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Use and perceived utility of [^{18}F]FDG PET/CT in neuroendocrine neoplasms: a consensus report from the European Neuroendocrine Tumor Society (ENETS) Advisory Board Meeting 2022.

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Abstract

Somatostatin receptor (SST) PET/CT is the gold standard for well-differentiated neuroendocrine tumours (NET) imaging. Higher grades of neuroendocrine neoplasms (NEN) show preferential [18F]FDG (FDG) uptake, and even low-grade NET may de-differentiate over time. FDG PET/CT's prognostic role is widely accepted; however, its impact on clinical decision making remains controversial and its use varies widely. A questionnaire-based survey on FDG PET/CT use and perceived decision-making utility in NEN was submitted to the ENETS Advisory Board Meeting attendees (November 2022, response rate=70%). In 3/15 statements, agreement was higher than 75%: i. FDG was considered useful in NET, irrespective of grade, in case of mis-matched lesions (detectable on diagnostic CT but negative/faintly positive on SST PET/CT), especially if PRRT is contemplated (80%); ii. in NET G3 if curative surgery is considered (82%) and iii. in NEC prior to surgery with curative intent (98%). FDG use in NET G3, even in the presence of matched lesions, as a baseline for response assessment was favoured by 74%. Four statements obtained more than 60% consensus: i. FDG use in NET G3 if locoregional therapy is considered (65%); ii. in neuroendocrine carcinoma before initiating active therapy as a baseline for response assessment (61%); iii. biopsy to re-assess tumour grade prior to a change in therapeutic management (68%) upon detection of FDG-positivity on the background of a prior G1-2 NET; iv. 67% were in favour to reconsider PRRT to treat residual SST-positive lesions after achieving complete remission on FDG of the SST-negative disease component.

Conclusion: Multidisciplinary opinion broadly supports the use of FDG PET/CT for characterisation of disease biology and to guide treatment selection across a range of indications, despite lack of full consensus in many situations. This may reflect existing clinical access due to lack of reimbursement or experience with this investigation, which should be addressed by further research.

Keywords: FDG, PET/CT, neuroendocrine tumours, neuroendocrine neoplasms

Introduction

The use of [^{18}F]FDG (2-deoxy-2-[18F]fluoro-D-glucose) positron emission tomography/computed tomography (FDG PET/CT) in neuroendocrine neoplasms (NEN) has been extensively debated [1, 2]. Lower grade neuroendocrine tumours (NET; Grade 1 and 2) show a slower growth rate and generally lower glucose metabolism (the latter being the target of FDG PET/CT imaging) as compared to more aggressive higher grades, such as well-differentiated G3 NET and neuroendocrine carcinoma (NEC). Several papers have investigated the potential utility of FDG PET/CT in NEN, but they were often difficult to compare since many included small and/or heterogeneous patient cohorts with different primary sites and grades (both factors are well-known to affect the probability of FDG-positivity), different criteria for positivity, and varying reference standards [3-8]. As a result, the impact of FDG PET/CT on clinical decision making in NEN is often difficult to establish, although its role in prognostication is widely accepted and possibly superior to WHO grading [8]. NEN's rarity [9], heterogeneous presentation, and varying clinical behaviour together with relatively long life-expectancy of most patients and different national FDG-reimbursement policies, accounts for its variable use across centres and countries over previous decades. Grading is crucial to select the most appropriate radiopharmaceutical for an examination with PET/CT; however, recent results have shown that the grade of a tumour may evolve during the clinical course of the disease. Therefore, it is hypothesised, that FDG PET/CT could play a larger role across tumour grades and entities in order to correctly stage, prognosticate, and stratify treatment options (especially Peptide Receptor Radionuclide Therapy, PRRT).

The decision to use FDG PET/CT for the previously mentioned indications can be based upon specific institutional protocols or based on a discussion at the multidisciplinary tumour board on a case-specific basis. We performed a questionnaire-based survey for the use and perceived utility of FDG PET/CT among the 66 multidisciplinary experts attending the November 2022 ENETS (*European Neuroendocrine Tumour Society*) Advisory Board Meeting.

METHODS

A set of statements describing the use of FDG PET/CT in NEN in different settings were initially proposed by two authors, VA and VP, and circulated within the ENETS theranostic task force for discussion (Gastroenterology n=3, Oncology n=3, Endocrinology n=5, Surgery n=2, Radiology n=2, Nuclear Medicine=4, Radiology+Nuclear Medicine n=1, Molecular Biology n=1, Pathology n=1),

revision, and final approval. The revised set of statements (15 in total, Table 1) was submitted to the attendees (attending either in presence or remotely) of the ENETS Advisory Board Meeting in November 2022. Respondents were asked to rate each statement using 4 categories: agree, disagree, neutral, not an expert. Respondents were encouraged to answer as if they had the possibility to perform both procedures. Completed forms were collected by the ENETS office employees. Answers of the respondents declaring themselves as "not an expert" in that particular setting were excluded from the analysis. Agreement among respondents was defined as concordance of at least 75% of answers.

RESULTS

Advisory Board meeting attendance included 66 people (onsite or remotely). The survey was distributed to 64 attendees (VA and VP, who drafted the initial set of statements, were excluded). Participants were encouraged to answer as if they had both FDG and somatostatin receptor (SST) PET/CT available/accessible. Forty-five of the AB attendees returned the forms, received either remotely after the meeting or collected onsite by the ENETS office representatives, resulting in an overall response rate of 70%. Most respondents of the survey were from Europe and represented *ENETS Centres of Excellence* (CoE) (29/45), with some respondents from other parts of the world (Table 2). The results of the survey are representative of a good mix of relevant disciplines in the management of NEN. In particular, endocrinology (27%) and gastroenterology (20%) were the most highly represented specialties, followed by surgery (16%), oncology (11%), pathology (9%) and radiology/nuclear medicine (radiology 4%, radiology+nuclear medicine 2%, nuclear medicine 9%). Non-respondents' (19/64; 30%) by specialty and roles within ENETS, are reported in Table 3.

Respondents' survey results are reported in Table 4. Full agreement (>75%) was only reached for 3 statements (3/15, 20%; # 1,5,7). Almost 80% of respondents (80%) were in favour of performing FDG PET/CT in NET, irrespective of grade, when mis-matched lesions (detectable on diagnostic CT but negative or faintly positive on SST PET/CT) are present, especially if PRRT is contemplated. Most attendees were also in favour of the use of FDG PET/CT in NET G3 if curative surgery is considered (#5; 82%), and were overwhelmingly so in NEC prior to surgery with curative intent (#7; 98%).

The participants of the survey also indicated a strong preference, while not reaching consensus (74%; #4), on the performance of FDG PET/CT in all NET G3, even in presence of matched lesions detectable on diagnostic CT and SST PET/CT, as a baseline for response assessment.

Although full agreement was not reached for the other settings, it is worth noting that four statements obtained more than 60% consensus. Specifically, most attendees supported performing FDG PET/CT in NET G3 if loco-regional therapy is considered (#6; 65%) and in NEC before initiating active therapy as a baseline for response assessment (#8; 61%). In the case of new FDG PET/CT-positive lesions on the background of a prior G1-2 NET, most attendees indicated that they would perform a biopsy to re-assess tumour grade prior to a change in therapeutic management (#14; 68%). Finally, 67% of the respondents were in favour of reconsidering PRRT in patients showing any residual SST-positive disease sites after achieving complete remission on FDG ("metabolic response") of the SST-negative disease component (#15).

There was no consensus on the use of FDG PET/CT in all G2 NET with Ki67>10% (#2), in G1-2 showing early progression within 6 months (#3), in NEC when a change of therapeutic management is considered (#9), in atypical lung carcinoid for either staging (#10) or before surgery (#11) or before PRRT (#12), or before PRRT of G2-3 even in case of matched lesions (detected at both diagnostic CT and SST PET/CT) (#13).

DISCUSSION

The present survey was carried out among experts attending the ENETS Advisory Board Meeting in 2022 to describe the real-life use and perceived utility of FDG PET/CT in NEN. Overall, the current survey shows strong consensus for 3 of 15 statements with an additional statement almost reaching the consensus agreement threshold. While four of the fifteen questions did not meet the agreement cut-off, more than 60% of the respondents thought that there is a benefit of performing FDG PET/CT in those specific scenarios as well. These real-life results show that the use of FDG PET/CT in NEN remains an issue of debate. Although, widely accepted to be prognostic [1,2,5,8,10], the impact of its use in clinical practice has been difficult to establish due to the high heterogeneity of published studies, many being retrospective and often including small heterogeneous cohorts, specifically in terms of tumour grade and primary site as well as treatment sequence. Tumour grade may increase during the natural course of the disease, specifically under therapeutic pressure. However, how rapidly this change in grade occurs, and in which particular subset of patients, is still unknown. That is why the timing of FDG PET/CT with respect to tumour grade evolution has not been fully addressed in the literature.

Besides cost and availability, major arguments against the use of FDG PET/CT in NEN patients are that it may be negative in lower grade tumours and that it may not impact management (in patients already studied with SST PET/CT and diagnostic CT/liver MRI). A recently published study included 319 metastatic/unresectable GEP (G1, G2, G3) NEN patients, studied with both SST and FDG PET/CT [11]. Patients were categorised into three cohorts by the so-called "NETPET" score (P1, P2–4, and P5), representing SST-positive/FDG-negative disease, SST-positive/FDG-positive disease, and SST-negative/FDG-positive disease, respectively). The authors reported that FDG-positivity (P2-5) was present in 73% of all cases, while SST-expression was lacking (P5) in 12% overall but in none, 10% and 41% of G1, G2 and G3 NEN, respectively [11]. These data should, however, be interpreted with caution. First of all, they are retrospective with therefore a potential systematic bias since many of these patients were studied with FDG PET/CT on a clinical need basis. Accordingly, to estimate the true prevalence of FDG PET/CT positivity, data from prospective studies would provide a better indication. Accordingly, in the study by Binderup *et al*. which prospectively enrolled G1 (n=57), G2 (n=83), and G3 (n=16), the FDG-positivity rate was 37% for G1, 58% for G2, and 94% for G3 [8] (the Ki67 value closest to the FDG PET/CT scan was considered, although the time-frame between pathological assessment and FDG PET/CT was not reported). It needs to be acknowledged that the overall rate of FDG-positivity in any given cohort will be influenced by the spectrum of grades and tumour primary site, since e.g. small intestinal NET are more often G1 than pancreatic NET that tend to be G2 or G3. While FDG-avidity tends to increase with the proliferative activity of tumours, it can also reflect hypoxia and inflammatory infiltrates and in G1 NET, in particular, may reflect these factors, and carry adverse prognostic implications that are independent of grade, e.g. increased radioresistance.

Moreover, it is also relevant to observe that many patients may be FDG-positive in only a fraction of the tumour bulk. In fact, from a therapeutic perspective, the FDG-positive metabolic tumour volume (MTV) rather than FDG-positivity *per se* (generally defined as uptake higher than the normal liver) may also be clinically relevant. The FDG-positive MTV was reported to increase with increasing grade (e.g. higher in G3) and to correlate with prognosis [12]. In a retrospective study including 190 NEN patients (35% G1, 38% G2, and 15% G3 by WHO 2010; unknown in 8% of cases), increasing grade was significantly correlated with increasing MTV and TLG (total lesion glycolysis, an indirect marker of disease heterogeneity) [12]. In multivariate analysis MTV (and TLG), grade, and the presence of extrahepatic disease, were predictive of poorer overall survival (OS) and progression-free-survival (PFS) [12]. However, FDG-avidity does not preclude favourable responses to PRRT [13].

Stratification of patient outcomes based on functional imaging with FDG PET/CT results was reported to be superior to pathologic grading in retrospective studies [10,14]. A 3-point scale, based on FDG results, was recently reported to better discriminate patients' outcomes in terms of both OS and PFS [14] in a retrospective cohort of 85 patients studied with both SST and FDG PET/CT. Patients were divided into three grades: FDG-neg (C1), FDG-positive with matched lesions (C2: more than one FDG-positive lesion, all of them positive to SST PET/CT) and FDG-positive with mismatched lesions (C3: more than one FDG-positive lesion, at least one of them negative on SST PET/CT). Median progression free survival (mPFS) was significantly different between the three groups: 40.1 months (C1 patients), 11.9 months (C2 patients) and 7.0 months (C3 patients), respectively.

Upon detection of FDG-positivity, clinical management is variably changed in different centres. In a retrospective study including 104 patients [15], a change of strategy was employed in 21% of cases (22/104) based on FDG PET/CT results alone and in 30% (32/104) of cases based on double tracer imaging (SST+FDG PET/CT). In particular, FDG-related treatment change (defined by the authors as addition of chemotherapy to the somatostatin analogues/PRRT scheme) was performed in 11/63 patients (17%; 3 patients with G1, 8 patients with G2) with low grade NETs (Ki67$\leq$5%) [16].

Respondents to the survey were in favour of using FDG PET/CT in case of mis-matched lesions which are detectable on diagnostic CT but negative on SST-PET/CT, regardless of grade, especially in patients eligible for PRRT. This is particularly relevant since the issue of whether to perform FDG PET/CT before PRRT is an open debate in many centres. In a multidisciplinary discussion among experts performed in 2020, FDG PET/CT was recommended as complementary investigation to SST PET/CT in patients with unresectable or disseminated G2/G3 NET and candidates for PRRT to exclude mismatch and for prognostication [17]. Several studies support the prognostic role of FDG PET/CT in patients with NEN [18,8], even when performed before PRRT [19,8]. A recent meta-analysis including 12 studies and 1492 patients reported that a negative FDG PET/CT before PRRT is associated with a higher disease control rate, longer PFS and OS [20]. Moreover, PRRT alone is generally contraindicated in patients presenting spatial FDG/SST-mismatch (FDG-positive/SST-negative lesions) [21]. Notwithstanding the above-mentioned data, FDG PET/CT is still not part of the routine pre-PRRT assessment in many centres and is not routinely included in most on-going PRRT trials. A recent study analysing data collected in a Spanish national database, including patients treated with at least one PRRT cycle, reported that FDG PET/CT was not performed before PRRT in approximately 70% of cases [22]. When performed, FDG PET/CT was discordant with SST PET/CT in 17% of cases and concordant in approximately 10% [22].

The respondents were in favour of the use of FDG in NET G3 before curative surgery, and in NEC before curative intended surgery, underlying the role of metabolic imaging to exclude the presence of distant metastasis that might force a change of treatment strategy. In clinical practice, high grade NEN, especially if metastatic, are often studied with diagnostic CT and/or MRI alone, as it is generally sufficiently precise when metastatic disease is present and palliative treatment is about to be initiated. In (potentially) localised disease, however, recently published ENETS guidelines on NEC support staging with FDG PET/CT before surgery as this may have therapeutic consequences [23]. Consensus was almost reached (74%) on the use of FDG PET/CT in NET G3 (even in case of fully matched lesions on diagnostic CT and SST PET/CT) as a baseline for response assessment.

Although not reaching consensus, more than 60% of respondents were in favour of reconsidering the use of PRRT to control the SST-expressing disease component provided that a complete metabolic response of the FDG-avid disease was reached following other systemic therapy. The eradication of subpopulations that have low or lack SST expression by chemotherapy or targeted agents may allow PRRT to be used subsequently if the remaining sites of disease have high SST-expression. Such sequencing of therapies, being considered complementary rather than considering them as competing approaches, is an interesting proposition. Biopsy of a new FDG-positive lesion in the background of prior G1-2 NET to reassess tumour grade prior to a change in therapeutic management was considered to be appropriate by more than 60% of respondents. Since FDG-avid second malignancies can be encountered, biopsy of a new FDG-positive lesion is also useful to exclude a synchronous non-NEN malignancy or to characterise a rapidly growing lesion on either conventional imaging or SST PET/CT.

Respondents were not in favour of the use of Ki67>10% [24] as a threshold to select candidates to FDG PET/CT among G2-NET patients. The reasons that might explain this finding may be related to the implications for management that may differ depending not only on grade but also on the primary tumour site, and on the related available treatment options (e.g. pancreatic NET for which alternative targeted therapies such as sunitinib and everolimus are options versus small intestinal NET where PRRT would be the preferred treatment based on NETTER-1 results). The current survey also indicates that most respondents are not in favour of performing FDG PET/CT in rapidly progressive cases to decide on a management change. The reasoning behind this is unclear.

There was no agreement on the use of FDG in cases of atypical lung carcinoids. This result was unexpected (especially in the staging and before-surgery settings) based on the observed high

glucose metabolism of these neoplasms [25] and on the absence or low levels of SST-expression in half of patients with atypical carcinoids [26]. In a recent report including 252 lung NEN, comprising 29 atypical and 61 large cells forms (LCNEC), FDG was performed before surgery in 90% (26/29) of atypical lung carcinoids and in 77 % (47/61) of LCNEC, being positive in almost all cases (atypical lung carcinoid: 96%, 25/26; LCNEC: 100%, 47/47) [27]. In a minority of cases, SST PET/CT was performed before surgery (24% and 10% respectively). The high preponderance of FDG PET/CT use in lung NENs can result from the fact that FDG PET/CT is recommended in the guidelines in the diagnostic characterisation of solitary pulmonary nodules, and is used for the staging of non-small cell lung cancer, with FDG PET/CT often scheduled before results of pathology are known. The absence of pulmonologists or lung-dedicated NEN expert/oncologists in the respondents' cohort might have affected this result.

In a retrospective review of 56 patients with biopsy-proven TC (22/56) or AC (34/56) undergoing both SST ([68Ga]Ga-DOTATATE) and FDG PET/CT at presentation (interval between scans: median 10 [1-90]days), the authors described marked phenotypic heterogeneity, with around half of patients having an unsuitable phenotype for PRRT regardless of the pulmonary NET subtype [28]. A 4-scale score was used to describe disease heterogeneity: score 1 (if all anatomical lesions suggestive of disease were negative on both tracers), score 2 (if all lesions were SST-positive/FDG-negative), score 3 (if all lesions were SST-positive but some/all were spatially concordant FDG-positive), and score 4 (spatially discordant FDG-positive and SST-negative lesions). Only score 2 and 3 were considered suitable for PRRT. On inter-patient dual-tracer analysis, scores 1, 2, 3 and 4 were 23%, 18%, 36% and 23% in TC and 3%, 15%, 32% and 50% in AC, respectively. While the proportion of patients score 1 was more common in TC (23% in TC versus 3% in AC), the distribution of other phenotypes was not statistically significant. Overall, these data showed marked disease heterogeneity in well-differentiated pulmonary NETs, highlighting the importance of dual-tracer imaging regardless of the subtype [28]. A working group of ENETS is developing further consensus guidelines for the management of pulmonary NENs and may further refine diagnostic approaches based on more recent experience.

The present survey was an attempt to describe the real-life use and perceived utility of FDG PET/CT in a selected international cohort represented by NEN experts attending the November 2022 ENETS AB meeting. Although mostly coming from *ENETS Centres of Excellence* (CoE), the different availability of imaging procedures (FDG and SST PET/CT) and reimbursement policies across countries certainly may have affected respondents' answers (although they were encouraged to

answer as if they had the possibility to perform both procedures). Full agreement was reached for the use of FDG PET/CT in case of mis-matched lesions between diagnostic CT and SST PET/CT regardless of grade (especially in cases considered for PRRT) and before curative surgery of NET G3 and NEC.

The survey results indicate that respondents are in favour of the use of FDG PET/CT in clinical practice when it may impact a change in management. Therefore, not only grade but also primary tumour site and primary site-specific availability of treatment options, in accordance with published guidelines, have likely influenced their responses.

World-wide, clinicians trust FDG PET/CT to assess disease heterogeneity, tumour biology and prognostic data in oncology. However, due to lack of prospective studies demonstrating the impact of FDG on clinical management in homogeneous and large NEN patient cohorts, the indication to FDG PET/CT generally follows a multidisciplinary case-centred discussion. This may even result in the performance of more or less FDG studies than ideal for clinical decision making. To ensure an international consensus regarding the detailed settings in which FDG should be employed, data from prospective studies including the assessment of the clinical impact and cost-effectiveness of FDG PET/CT as well as the FDG-avid tumour volume should be analysed. Considering the relatively long life-expectancy of most NEN patients, and the possibility of high-grade-progression even years after the first diagnosis, the collection of such data needs an international effort.

Conclusion: Multidisciplinary opinion broadly supports the use of FDG PET/CT for characterisation of disease biology and to guide treatment selection across a range of indications despite lack of full consensus in many situations. This may reflect existing clinical access due to lack of reimbursement or lack of experience with this investigation, which should be addressed by further research.

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TABLES

Table 1. Statements to be rated

1. ^{18}F-FDG PET/CT should be performed in NET irrespective of grade when mis-matched lesions (diagnostic CT-visible and SST PET-negative or faintly positive) are present, especially if PRRT is contemplated
2. ^{18}F-FDG PET/CT should be performed in all G2 NET with Ki67>10%
3. ^{18}F-FDG PET/CT should be used in NET G1 and G2 showing early progression within 6 months (even in the absence of mis-matched lesions on diagnostic CT and SST PET/CT)
4. ^{18}F-FDG PET/CT should be performed in all NET G3 (even in presence of matched lesions on diagnostic CT and SST PET/CT) as a baseline for response assessment
5. ^{18}F-FDG PET/CT should be done in NET G3 if curative surgery is considered
6. ^{18}F-FDG PET/CT should be done in NET G3 if locoregional therapy is considered
7. ^{18}F-FDG PET/CT should be performed in NEC before curative intended surgery
8. ^{18}F-FDG PET/CT should be performed in NEC before initiating active therapy as a baseline for response assessment
9. ^{18}F-FDG PET/CT should be done in NEC when a change of therapeutic management is considered
10. ^{18}F-FDG PET/CT should be performed in staging of all atypical lung carcinoid
11. $^{18F-}$FDG PET/CT should be performed before surgery in atypical lung carcinoid
12. $^{18F-}$FDG PET/CT should be performed before PRRT in atypical lung carcinoid
13. ^{18}F-FDG PET/CT should be performed before PRRT in NET G2/G3, even in case of matched lesions (diagnostic CT-visible and SST PET-positive).
14. In case of new ^{18}F-FDG PET/CT-positive lesions on the background of prior G1-2 NET, biopsy should be employed to re-assess tumour grade prior to a change in therapeutic management
15. PRRT should not be considered in patients with FDG-avid lesions lacking SST PET positivity but can be reconsidered if a complete metabolic response is achieved in this component of the disease following other systemic therapy but residual SST positive disease sites

Legend: SST: somatostatin receptors; NET: neuroendocrine tumour; G: grade; NEC: neuroendocrine carcinoma; PRRT: Peptide Receptor Radionuclide Therapy

Table 2. Expert respondents characteristics (n=45)

	n	%
Area of expertise		
Radiology	2	4
Radiology+nuclear medicine	1	2
Nuclear Medicine	4	9
Surgery	7	16
Endocrinology	12	27
Gastroenterology	9	20
Molecular Biology	1	2
Oncology	5	11
Pathology	4	9
Country		
Germany	8	18
France	2	4
Argentina	1	2
United Kingdom	4	9
Spain	3	7
Switzerland	3	7
Belgium	1	2
Italy	6	13
Israel	1	2
Netherlands	1	2
Greece	2	4
Denmark	1	2
Poland	1	2
Sweden	4	9
Ireland	1	2
Portugal	1	2
Austria	2	4
United States	1	2

Australia	1	2
India	1	2
Role within ENETS		
EC member	6	13
AB member	34	76
Guest	2	4
CoE auditor	3	7

Legend: EC: Executive Committee; AB: advisory board; CoE: Center of Excellence

Table 3. Non-respondents (n=19)

	n	%
Specialty		
Oncology	7	37
Pathology	2	11
Endocrinology	3	16
Gastroenterology	3	16
Surgery	2	11
Nuclear Medicine	1	5
Radiology	1	5
Country		
Spain	3	16
France	3	16
Netherlands	4	21
Italy	2	11
Denmark	1	5
United Kingdom	2	11
China	2	11
Brazil	1	5
Canada	1	5
Role within ENETS		
EC member	3	16
AB member	13	68
CoE auditor	2	11
ERN-EURACAN	1	5

Legend: EC: Executive Committee; AB: Advisory Board; CoE: Center of Excellence

Table 4. Expert respondents survey results

Statement number	Expert Respondents number	Agree		Disagree		Neutral	
		n	%	n	%	n	%
1	44	35	80	8	18	1	2
2	43	18	42	20	47	5	12
3	44	18	41	18	41	8	18
4	43	32	74	8	19	3	7
5	44	36	82	2	5	6	14
6	43	28	65	6	14	9	21
7	44	43	98	0	0	1	2
8	44	27	61	11	25	6	14
9	43	17	40	18	42	8	19
10	40	17	43	14	35	9	23
11	40	22	55	10	25	8	20
12	40	22	55	13	33	5	13
13	42	21	50	16	38	5	12
14	44	30	68	7	16	7	16
15	42	28	67	3	7	11	26

CONFLICT OF INTEREST STATEMENT

Valentina Ambrosini received speaker honoraria from ESMIT/EANM/ESMO/Cineca/Elma Academy in the past 3 years.

Martyn Caplin has received speakers' fee and research funding from IPSEN and AAA-Novartis.

Justo Castano received consulting, travel support or speaker honoraria from Ipsen, AAA, and Novartis.

Emanuel Christ has received honoraria for speaker engagements, from Novartis, Ibsen, Pfizer, HRA Pharma, Novo Nordisk and AAA and for advisory boards from AAA, Pfizer, HRA Pharma, Ricordati Pharma GmbH and Novo Nordisk.

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Christophe M. Deroose is/has been a consultant for: Sirtex, Advanced Accelerator Applications, Novartis, Ipsen, Terumo, PSI CRO. He has received travel fees from: GE Healthcare, Sirtex.

Clarisse Dromain received consultant fees from Ipsen.

Massimo Falconi has no conflicts of interest to declare.

Simona Grozinsky-Glasberg has no conflicts of interest to declare.

Rodney J. Hicks has no conflicts of interest to declare.

Johannes Hofland has received speaker and/or advisory board fees from Ipsen, Serb and Novartis.

Andreas Kjaer has no conflicts of interest to declare.

Ulrich Knigge has received research grants from Novartis, Ipsen, MSD and Debiopharm. He has also received honoraria for speaker engagements from Novartis, Ipsen and Pharmanovia.

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Anna Koumarianou received educational support from Faran SA, Ipsen and Novartis, speaker Ipsen and Faran SA.

We are not aware of any conflicts of interests for B.A. Krishna.

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Anders Sundin has no conflicts of interest to declare.

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