Evaluation of Multidisciplinary Team decisions in the management of neuroendocrine tumors: impact of expert centers

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ABSTRACT

Introduction: Guidelines require to discuss all patients with a neuroendocrine tumor (NET) in a multidisciplinary team (MDT) but the true value of the MDT for NETs has never been assessed on a multicenter level.

Methods: All newly referred GEP-NET patients discussed in the MDT, from April 1st to October 1st 2017, in the MDT of seven European expert centers were prospectively included. The referral letter was reviewed for histopathological diagnosis, biomarkers and imaging according to ENETS guidelines. The recommendations for new diagnostic and/or therapeutic procedures were recorded after MDT. A significant change for the patient was defined as a change in diagnosis, grade, stage or treatment.

Results: A total of 292 patients were included mainly with pancreatic (28%) and small intestinal NET (32%) and with distant metastases (51%). Patients had received prior surgery in 43% and prior medical treatment in 32% of cases. A significant change occurred in 61% of cases of which 7% change in diagnosis, 16% change in stage and 8% change in grade. The indication to start a new treatment was recommended by the MDT for 51% of patients, mainly surgery (9%) or somatostatin analogues (20%). A significant change was most frequently observed in patients with stage IV disease (HR 3.6, 95% CI: 1.9-6.9 vs stage I) and grade 2 NETs (HR 2.1 95% CI 1.2-3.8 vs G1).

Conclusion: NET-dedicated MDT discussion in expert centres yield significant management changes, especially those with in stage IV and/or G2 NETs. Hence, MDT discussion in an expert centre adds value to diagnosis and management of NEN patients should be systematic.

INTRODUCTION

Recent years have shown a significant increase in treatment options for patients with neuroendocrine tumors (NETs).[1] The recognized increase in incidence of these relatively rare neoplasms and the change in treatment paradigms justify the essential role of multidisciplinary teams (MDTs) to optimize the management of these patients.[2,3] Indeed, multidisciplinary expertise is mandatory to find solutions to the numerous challenges in diagnostics and therapeutics, and translate them into patient tailored management. Although the number of therapeutic options has increased over the last decades, few direct comparisons have been made between treatments. For inoperable metastatic low-grade neuroendocrine tumors (NETs) the first line of therapy is often a somatostatin analogue (SSA).[4-6] However, data regarding therapeutic sequences are lacking and there is currently no preferred second line treatment. Chemotherapy, peptide receptor radionuclide therapy (PRRT) using a radiolabeled SSA and targeted therapies are in fact all registered for NETs that progress despite treatment with a SSAs.[4] The appropriate choice of diagnostics can also be challenging due to the various options, including different functional imaging techniques for somatostatin receptor imaging (SRI), as DOTA-TOC, DOTA-TATE and DOTA-NOC or PET/CT with ^{18}F-FDG.[7,8] Therefore the management of patients with NETs requires cooperation between a wide variety of medical professionals in a MDT meeting, including medical oncologists, gastroenterologists, endocrinologists, surgeons, pathologists, radiologists and nuclear medicine physicians. The need for a MDT meeting is highlighted in different national NET guidelines[9,10] and the benefits have been demonstrated in several kinds of malignancies and in many countries.[11] It generally yields changes in management and an increased adherence to guidelines.[12] Most importantly, in some studies, discussing cases in MDT meetings is associated with a better survival.[13,14] The impact of the MDT meeting on the management of patients has not been specifically assessed so far, in multiple NET centers with quantifiable outcomes. The aim of this study was to evaluate the impact of MDT meetings on the management of NET patients. through the evaluation of the changes in diagnosis and/or treatment strategy after discussion in the MDT meeting in NET-dedicated expert centers.

PATIENTS AND METHODS

A prospective study was performed including all consecutive newly referred NET patients discussed in a NET-dedicated between April 1st to October 1st 2017, in seven European NET expert centers. These expert centers were deemed eligible for entry into the study as they fulfilled the minimum threshold of new referrals defined by ENETS of at least 80 new patients with a NET per year. Data collection was performed in line with the regulations of the respective expert centers. Patient data were anonymized, stored and collected respecting

the Caldicott principles or the country specific local guidelines. The study was registered as appropriate for the individual expert centers.

MDT meetings were attended by medical oncologists, surgeons, gastroenterologists, radiologists and pathologists and several centers also included endocrinologists and nuclear medicine physicians. The MDT meetings were held on a weekly basis in all centers. After discussion in the MDT meeting the generated outcome was advised. This advice from the expert center was noted and recorded in the database.

All new patients discussed in the MDT meeting were included and recommendations by the MDT were noted. Firstly the data parameters provided by the referring centers were reviewed to asses completeness and adherence to current ENETS guidelines with regard to pathology and imaging. Therefore, the referral to the NET center was reviewed for 1) baseline histopathological report including neuroendocrine markers (chromogranin, synaptophysin), differentiation and proliferation index (Ki67 and/or mitotic index); 2) baseline imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) in combination with SRI; 3) circulating biomarkers: plasma chromogranin A (CgA) concentration and urinary 5-hydroxyindoleacitic acid (5-HIAA) excretion for small-intestinal NET.

All these variables were collected initially by the local expert center and then merged into a common database for statistical analysis. Referral data were directly compared with the conclusions from the MDT. Specifically, revision of the pathology was recorded including diagnosis (new diagnosis of NET or revision to other neoplasm than NET), grading and staging. Tumors were graded and staged in accordance with the WHO 2010 and the ENETS guidelines.[15-18] The advice of the MDT meeting on further diagnostics and therapy was also registered. Patients were stratified into three subgroups, depending on prior therapies: 1) treatment-naïve, 2) prior surgery alone and 3) patients with prior medical therapy (and potentially surgery).

The primary endpoint was defined as a significant change after MDT and was measured as following: 1) change in diagnosis, 2) change in ENETS grade or stage, 3) recommendation for new treatment or 4) advice to discontinue therapy. Additional recommendations for diagnostics were not considered a significant change as it does not always result in a change of prognosis or treatment the patient. Statistical analyses were performed with SPSS for Windows software (version 23.0, SPSS Inc.) Qualitative variables were described using their frequencies (percentages) and compared using the Chi-2 test. Logistic regression was used to calculate hazard ratios for a significant change in diagnosis or therapy. All tests were two-sided and any p-value < 0.05 was considered statistically significant.

RESULTS

A total of 292 newly referred NET patients were included. Patients were mostly referred with the intention of a formal clinical review (72%) or a second opinion (28%). Their features before the MDT meeting are presented in Table 1. Patients mainly had a NET that originated from the pancreas (28%), small intestine (32%) or stomach/duodenum (11%). At referral, these NETs were mainly classified as grade 1 (43%) and 51% of patients had distant metastases (stage IV). At referral 93 patients (32%) were receiving or had received previous treatment, including SSAs in 63 of them (62%). Other previous therapies included PRRT (n=24, 24%), everolimus (n=10, 10%) and chemotherapy (n=28, 28%). Furthermore, 124 (43%) of patients had previously undergone surgery.

Table 1: Referral characteristics (n=292)

Type of Referral	
Full referral, n (%)	209 (71.6)
Second opinion, n (%)	83 (28.4)
Primary Tumor, n (%)	
Pancreas	82 (28.1)
Small intestinal	94 (32.2)
Gastroduodenal	32 (11.0)
Rectum	24 (8.2)
Appendix	13 (4.6)
Other GI	14 (4.8)
Unknown	33 (11.3)
Grade, n (%)	
Grade 1	125 (42.8)
Grade 2	79 (27.1)
Grade 3	35 (12.0)
Missing	53 (18.2)
Stage IV, n (%)	151 (52.2)
Prior medical treatment, n (%)	93 (31.8)
Prior surgical treatment, n (%)	124 (42.5)

Referral

All referral letters were screened for the reporting of the pathology, imaging and biomarkers (Figure 1). The pathology reports from referring centers had documented the immunohistochemistry of synaptophysin in 195 (67%) and chromogranin in 185 cases (63%). Chromogranin was most frequently reported in gastroduodenal (84%) and rectal NETs (75%), but only in 56% referrals of small-intestinal (si)NETs (p=0.005). This was similar for synaptophysin, which was reported most frequently reported in gastroduodenal (88%) and appendix NETs (85%)

than in small intestinal NETs (59%, p=0.01). Grade was reported in 78% of patients with no difference between primary tumors (p=0.16). Grading was mainly determined using the Ki67 index (78%) whereas mitotic count was less frequently used (29%). In total 63% of referrals reported all neuroendocrine markers, grading and stage.

With respect to the imaging at referral, the referring centers had performed prior cross-sectional imaging in 92% of patients, which mainly consisted of CT (82%). In addition, 52% of patients had prior somatostatin-receptor imaging. Overall, 88% of referrals included staging of the patient. In terms of biochemical assessments it was noted that in patients with small intestinal NET, 59% were screened for serotonin secretion with plasma or urinary 5-HIAA. Lastly, plasma chromogranin A was determined by the referring center in 56% of referred patients.

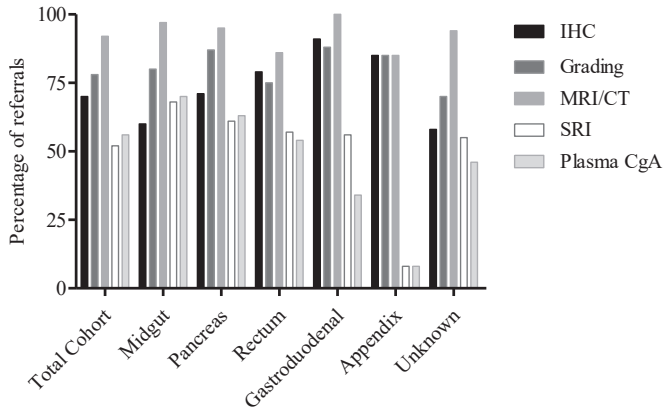

Figure 1: Diagnostics performed prior to referral
IHC: immunohistochemistry; SRI: somatostatin receptor imaging; CgA: chromogranin A

MDT Outcome: diagnostics

After selected pathology revision in the expert center MDT, in 5 cases (2%) a diagnoses of NET was excluded. In a further 15 patients (5%) the pathological diagnosis was changed from a non-neuroendocrine neoplasm to a NET. Of 239 patients with prior grading the Ki67 was changed in 121 (51%) patients and this resulted in a change of ENETS grade in 22 patients (9%). In 24 patients no grading could be performed.

During MDT, additional cross-sectional or nuclear imaging was advised for 59% of patients consisting of CT-scan (n=54, 19%), MRI (n=50, 17%), SRI (n=86, 30%), or another nuclear imaging like ^{18}FDG-PET (n=19, 7%). Among 125 treatment-naïve patients additional imaging was advised in 64% of them (Figure 2a). SRI was mostly advised (54%), sometimes in combination with CT (CT+SRS: 13%). In patients with prior surgery alone, additional imaging was advised in 45% of patients and mainly morphological imaging (23%), SRI (16%) or both (11%) were advised (Figure 2b). In patient with prior treatment for a NET an MRI was advised in 24% of patients (Figure 2c).

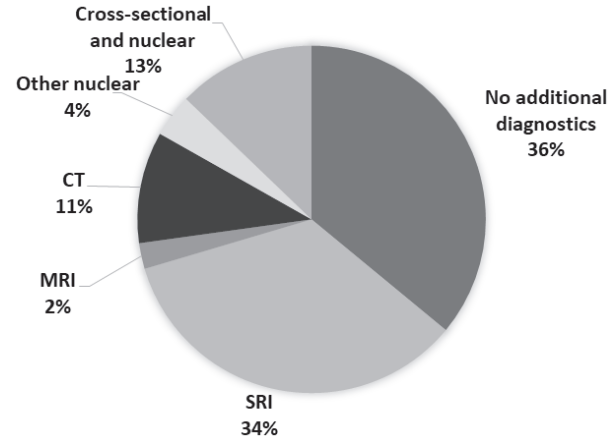

Figure 2a: Diagnostics advised by MDT in treatment-naïve patients

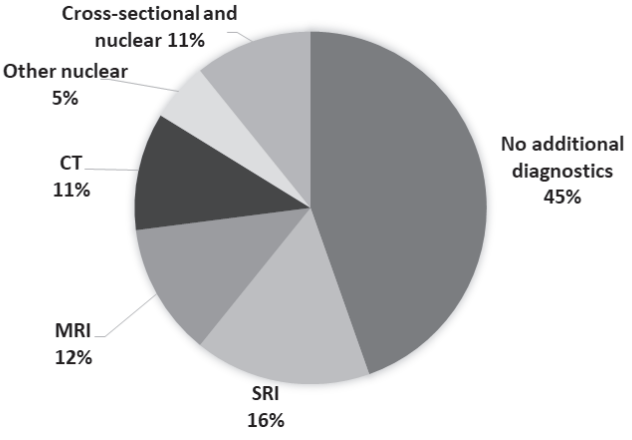

Figure 2b. Diagnostics advised by MDT in patients with prior surgery

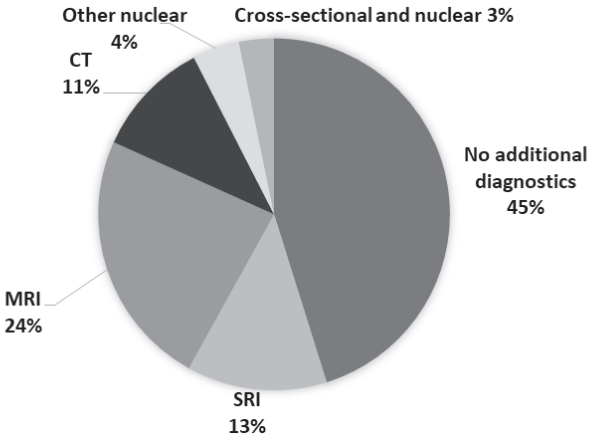

Figure 2c. Diagnostics advised by MDT in patients with prior medical treatment

ENETS stage after MDT was concordant with stage of referral in 93% of patients, but in a further 7% revision in the MDT meeting resulted in a higher stage (Table 2). This occurred mostly for patients with a stage III NET (29%, p=0.03). Of 35 patients without staging at referral, 29 (83%) could be staged with new imaging or pathology.

Table 2: Staging before and after MDT

		Stage before MDT					
		I	**II**	**III**	**IV**	**NA**	**Total**
Stage after MDT	**I, n(%)**	**53 (91.3)**	0	0	0	5 (14.4)	57
	II, n(%)	2 (3.5)	**11 (91.7)**	0	0	4 (11.4)	17
	III, n(%)	1 (1.7)	0	**27 (71.1)**	1 (0.7)	7 (20.0)	36
	IV, n(%)	2 (3.5)	1 (8.3)	11 (28.9)	**148 (99.3)**	13 (37.1)	173
	NA, n(%)	0	0	0	0	6 (17.1)	9
		58	12	38	149	35	292

MDT outcome: treatment

In patients without previous medical or surgical treatment (n=125, 43%) follow-up alone was advised in 46% of them (Figure 2a). This group consisted largely of patients with stage I or II gastroduodenal (n=15, 26%) or rectal NET (n=14, 25%), but follow-up was also suggested in stage III and IV small intestinal (n=7), pancreatic (n=5), appendix (n=2) and stomach NET (n=1). For three patients with a localized stage I pNET follow-up was advised as well. In the remaining 68 patients (54%) a large variety of first line therapies was selected. In 19 patients (15%) a surgical resection was suggested. First line medical therapies included SSA (n=35, 28%) and chemotherapy (n=11, 7%). In 27% of patients (n=26) follow-up was preferred and no therapy was started.

After surgery alone (n=74), for 70% (n=52) of patients follow-up was advised. This group consisted largely of patients with localized disease (76%). In 34% of patients with stage IV disease (n=11) follow-up was advised and in another 31% of patients (n=10) a SSA was advised. Among previously treated patients, a SSA was either started or continued in 53% of them. Other therapies included PRRT (17%), chemotherapy (8%) and targeted therapy (5%).

Stage at referral highly determined therapy as indeed low stage NETs are mainly followed-up (after resection) whereas a higher incidence of therapy change was noted for stage 4 tumors (Table 3, p<0.001).

MDT outcome: impact

Altogether the MDT meetings resulted in a significant change for 61% of patients. Twenty patients (7%) had a change in diagnosis, 47 (16%) a change in stage (including unknown stage at referral) and another 22 (8%) a change in grade. In addition in 150 patients (51%) a new line of therapy was advised. A significant change was most frequent for patients with

Table 3: Advised therapy stratified for stage

		Stage				
		I	**II**	**III**	**IV**	**NA**
Therapy	**SSA, n(%)**	3 (5.2)	0	4 (11.1)	48 (27.4)	2 (33.3)
	PRRT, n(%)	0	0	2 (5.6)	17 (9.7)	0
	Targeted therapy, n(%)	0	0	0	8 (4.6)	0
	Chemotherapy, n(%)	1 (1.7)	0	2 (5.6)	16 (9.1)	0
	Resection, n(%)	5 (8.6)	4 (23.5)	5 (13.9)	9 (5.1)	2 (33.3)
	Follow-up/no change, n(%)	49 (84.5)	12 (70.6)	21 (58.4)	74 (42.3)	0
	Other, n(%)	0	1 (5.9)	2 (5.6)	3 (1.7)	2 (33.3)
		58	17	36	175	6

SSA: somatostatin analogue
PRRT: peptide receptor radionuclide therapy

ENETS stage IV NET (HR 3.6, 95% CI: 1.9-6.9 vs stage I) and grade 2 tumors (HR 2.1 95% CI:1.2-3.8 vs. grade 1). For patients with a primary tumor from the rectum, appendix or stomach a significant change was less frequent when compared to cases with unknown primary (Table 4)

Table 4: Hazard ratios for a significant change (e.g. change in diagnosis, grade, stage or therapy)

Primary Tumor (HR ± 95% CI)	
Unknown	*Reference*
Pancreas	0.52 (0.20-1.33)
Small intestinal	0.49 (0.19-1.27)
Gastroduodenal	0.24 (0.08-0.70)
Rectum	0.14 (0.04-0.41)
Appendix	0.17 (0.04-0.68)
Other GI	0.67 (0.16-2.81)
Grade	
Grade 1	*Reference*
Grade 2	2.13 (1.18-3.83)
Grade 3	1.31 (0.6-2.79)
Stage	
Stage I	*Reference*
Stage II	1.36 (0.38-4.83)
Stage III	2.61 (1.13-6.06)
Stage IV	3.65 (1.93-6.91)

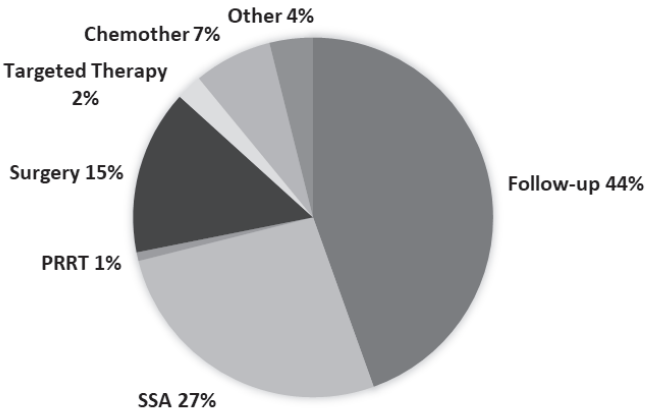

Figure 3a. Therapy selection in patients without prior treatment.

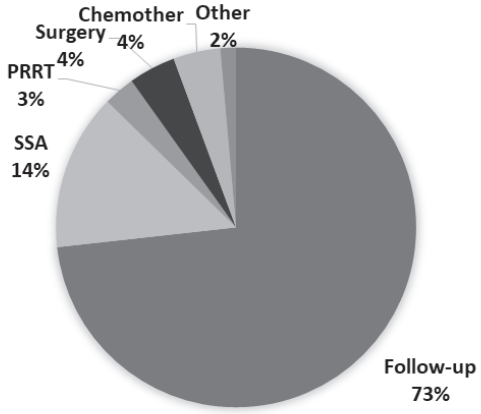

Figure 3b. Therapy selection in patients with prior surgery alone.

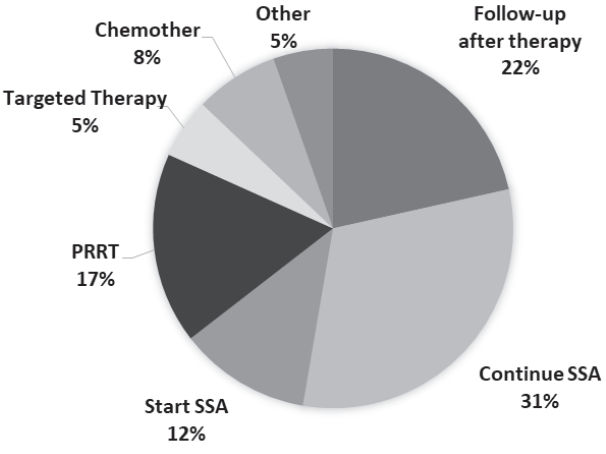

Figure 3c. Therapy selection in patients with prior medical treatment

DISCUSSION

Although the incidence of NET is increasing, they are still regarded as rare.[19] Furthermore, the treatment of these patients is highly individualized because of paucity of guidelines for therapy sequencing.[4] For these reasons it is advocated to refer patients to expert centers and to discuss cases in a MDT meeting, but the true benefit has not yet been quantified for NETs to date. This international study, including patients from seven European expert centers, demonstrates a significant change for the management of NET patients following MDT discussion. Firstly, the review of histopathology changed the diagnosis in 7% of patients and tumor grade in 8%. Also, for a large number of patients new imaging was performed, mainly MRI or nuclear imaging. Together with the revision of previous imaging this resulted in a change of ENETS stage in 16% of patients. Lastly, 51% of patients were offered a new line of therapy..

The referral itself was studied for reporting of previous diagnostics. Altogether 63% of referrals were complete for pathology (neuroendocrine immunohistochemistry and grading) and ENETS stage. This should be considered as a minimum standard for referral as circulating biomarkers and cross-sectional imaging are not always indicated in all NET. As most referrals will come from non-expert centers the referral process might benefit from a standardized form for referral or consultation prior to referral. This can also benefit the efficiency of the MDT meeting as the MDT meeting mainly impacts patients with stage III or IV NETs and less likely impacts patients with low stage appendix, rectal or gastroduodenal NET (Table 4). In general, referral to an expert MDT increases the consistency of the clinical work-up of patients with a NET, as was shown in a previous study.[2] An increased adherence to guidelines has also been demonstrated in esophageal cancer as in patients discussed in MDT adherence was 98% compared to 83% in patients not discussed.[20]

The MDT meeting has mainly been studied in other cancers than NET. In a systematic review the MDT meeting was shown to change patient management in 5-52% and diagnostic reports in 4-35% of cases with gastrointestinal, lung, urological and gynecological cancer.[11] In the current study we demonstrate a comparable change of 61% for diagnostic reports and patient management combined. However, a limitation of our study is that while we demonstrated a change in diagnosis or treatment in a majority of patients it remains unclear whether it influences survival or quality of life. To date, an increase of overall survival has not been reported in any randomized controlled trial including patients with low-grade NET. Still, studies demonstrated that survival has increased in recent years with new therapies becoming available.[19] In a single study, patients with NETs treated in expert centers had a longer average survival than patients treated outside the centers. *Townsend et al.* reported a median survival of 112 months for NET patients treated in a specialized center in Australia versus only 32 months for patients treated elsewhere in the same period.[3] Although this might be partly caused by patients receiving more lines of therapy such large difference in

median survival suggests a certain bias. In various other types of other malignancies the MDT is associated with an increase in overall survival. In a study by *Lordan and colleagues* in patients with metastatic colorectal cancer the 3- and 5-year survival were respectively 68% and 50% in the expert center and 54 and 43% in the local MDT.[21] But also higher survival rates for patients discussed in an MDT for head neck and oral cancers have been reported.[22,23] In other types of cancer the MDT has been associated with an increase of patient and clinician satisfaction due to an improvement in communication[24].

CONCLUSION

Several national guidelines advise discussing patients with a NET in a MDT. The current study demonstrates a significant change in diagnosis and management in 61% of patients, newly referred to an expert MDT. Together with evidence from other cancers this emphasizes the need to discuss all patients with a NET in expert NET specific MDT. This paper provides further evidence for the need for discussion in these frequently complex and rare cases. Future studies may be able to review the impact on survival but this may prove difficult to assess

REFERENCE

1. Zandee WT, de Herder WW. The Evolution of Neuroendocrine Tumor Treatment reflected by ENETS Guidelines. *Neuroendocrinology* 2018.
2. Tamagno G, Sheahan K, Skehan SJ, et al. Initial impact of a systematic multidisciplinary approach on the management of patients with gastroenteropancreatic neuroendocrine tumor. *Endocrine* 2013; **44**(2): 504-9.
3. Townsend A, Price T, Yeend S, Pittman K, Patterson K, Luke C. Metastatic carcinoid tumor: changing patterns of care over two decades. *Journal of clinical gastroenterology* 2009; **44**(3): 195-9.
4. Pavel M, O'Toole D, Costa F, et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. *Neuroendocrinology* 2016; **103**(2): 172-85.
5. Rinke A, Muller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol* 2009; **27**(28): 4656-63.
6. Caplin ME, Pavel M, Ruszniewski P. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 2014; **371**(16): 1556-7.
7. Poeppel TD, Binse I, Petersenn S, et al. 68Ga-DOTATOC versus 68Ga-DOTATATE PET/CT in functional imaging of neuroendocrine tumors. *J Nucl Med* 2011; **52**(12): 1864-70.
8. Velikyan I, Sundin A, Sorensen J, et al. Quantitative and qualitative intrapatient comparison of 68Ga-DOTATOC and 68Ga-DOTATATE: net uptake rate for accurate quantification. *J Nucl Med* 2014; **55**(2): 204-10.
9. Ramage JK, Ahmed A, Ardill J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut* 2012; **61**(1): 6-32.
10. Neuro-endocrine tumoren. Versie 1.0. Utrecht: IKNL. 2013.
11. Pillay B, Wootten AC, Crowe H, et al. The impact of multidisciplinary team meetings on patient assessment, management and outcomes in oncology settings: A systematic review of the literature. *Cancer Treat Rev* 2016; **42**: 56-72.
12. van Hagen P, Spaander MC, van der Gaast A, et al. Impact of a multidisciplinary tumour board meeting for upper-GI malignancies on clinical decision making: a prospective cohort study. *Int J Clin Oncol* 2013; **18**(2): 214-9.
13. Bydder S, Nowak A, Marion K, Phillips M, Atun R. The impact of case discussion at a multidisciplinary team meeting on the treatment and survival of patients with inoperable non-small cell lung cancer. *Intern Med J* 2009; **39**(12): 838-41.
14. MacDermid E, Hooton G, MacDonald M, et al. Improving patient survival with the colorectal cancer multi-disciplinary team. *Colorectal Dis* 2009; **11**(3): 291-5.
15. Bosman FT, World Health O. WHO classification of tumours of the digestive system. Lyon, France.: IARC Press; 2010.
16. Niederle B, Pape UF, Costa F, et al. ENETS Consensus Guidelines Update for Neuroendocrine Neoplasms of the Jejunum and Ileum. *Neuroendocrinology* 2016; **103**(2): 125-38.
17. Delle Fave G, O'Toole D, Sundin A, et al. ENETS Consensus Guidelines Update for Gastroduodenal Neuroendocrine Neoplasms. *Neuroendocrinology* 2016; **103**(2): 119-24.
18. Falconi M, Eriksson B, Kaltsas G, et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. *Neuroendocrinology* 2016; **103**(2): 153-71.

19. Dasari A, Shen C, Halperin D, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol* 2017; **3**(10): 1335-42.
20. Freeman RK, Van Woerkom JM, Vyverberg A, Ascioti AJ. The effect of a multidisciplinary thoracic malignancy conference on the treatment of patients with esophageal cancer. *Ann Thorac Surg* 2011; **92**(4): 1239-42; discussion 43.
21. Lordan JT, Karanjia ND, Quiney N, Fawcett WJ, Worthington TR. A 10-year study of outcome following hepatic resection for colorectal liver metastases - The effect of evaluation in a multidisciplinary team setting. *Eur J Surg Oncol* 2009; **35**(3): 302-6.
22. Wang YH, Kung PT, Tsai WC, Tai CJ, Liu SA, Tsai MH. Effects of multidisciplinary care on the survival of patients with oral cavity cancer in Taiwan. *Oral Oncol* 2012; **48**(9): 803-10.
23. Friedland PL, Bozic B, Dewar J, Kuan R, Meyer C, Phillips M. Impact of multidisciplinary team management in head and neck cancer patients. *Br J Cancer* 2011; **104**(8): 1246-8.
24. Prades J, Remue E, van Hoof E, Borras JM. Is it worth reorganising cancer services on the basis of multidisciplinary teams (MDTs)? A systematic review of the objectives and organisation of MDTs and their impact on patient outcomes. *Health policy (Amsterdam, Netherlands)* 2014; **119**(4): 464-74.