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SPECIAL SECTION: NEUROENDOCRINE NEOPLASMS

Preliminary experience with a new institutional tumor board dedicated to patients with neuroendocrine neoplasms

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Abstract

Purpose To determine the decision patterns of a neuroendocrine neoplasm (NEN) tumor board (TB) and the factors behind those.

Methods We retrospectively reviewed all NEN-TB recommendations from 07/2018 to 12/2021 and recorded patient characteristics, TB outcomes and associations between them.

Results A total of 652 patient entries were identified. Median age of participants was 61 years and an equal number of men and women were presented. Most patients (33.4%) had tumors originating in the small bowel with 16.8% of high grade and 25.9% of pancreatic origin. Imaging was reviewed 97.2% of the time, with most frequently reviewed modalities being PET (55.3%) and CT (44.3%). Imaging review determined that there was no disease progression 20.8% of the time and significant treatment changes were recommended in 36.1% of patients. Major pathology amendments occurred in 3.7% of cases and a clinical trial was identified in 2.6%. There was no association between patient or disease presentation with the tumor board outcomes. There was a slight decrease in number of patients discussed per session, from 10.0 to 8.2 ($p < 0.001$) when the TB transitioned to a virtual format during the COVID-19 pandemic but all other factors remained unchanged.

Conclusion NEN-TB relies heavily on image review, can impact significant treatment changes in patients with rare tumors like NENs, and was not affected by the switch to a virtual format. Finally, none of the examined factors were predictive of the tumor board recommendations.

Keywords Neuroendocrine neoplasm · Carcinoid · Multidisciplinary tumor board · Recommendations

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Introduction

Patients with rare tumors such as neuroendocrine neoplasms (NENs) are treated with a variety of differing approaches because of limited prospective high quality data. This is an inherent problem in a group of tumors that can arise in most organ systems and have significant heterogeneity and long disease courses, among other things. Patients with slow growing NENs of the small bowel for example can live for more than 10 years, even in the metastatic setting, but can suffer from hormone hypersecretion syndromes, such as the carcinoid syndrome. At the same time, tumors can evolve over time from a slow growing, well-differentiated histology to a fast growing, dedifferentiated and aggressive form, necessitating change in treatments and recalculation of estimated survival. Patients with low or intermediate grade disease are recommended as appropriate to get somatostatin receptor imaging, as it is usually more sensitive to detect disease and can inform use of

somatostatin analogues and PRRT. The variation in imaging and abundance of clinical behaviors makes it easy to under or overtreat certain patients and thus, consultation with a specialized center is recommended at least once after diagnosis.

While several frameworks have been proposed and updated by national and international societies including the National Comprehensive Cancer Network (NCCN) [1], the North American Neuroendocrine Tumor Society (NANETS) and the European Neuroendocrine Tumor Society (ENETS), adherence to that varies by institution and specialist. Moreover, the sequencing of treatments and the adoption of new agents, the most recent example of which is peptide receptor radionuclide therapy (PRRT), usually relies on expert opinion or at least on multidisciplinary input. Thus, most tertiary centers seeing a high percentage of NEN patients will consider a disease specific NEN tumor board (TB) consisting of individuals with specific interest in these rare tumors and expertise based on their clinical experiences.

In our institution, a NEN clinic and its accompanying TB was established in the beginning of 2018, given the significant numbers of NEN patients that were seeking a multidisciplinary approach for their disease. The clinic sees more than 120 new patients with NENs annually, with the exception of lung NENs (seen by the thoracic service) and Merkel cell tumors (seen by the melanoma team). The TB includes standing representatives from pathology (1+), radiology (1+), surgery (1+), nuclear medicine (2+), medical oncology (2+), radiation oncology (1+), and interventional radiology (2+) with occasional participation of referring oncology providers, nurse practitioners, endocrinologists, and allied healthcare professionals. The minimum number of representatives for the major specialties is 1, with the maximum ranging from 3 and 4. This includes trainees and presenting outside physicians.

The question remains if a NEN dedicated TB is of added value or redundant, as it is occupying significant resources and devotes high functioning professionals to drawn-out discussions that could be used for personal time or patient care. Over the course of several years, hundreds of opinions and treatment recommendations have been recorded but, to date, there had not been an assessment of the patterns, outcomes and influences of the TB. This is not an isolated finding. Our review of the literature also revealed limited published information on the efficacy or outcomes of NEN specific tumor boards. Thus, the purpose of this work was to appraise the findings of NEN-TB recommendations and determine their impact on patient treatment decisions.

Methods

We used an institutional IRB to collect the local neuroendocrine tumor board minutes and recommendations from inception (08/07/2018) to 09/17/2021. We limited the input to the recorded TB information; no patients or relatives were contacted. The following deidentified data was extracted: TB session date, patient age, sex, tumor origin and grade, review of pathology or imaging (binary), actual imaging modalities reviewed, summary of consensus findings and treatment plan changes. The outcomes included tumor board recommendation ("Leaning towards surgical interventions", "Leaning towards nuclear medicine/IR interventions", and "Leaning towards multidisciplinary clarifications") and treatment plan changes (Yes vs. No). "Leaning towards" was a term coined to describe the majority preference for the next best step and the fact that the recommendation might or might not be ultimately adopted by the consulting physicians. Plan changes were determined based on the original plan followed by primary treating physician and the amended plan after the TB. If the consensus was to remain on current treatment, "plan change" was coded as "No". "Leaning towards multidisciplinary clarifications" was an umbrella term for all the other cases where combined surgical imaging and pathology input was needed. Each NEN-TB entry was given a separate ID, even though some corresponded to a re-represented patient at different time points. We established categories of summary recommendations based on the question posed and the most valuable part of the discussion. This was facilitated by the fact that the tumor board mainly made decisions on the next best step and clarified a specific question rather than make a full future care plan. Demographic and clinical characteristics were summarized using descriptive statistics. Continuous and categorical variables across summary of consensus findings were compared by a Kruskal–Wallis test and the Chi-square test, respectively. Univariate logistic regression model was used to model the either outcome (plan change or not). Multivariate analysis through stepwise selection was presented to examine the relationship between the outcome and independent predictors in Table 1, a significance level of 0.3 is required to allow a predictor into the model, and a significance level of 0.35 is required for a predictor to stay in the model. All the tests were two-sided and the significance level was set at 0.05. The statistical package SAS 9.4 was used for all the statistical calculations (SAS Institute Inc., Cary, NC).

Results

Between 7/24/2018 and 12/17/2021, a total of 652 patient entries were recorded with missing data on 70 days from 08/21/2018 to 10/30/2018 (due to staffing error). Median age of participants was 61 (range 18–91) with equal representation of male/female sex. A breakdown of detailed characteristics of cases is provided in Table 1 and on a separate Appendix section. When the primary was known, most tumors originated in the small bowel (33.4%), followed by

Table 1 Patient demographics

Parameter	N	Percent
Sex		
Female	338	51.8
Male	313	48.0
Missing	1	0.2
Tumor origin		
Small bowel	218	33.4
Pancreas	169	25.9
Other	188	28.8
Unknown	77	11.8
Tumor grade		
High	110	16.9
Low/intermediate	534	81.9
Unknown	8	1.2

Table 2 Tumor board characteristics

Parameter	N	Percent
TB modalities		
Pathology reviewed	255	39.1
Pathology not reviewed	397	60.9
Radiology reviewed	634	97.2
Radiology not reviewed	18	2.8
Imaging studies per patient case		
0	18	2.8
1	433	66.4
2	186	28.5
3	15	2.3
Imaging modality		
CT	289	34.0
MRI	184	21.6
PET	369	43.4
Post PRRT SPECT/Octreoscan	8	1.0
Total	850	100.0
TB consensus		
Significant plan change	236	36.2
Non significant plan changes	416	63.8
Clinical trial identified	17	2.6
Significant pathology revision	24	3.7

pancreas (25.9%), whereas unknown origin applied to 11.8% of the cases. Most NEN-TB cases were of low or intermediate grade (534/652 or 81.9%); high grade tumors made up 110/652 or 16.8% of cases.

Regarding reviewed materials, radiology image interpretation was performed in the majority of entries (97.2%), with pathology reviewed 39.1% of the time. About two thirds (66.4%) of case presentations had only one imaging study reviewed. A total of 850 combined imaging studies were recorded, 186 included two while 15 included three. Regarding the specific imaging modality, PET (FDG or SSTR scintigraphy) was reviewed 55.3% of the cases, CT was reviewed in 44.3% of the time, and MRI in 28.2%. Limited entries included octreotide scan (6 total) and post PRRT SPECT [2].

NEN-TB consensus

A breakdown of decision subcategories is included in Table 2. The most common TB outcome was clarification of no disease progression despite official radiology report mentioning increased/new lesions (136/652) which occurred in 20.8% of the cases, followed by recommendations for a new biopsy based on radiological information (57/652) in 8.7% of the cases. Disease progression was established by demonstration of new lesions or progression by RECIST 1.1 criteria. Common reasons for image misinterpretation as nonresponse were (1) stable disease on somatostatin analogues, (2) misidentification of new lesions (present in retrospect in older images), (3) misinterpretation of comparator imaging with regards to new treatment initiation, (4) different phase of contrast and (4) nonadherence to RECIST criteria. The decision for biopsy usually was related to the presence of a (1) new and enlarging lesion or a (2) tumor area that changed characteristics on perfusion or somatostatin receptor imaging. Unfortunately, these details were not recorded in the final TB recommendations. In general, radiology report clarifications (confirmations or rebuttals) were recorded in 248/652 cases or 38% of the time, surgical decisions were made in 63/652 or 9.7% of the time, IR and radiation oncology (mainly PRRT related) questions were answered in 103/652 cases or 15.8% of the time. With regards to significant plan changes (these that necessitated a change in treatment compared to pre-tumor board plan), these were noted in 236/415 cases or 36.1% patients. More interestingly, pathology was amended/clarified in 44/652 or 6.7% of the time including 24 cases (3.7%) where the pathology was changed completely to a different grade NEN, different origin NEN, MiNEN or non NEN (adenocarcinoma, sarcoma) histology (See Appendix). In 17/652 or 2.6% of the cases, the recommendation included options for a specific clinical trial.

Effect of patient variables and imaging modality review on tumor board decisions

For our analysis, we grouped the tumor board recommendation in three major categories: "Leaning towards surgical interventions", which occurred 9.7% of the time, "Leaning towards nuclear medicine/IR interventions", which occurred 15.8% of the time and "Leaning towards multidisciplinary clarifications", which happened 74.4% of the time. A univariate analysis for the tumor board recommendation and

treatment plan changes is shown on Table 3. Imaging studies per patient case had no significant effect on predicting the "Leaning towards surgical interventions" (OR = 1.305 (0.962–1.770), $p = 0.0872$). Pathology review had no significant effect on predicting the treatment plan changes (OR = 1.345 (0.971–1.863), $p = 0.0743$). There was no effect of age, gender, tumor grade or origin, imaging review, number of studies reviewed on the possibility of major plan changes after NET TB consensus.

No variable was chosen in the stepwise model to be included in the multivariate analysis for both outcomes (Table 4).

PRRT approval and COVID-19 effect on NET-TB

As the tumor board was created after the approval of Lutetium Dotatate by the FDA (01/26/2018) and shortly after the time of institutional clearance of PRRT use (04/2018), we sought to see if the nuclear medicine/PRRT related discussion volume changed over time. We found that decisions related to PRRT clustered around the first and second quarter of 2019 (Fig. 1) reflecting the need for consensus approval of the new treatment. They subsequently decreased, as the group collectively became more accustomed to the indications and administration of Lutetium Dotatate. We then compared tumor board data before and after 03/2020, when the COVID-19 lockdown forced all tumor boards to switch to virtual format. Average case presentations decreased significantly from 10 (SD 1.74) to 8.18 (SD1.7), $p < 0.001$. However, there was no difference in patient representation with regards to numbers, age, sex, original histology and no change in major decision types from the tumor board (data not shown) since all the involved parties of NEN-TB were able to successfully participate in the meeting virtually.

Discussion

In this paper, we present the first three-and-a-half-year experience from a NEN-TB that accompanied a newly minted NEN clinic at a tertiary institution. The NEN-TB for now focuses on radiology and usual representation is by one professional on a rotating basis, while nuclear medicine and medical oncology routinely have more than one participant. Despite the general assumption that NENs are rare, we noticed a significant number of case discussions (about 186/year) with significant treatment change recommendations in about 36% of the cases. There was equal representation of both genders. Patients with the rarer high-grade disease were represented in about 17% of the cases, possibly due to the complexity of their care requiring repeat discussions. Similarly, patients with the usually more rapidly progressing Pan-NENs were discussed in about 26% of the time when their reported cumulative percentage is about 9% of all diagnosed

Table 3 Decision subcategories

Leaning towards multi-D clarifications (systemic treatments or no treatments, clarification of pathology, imaging etc.)	486/652
Radiology report clarified, no (significant) progression noted	136
Systemic treatment recommendations	79
New radiological information, need for biopsy	57
Radiology report clarified, progression noted	55
More imaging needed	50
Pathology amended, Radiology clarified	44
Radiology report clarified, no recurrence	39
Radiology report clarified, improvement noted	15
New patient recommendations	4
Radiology report clarified, recurrence suspected	3
Avoid biopsy	1
Neoplasm with high risk behavior	1
Radiology report clarified,origin noted	1
Suspicious finding clarified	1
Leaning towards nuclear medicine /IR interventions (whether advising for or against)	103/652
PRRT suitable	53
IR/ liver directed intervention suggested	41
PRRT unsuitable	9
Leaning towards surgical interventions (whether advising for or against)	63/652
Surgical candidate	43
Not surgical candidate	17
No need for emergent surgery	3

Table 4 Univariate models for predicting Surgical interventions and Significant plan change

Parameter	Surgical interventions			Significant plan change		
	Odds ratio	CI	P value	Odds ratio	CI	P-value
Age	1.002	0.988–1.015	0.8176	1.007	0.995–1.019	0.2764
Male vs. Female	0.838	0.590–1.189	0.3215	0.907	0.659–1.249	0.5509
Tumor characteristics						
Lung vs. Small bowel	0.633	0.274–1.463	0.2235	0.845	0.406–1.757	0.3725
Other vs. Small bowel	0.676	0.445–1.026		0.844	0.576–1.237	
Pancreas vs. Small bowel	0.701	0.445—1.103		0.683	0.447—1.043	
Tumor grade (high versus low-intermediate)	0.795	0.489–1.291	0.3533	0.896	0.581–1.381	0.6176
Tumor board review						
Pathology reviewed vs. not reviewed	1.091	0.757–1.543	0.6678	1.345	0.971–1.863	0.0743
Radiology reviewed vs. not reviewed	> 999.999	< 0.001–> 999.999	0.9792	0.702	0.273–1.804	0.4624
Imaging studies per patient case	1.305	0.962–1.770	0.0872	1.096	0.825–1.457	0.528

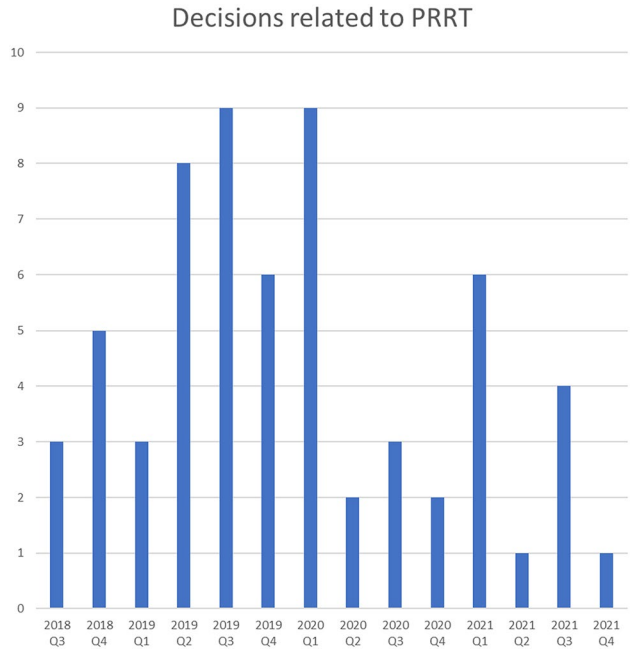

Fig. 1 Timeline of peptide receptor radionuclide treatment related decisions over time

NENs in national databases [2]. Radiology assessments (CT and Dotatate PET) dominated the discussion process, with clarifications occurring about 38% of the time and about 20% of patients continued on a prior treatment after clarification of "no disease progression". Whether these patients would be considered to have disease progression/treatment failure in the absence of a tumor board is not known, but possible. We acknowledge that some of these decisions might have been reached outside a tumor board if radiologists were allowed ample time and a detailed clinical history for each patient, access to distant imaging or different phase of contrast that can show the presence of prior lesions. This paper also highlights that radiologists might be reporting slight increases in tumor size or nonshrinkage of lesions that might not always be clinically significant for patients with NENs. Treatment failure is a particularly bothersome issue since patients with low grade disease can live for multiple years and have very limited options (somatostatin analogues, small molecules and PRRT mainly). In the event of real progression, barring a clinical trial option, they will be offered radiation or cytotoxic chemotherapy sooner, which can significantly alter their quality of life.

Studies in hepatobiliary TBs [3] have shown that expert radiology review can impact further treatment decisions by clarifying discordant findings and a study on the early adoption of somatostatin receptor imaging [4] in conjunction with TB recommendations in NEN patients showed up to 47% change in management. Equally important is that clinical trials were identified in about 2.6% of the patients and in 3.5% of the cases the pathology was revised completely including a non NEN histology. The decision to bring the pathology for review was based on unexpected/atypical clinical behavior such as concern for transformation (during tumor treatment/evolution), rapid progression through classic treatments or, most frequently, because of vague/nonspecific original pathology report. Regarding pathology, the reviewed cases were (1) graded more accurately with manual counting of proliferation markers such as the Ki-67, (2) underwent more staining, (3) included immunohistochemistry or next generation sequencing data to amend the diagnosis or, in rare cases (4) did not need extra testing.

We were also able to show that there is no way to predict the tumor board outcome. Recommendations remained unaltered through time and with the switch to virtual meetings during the COVID-19 pandemic. Patient characteristics, review of imaging/pathology data and tumor board maturity over time were not associated with any specific treatment recommendations.

Management of rare tumors is still an expert opinion driven process. Cumulative, high-quality data are missing and the guidelines, while rigorously developed and updated, contain little useful information on sequencing and prioritization of interventions. A multidisciplinary approach combines the intelligence and experience from different specialties and has the potential to minimize mistakes by looking at the same problem from various angles. It is thus less error prone than an individual plan, at least in theory. In the experience above, the NEN-TB was also able to adjust to new realities. It formalized the institutional approach to NENs in the face of new, emerging treatments such as PRRT, clinical trials and on few but notable occasions, completely changed the approach by revising the tumor pathology. The lack of predictive factors for treatment recommendations was rather anticipated; expert consensus remains a black box which provides individualized outcomes regardless of input and as such, can be considered to be impartial.

To our knowledge, there are no studies evaluating a NEN-TB and its recommendations, or the relationship of a NEN-TB outcomes to the case presentation. The closest would be data on endocrine tumor boards, where on study demonstrated a significant number of management changes (15% of presentations) with additional imaging requested in 43% of those cases [5]. The literature, however, has multiple examples of the effect of multidisciplinary teams on cancer patient management. This includes national and regional TBs on diseases such as meningiomas [6], head and neck cancer [7], pancreatic diseases [8], lung and colorectal cancer [9] and pediatric cancer [10]. The common underlying theme is that TBs have the potential to induce treatment variations by changing the diagnosis or subsequent treatment strategy. There is some published evidence suggesting that higher number of discussions per patient have the potential to lead to better outcomes [11, 12] although other studies have shown little association with measures of use or survival [13]. A study on head and neck cancer TBs [7] showed better adherence to guidelines and less adjuvant treatment when tumor board group guidelines were standardized. Studies in non NEN tumor boards have also shown higher patient and clinician satisfaction rates [5] and higher odds of participation in clinical trials [9]. Our data showed that a small percentage of patients were found to be eligible for a clinical trial after TB discussion.

On the other hand, the actual impact of TBs has not been well established metric-wise. An umbrella review of five systematic reviews [14] in a wide range of tumors identified gaps in actual evidence that the TB impacts quality of care but did conclude that multidisciplinary care is important for complex cancer patients. Similarly, a systematic review of the literature [15] showed little evidence of improvement in clinical outcomes, although data were impacted by significant selection bias and use of historic cohorts.

In the end is a specialized neuroendocrine tumor board really necessary? We feel that our study provides a positive argument with regards to treatment optimization, but there are some significant limitations. These include the retrospective nature, selection bias and limited recorded data, including no information on patient survival outcomes. Even though significant management changes were established, most patients presented at a TB have been at crossroads in their treatment or, at best, the treating physician has serious misgivings about the report of a scan or pathology report. Thus, the high percentage of change in management should be interpreted cautiously and in the setting of a higher pretest probability. Our paper also did not prospectively follow the patients for outcomes, such as progression-free survival (PFS) or overall survival (OS). Differences in survival in NEN patients can be difficult to prove, as most have long disease courses spanning multiple treatments. Indeed, most of our NEN patients with low grade disease are currently alive. We feel that there would be a bias in any survival analysis, because patients discussed at a multi-disciplinary TB usually are more fit and eligible for treatment changes. Indeed, no recommendations for hospice or palliative care were made in all of our 652 cases.

A tumor board is resource intensive, requiring participation and time commitment (mostly uncompensated) from multiple specialties. The location constraints can be minimized with the use of audiovisual equipment, a necessity turned to reality with the COVID-19 pandemic, without major impact on the function of the TB. Last but not least, additional positive outcomes, such as the quick adoption/standardization of new treatments (in this case PRRT, as seen in other institutions [16]) or the formation of a common interdepartmental interest group and generation of disease specific publications, presentations and grant submissions cannot be easily calculated and thus are not reportable. However, they are vital for the advancement of knowledge and the evolution of a rare tumor clinic.

Appendix

A. Tumor origin subsites

Site	N	Percent
Small bowel	218	33.4
Pancreas	169	25.9
Unknown	77	11.8
Colon	51	7.8
Lung	36	5.5

A. Tumor origin subsites

Site	N	Percent
Adrenal/pheochromocytoma and paraganglioma	40	6.1
Stomach	19	2.9
Renal	18	2.8
Breast	9	1.4
Presacral	4	0.6
Adnexa	3	0.5
Hepatobiliary / gallbladder	3	0.5
Esophageal	2	0.3
Brain	1	0.2
Endometrial	1	0.2
Middle ear	1	0.2

B. Imaging review modalities

Modality	N	Percent
CT	289	34
MRI	184	21.6
PET	369	43.4
Post PRRT SPECT / Octreoscan	8	1

C. Plan changes

Recommendations	N	Percent
Significant plan change	236	36.2
Non significant plan changes	416	63.8
Clinical trial identified	17	2.6
Significant pathology revision	24	3.7

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Declarations

Conflict of interest The authors declare no conflict of interest.

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