against tumor spread, but thyroid hormone supplementation might contrast this action (8). This might be supported by some small clinical studies that observed that lowering of serum-free T4 may be associated with extended survival in patients with some terminal cancers, though, remain only hypothesis (21).

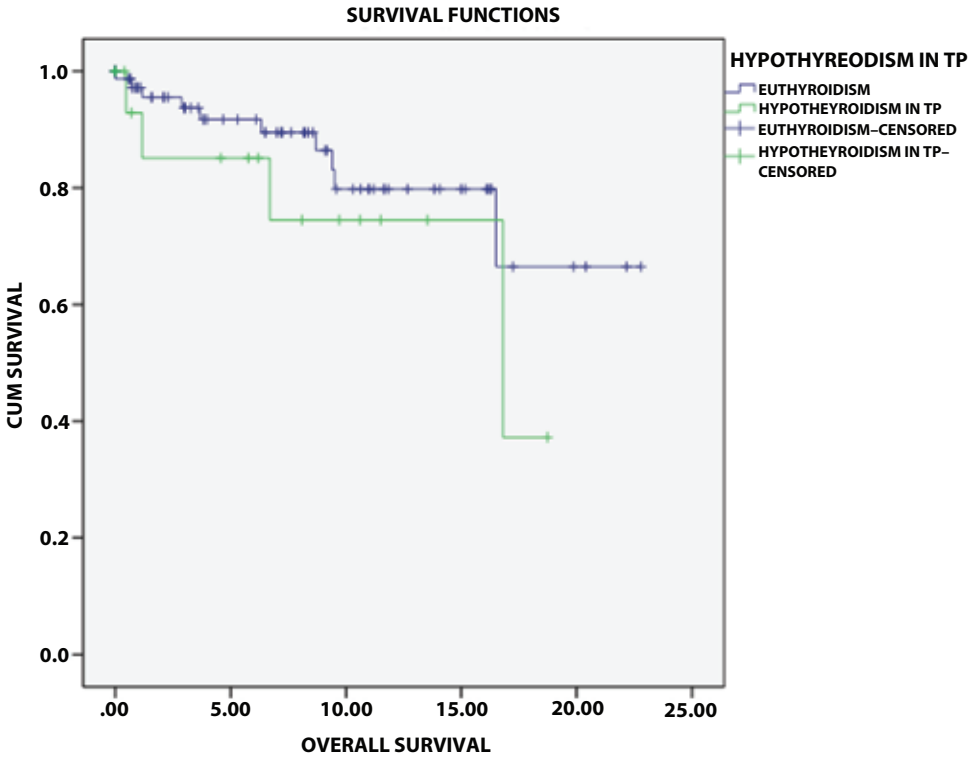

Figure 3. Overall survival in patients with radically resected PDAC with recurrence with or without thyroid disorders. OS was not significantly different between the two groups of PDAC patients with recurrence with hypothyroidism and euthyroidism (p=0.352).

In our study, due to small number, we were not able to establish the correlation between perineural invasion and hypothyroidism. Perineural invasion plays a role as important factor involved in progression and invasion in PDAC (22). Crippa *et al.* showed that perineural invasion is associated with worse DFS in patients who underwent surgical resection for PDAC (23). Moreover, another limitation of our study was little information available regarding the diagnosis of hypothyroidism, in particular duration of hypothyroidism and thyroid hormone supplementation, TSH measurement was not used at the diagnosis of PDAC).

Conclusion

In conclusion, we observed high prevalence of hypothyroidism on levothyroxine supplementation therapy among PDAC patients. Further studies with a larger study population is necessary to confirm the impact of thyroid disorders on pancreatic cancer.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol. 2018; 24(43):4846-4861.
2. Tonini V, Zanni M. Pancreatic cancer in 2021: What you need to know to win. World J Gastroenterol. 2021; 27(35):5851-5889.
3. Balsano R, Tommasi C, Garajova I. State of the Art for Metastatic Pancreatic Cancer Treatment: Where Are We Now? Anticancer Res. 2019; 39(7):3405-3412.
4. Digiacomo G, Volta F, Garajova I, Balsano R, Cavazzoni A. Biological Hallmarks and New Therapeutic

Approaches for the Treatment of PDAC. Life (Basel). 2021; 11(8):843.
5. Brown AR, Simmen RC, Simmen FA. The role of thyroid hormone signaling in the prevention of digestive system cancers. Int J Mol Sci. 2013; 14(8):16240-57.
6. Tang HY, Lin HY, Zhang S, Davis FB, Davis PJ. Thyroid hormone causes mitogen-activated protein kinase-dependent phosphorylation of the nuclear estrogen receptor. Endocrinology. 2004; 145(7):3265-72.
7. Pinto M, Soares P, Ribatti D. Thyroid hormone as a regulator of tumor induced angiogenesis. Cancer Lett. 2011; 301(2):119-26.
8. Sarosiek K, Gandhi AV, Saxena S, et al. Hypothyroidism in Pancreatic Cancer: Role of Exogenous Thyroid Hormone in Tumor Invasion-Preliminary Observations. J Thyroid Res. 2016; 2016:2454989..
9. Wu CC, Islam MM, Nguyen PA, et al. Risk of cancer in long-term levothyroxine users: Retrospective population-based study. Cancer Sci. 2021; 112(6):2533-2541.
10. Pinto A, Glick M. Management of patients with thyroid disease: oral health considerations. J Am Dent Assoc. 2002; 133(7):849-58.
11. Rennert G, Rennert HS, Pinchev M, Gruber SB. A case-control study of levothyroxine and the risk of colorectal cancer. J Natl Cancer Inst. 2010; 102(8):568-72.
12. Kuijpens JL, Nyklíctek I, Louwman MW, Weetman TA, Pop VJ, Coebergh JW. Hypothyroidism might be related to breast cancer in post-menopausal women. Thyroid. 2005; 15(11):1253-9.
13. Goldman MB, Monson RR, Maloof F. Cancer mortality in women with thyroid disease. Cancer Res. 1990; 50(8): 2283-9.
14. Bensenor IM, Olmos RD, Lotufo PA. Hypothyroidism in the elderly: diagnosis and management. Clin Interv Aging. 2012; 7:97-111.
15. Cappola AR, Fried LP, Arnold AM, et al. Thyroid status, cardiovascular risk, and mortality in older adults. JAMA. 2006; 295(9):1033-41.
16. Benseñor IM, Goulart AC, Lotufo PA, Menezes PR, Scazufca M. Prevalence of thyroid disorders among older people: results from the São Paulo Ageing & Health Study. Cad Saude Publica. 2011; 27(1):155-61.
17. Kapdi CC, Wolfe JN. Breast cancer. Relationship to thyroid supplements for hypothyroidism. JAMA. 1976; 236(10): 1124-7.
18. Cornelli U, Belcaro G, Recchia M, Finco A. Levothyroxine and lung cancer in females: the importance of oxidative stress. Reprod Biol Endocrinol. 2013; 11:75.
19. Strzałka A, Hogendorf P, Skulimowski A, Spychalski M, Strzelczyk J, Durczynski A. Thyroid hormones concentration in portal and peripheral blood in patients with pancreatic cancer: Preliminary study. Cancer Biomark. 2020; 29(3):301-306.
20. Aranda A, Martínez-Iglesias O, Ruiz-Llorente L, García-Carpizo V, Zambrano A. Thyroid receptor: roles in cancer. Trends Endocrinol Metab. 2009; 20(7):318-24.
21. Hercbergs A, Johnson RE, Ashur-Fabian O, Garfield DH, Davis PJ. Medically induced euthyroid hypothyroxinemia may extend survival in compassionate need cancer patients: an observational study. Oncologist. 2015; 20(1):72-6.
22. Gasparini G, Pellegatta M, Crippa S, et al. Nerves and Pancreatic Cancer: New Insights into a Dangerous Relationship. Cancers (Basel). 2019; 11(7):893. doi: 10.3390/cancers11070893. PMID: 31248001; PMCID: PMC6678884.
23. Crippa S, Pergolini I, Javed AA, et al. Implications of Perineural Invasion on Disease Recurrence and Survival After Pancreatectomy for Pancreatic Head Ductal Adenocarcinoma. Ann Surg. 2020.

Correspondence:
Received: 19 June 2022
Accepted: 8 July 2022
Dr. Ingrid Garajová,
Medical Oncology Unit,
University Hospital of Parma, Parma, Italy;
Tel: +39-521-702660, Fax: +39-521-702678,
E-mail: ingegarajova@gmail.com