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The size of well differentiated pancreatic neuroendocrine tumors correlates with Ki67 proliferative index and is not associated with age

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ABSTRACT

Background: Concerns exist about a conservative management of well-differentiated nonfunctioning small pancreatic neuroendocrine tumors (NF-PanNET) in young patients and when preoperative Ki67 proliferative index is ≥3%.
Aim: To evaluate an association between age, tumor size and grading in patients with sporadic NF-PanNET who underwent curative resection.
Methods: Patients who underwent surgery for sporadic NF-PanNET (excluding G3) were retrospectively analyzed. Linear regression analysis was performed to evaluate a possible correlation between continuous variables, whereas multiple logistic regression analysis was performed for determining predictors of NF-PanNET-G2.
Results: Overall, 235 patients with NF-PanNET-G1/G2 were included. The median largest radiological diameter was 25 mm. Age correlated neither with tumor size ($P = 0.675$) nor with Ki67 index ($P = 0.376$). On multivariate linear regression analysis, factors independently associated with Ki67 index were NF-PanNET size ($P = 0.031$), perineural invasion ($P = 0.004$), microvascular invasion ($P = 0.001$) and necrosis ($P = 0.009$). The most accurate NF-PanNET size for predicting NF-PanNET-G2 was 25 mm. On multivariate analysis, a NF-PanNET size >25 mm was independently associated with the risk of having a PanNET-G2 ($P = 0.025$).
Conclusion: No correlations exist between age and NF-PanNET size or proliferative index. Therefore, an a priori aggressive attitude is not justified in young patients with small NF-PanNET, as a long-life expectancy is probably unlikely to increase the risk of malignant transformation.

1. Introduction

Well-differentiated pancreatic neuroendocrine tumors (PanNET) have been traditionally regarded as rare lesions, but they are now representing increasingly recognized entities. It has been estimated that the incidence of PanNET has raised from 0.4 per 100 000 inhabitants/year to 0.8 per 100 000 inhabitants/year in the last decade [1].

The main reason is probably related to the widespread use of high-quality imaging examinations resulting in an improved detection of small and asymptomatic nodules [2]. This hypothesis is supported by the analysis of data obtained from the Surveillance, Epidemiology, and End Results (SEER) database, demonstrating that the incidence of PanNET ≤ 2 cm increased by 710.4% between 1988 and 2009 [3].

Asymptomatic, small, low-grade PanNET are usually indolent neoplasms that can be cured in 80–95% of cases after curative resection [4–7]. However, pancreatic surgery is usually associated with a high-risk of postoperative complications and long-term impairment of pancreatic function. Therefore, the surgical management of small, often indolent, PanNET may result in an overtreatment in

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the majority of cases. As a consequence, some authors proposed a watchful strategy in the management of asymptomatic, nonfunctioning (NF), PanNET [8–11]. Preliminary data on this approach seem to confirm the safety of a conservative attitude [12,13]. However, there are several issues that still need to be addressed. In particular, some concerns remain in offering an observational management of small NF-PanNET in young patients. There are no clear data on their natural history and results on long-term outcomes of observed sporadic small NF-PanNET are still lacking. In the context above, the long-life expectancy of young and healthy patients may persuade physicians to a more aggressive attitude toward these lesions.

Aim of this study was to evaluate an association between age, tumor size and tumor grading in patients with sporadic NF-PanNET who underwent curative surgical resection.

2. Materials and methods

Overall 458 patients affected by PanNET were submitted to surgical resection, between 2000 to 2016, in three hospitals: San Raffaele Scientific Institute, "Sacro Cuore-Don Calabria" Hospital Negrar and University Hospital of Polytechnic University of Marche Region. All the surgical procedures were performed or supervised by experienced pancreatic surgeons (MF, GB, SC, SP). An informed consent for surgery was obtained from every patient. Since the study was retrospective, an approval by the ethical committee was waived.

All demographic and clinical data were collected. For the purpose of the present study, only patients with pancreatic, non-functioning, sporadic neuroendocrine tumors were considered. Patients with a diagnosis either incidental or due to the presence of signs or symptoms of the disease were included. Patients submitted to previous treatments were excluded as well as those patients diagnosed with NF-PanNET G3 and NF-PanNEC G3, according to the latest World Health Organization (WHO) classification [14].

Diagnostic work-up always included at least one high quality imaging examination (computed tomography [CT] and/or magnetic resonance imaging [MRI]). All the patients underwent a contrast-enhanced CT scan; MRI was performed only when a suspicion of liver metastases was present or when the patient had already undergone this examination in other institutions. Somatostatin receptor imaging (SRI) included ^{111}In-pentetreotide scintigraphy (OCTREOSCAN®) until 2012. From 2012 ^{68}Ga-DOTATOC PET/CT scan was routinely performed in all the patients. Preoperative endoscopic ultrasound (EUS) with fine needle aspiration (FNA) was performed in the majority of cases but not routinely.

Surgical resection was planned according to the site of the tumor and its dimension. Atypical resections, including middle pancreatectomy (MP) and enucleation, were performed in the presence of NF-PanNET less or equal than 2 cm in size. Enucleation was not routinely associated to a lymph node sampling, regardless of tumor size. Lymph node sampling was performed at discretion of the surgeon and when the presence of lymph node metastases was suspected. NF-PanNET $\leq$ 2 cm with a strict relationship with the main pancreatic duct (MPD) were excluded from enucleation. Typical resection included pancreaticoduodenectomy (PD), distal pancreatectomy (DP) with or without splenectomy and total pancreatectomy. Surgical complications were also recorded and classified according to the Clavien-Dindo Classification of Surgical Complications [15]. Pancreatic fistula was classified according to the latest International Study Group on Pancreatic Fistula (ISGPF) classification [16].

Surgical margins were classified into three categories: R0 (no residual tumor), R1 (microscopic residual tumor), R2 (macroscopic residual tumor). T, N and M stage was classified according to the current ENETS classification [17]. Ki67 index was assessed in the surgical specimen by MIB1 antibody staining and evaluated by measuring the percentage of cells with positive nuclear staining after the count of 2000 cells in the area of highest nuclear labelling. Tumor grade was classified according to the latest WHO classification into 2 categories: NF-PanNET-G1 (Ki67 index <3%), NF-PanNET-G2 (Ki67 index between 3–20%).

All the patients included in the study were followed regularly after surgery. Follow-up protocol included a six-month high-quality imaging examination and outpatient visit on a yearly basis. Last follow up was updated in January 2018. Survival and risk factor analyses were performed only on patients submitted to a curative resection (R0-R1).

2.1. Statistical analysis

Continuous data were reported as median and interquartile range (IQR). For categorical data, the number and proportion (%) were displayed. The comparison between subgroups was carried out using Student's t-test, or Mann–Whitney U test, for continuous variables. Qualitative data were compared by the Chi square test or Fischer exact test when necessary. The correlation between continuous variables was evaluated by univariate and multivariate linear regression analyses. Those variables that were significant at univariate analysis were selected for multivariate analysis. Multivariate analysis was performed using the backward conditional method. Receiver operating characteristic (ROC) analysis was performed to determine the most suitable cut-off for grading. Multiple logistic regression analysis was performed to evaluate predictors of PanNET-G2. Statistical analyses were performed in SPSS 16.0 for Windows software (SPSS Inc, Chicago, Illinois, USA). *P* values were considered significant when less or equal than 0.05.

3. Results

Overall, 235 patients affected by NF-PanNET-G1 and G2 who underwent pancreatic resection were included in the study. Demographic and perioperative details are summarized in Table 1, whereas pathological findings are listed in Table 2. The median largest radiological diameter was comparable with the median largest histological diameter (25 versus 24 mm, $P = 0.089$). Age was correlated neither with tumor size ($r = 0.028$, $P = 0.675$) nor with Ki67 proliferative index ($r = 0.058$, $P = 0.376$). No correlation between age, tumor size and/or Ki67 proliferative index was found also when limiting the analysis to pT1 NF-PanNET, pT2 NF-PanNET, pT3 NF-PanNET, or pT4 NF-PanNET. No correlation between the same variables was found also when considering only N1 NF-PanNET. The median age of patients with a NF-PanNET $\leq$ 2 cm was 60 years (IQR 50; 69 years) compared to 62 years (IQR 50; 69 years) in patients with a 2 cm < NF-PanNET $\leq$ 4 cm and 61 years (IQR 52; 68 years) for those with a NF-PanNET > 4 cm ($P = 0.993$). Patients with NF-PanNET-G1 had a median age of 60 years (IQR 49; 66 years) compared to 64 years (IQR 53; 70 years) for patients with NF-PanNET-G2 ($P = 0.152$). On univariate linear regression analysis, tumor size was significantly correlated with Ki67 proliferative index ($\beta = 0.272$, $P < 0.001$) (Table 3). On multivariate linear regression analysis (Table 3), factors independently associated with Ki67 proliferative index were NF-PanNET size ($\beta = 0.128$, $P = 0.031$), perineural invasion ($\beta = 0.206$, $P = 0.004$), microvascular invasion ($\beta = 0.240$, $P = 0.001$), and necrosis ($\beta = 0.161$, $P = 0.009$). Receiver Operating Characteristics (ROC) curve was performed in order to evaluate a possible tumor size cut-off to accurately predict the risk for patients of having a NF-PanNET-G2 (Fig. S-1). The most accurate NF-PanNET size cut-off was 25 mm. The same cut-off was found also when considering radiological NF-PanNET size. The NF-PanNET cut-

Table 1
Demographic and perioperative characteristics of 235 patients with histologically proven nonfunctioning pancreatic neuroendocrine tumors (NF-PanNET) G1-G2.

Variable	*n* (%)
Age, years[a]	61 (40;67)
Gender	
Male	133 (57)
Female	102 (43)
Incidental diagnosis	
No	61 (26)
Yes	174 (74)
Type of surgical intervention	
Pancreaticoduodenectomy	56 (25)
Distal pancreatectomy	136 (58)
Total pancreatectomy	4 (1)
Middle pancreatectomy	5 (2)
Enucleation	34 (14)
LOS[b], days[a]	9 (8;12)
Operative time, minutes[a]	225 (170;290)
Complications [15]	
0	74 (31)
1	53 (23)
2	78 (33)
3a	20 (9)
3b	8 (3)
4	0 (0)
5	2 (1)
Pancreatic fistula [16]	
No	123 (52)
Biochemical leak	81 (34)
Grade B	25 (11)
Grade C	6 (3)

[a] Expressed as median (IQR).
[b] LOS: Length of stay.

Table 2
Histological findings after pancreatic resection of 235 nonfunctioning pancreatic neuroendocrine tumors (NF-PanNET) G1-G2.

Variable	*n* (%)
PanNET largest diameter, mm[a]	25 (15;40)
PanNET Grade [14]	
G1	139 (59)
G2	96 (41)
T stage [17]	
T1	90 (38)
T2	75 (32)
T3	51(22)
T4	19 (8)
N stage [17]	
Nx	30 (13)
N0	135 (57)
N1	70 (30)
M stage [17]	
M0	211 (90)
M1	24 (10)
Resection margins	
R0	23 (10)
R1	23 (10)
R2	9 (4)
Microvascular invasion	
No	159 (68)
Yes	76 (32)
Perineural invasion	
No	191 (81)
Yes	44 (19)
Necrosis	
No	217 (92)
Yes	18 (8)

[a] Expressed as median (IQR).

off of 25 mm was evaluated as possible predictor of PanNET-G2 in a univariate and multivariate logistic regression model (Table 4). On multivariate analysis a NF-PanNET size >25 mm was independently associated with the risk of having a PanNET-G2 (Odds Ratio [OR]: 2.244, $P = 0.025$). Other factors associated with PanNET-G2 were the presence of microvascular invasion (OR: 3.700, $P = 0.003$) and necrosis (OR: 4.095, $P = 0.047$). Among those 131 patients who had a NF-PanNET ≤ 2.5 cm, only 22 (17%) had a NF-PanNET-G2.

Table 3
Univariate and multivariate linear regression analysis of the effect of demographics and pathological variables on Ki67 value.

Variable	Univariate			Multivariate		
	β value	95% C.I.	P	β value	95% C.I.	P
Gender			0.248			
Male	1	–				
Female	−0.076	−1.713–0.445				
Age	0.058	−0.023–0.062	0.376			
PanNET[a] largest diameter	0.272	0.025–0.067	<0.001	0.128	0.002–0.041	0.031
N stage						
N0	1	–	<0.001			
N1	0.419	1.306–2.319				
M stage						
M0	1	–	0.003			
M1	0.196	0.943–4.394				
Perineural invasion						
No	1	–	<0.001	–	–	
Yes	0.427	3.307–5.793		0.206	0.713–3.675	0.004
Microvascular invasion						
No	1	–	<0.001	–	–	
Yes	0.466	3.124–5.153		0.240	0.842–3.420	0.001
Necrosis						
No	1	–	–	–	–	
Yes	0.354	3.646–7.417	<0.001	0.161	0.630–4.409	0.009

[a] PanNET: pancreatic neuroendocrine tumor.

Table 4
Univariate and multivariate logistic regression analysis of predictors of pancreatic neuroendocrine tumor (PanNET) G2.

Variable	Univariate			Multivariate		
	OR	95% C.I.	*P*	OR	95% C.I.	*P*
Gender						
Male	1	–	0.721			
Female	0.903	0.515–1.583				
Age						
≤60 years	1	–	0.113			
>60 years	1.578	0.898–2.775				
PanNET[a] largest diameter						
≤25 mm	1	–	<0.001	1	–	
>25 mm	4.588	2.522–8.344		2.244	1.105–4.558	0.025
N stage						
N0	1	–	<0.001			
N1	3.670	1.989–6.722				
M stage						
M0	1	–	<0.001			
M1	5.636	2.285–13.901				
Perineural invasion						
No	1	–	<0.001			
Yes	5.847	2.902–11.780				
Microvascular invasion						
No	1	–	<0.00	1	–	
Yes	8.687	4.628–16.306		3.700	1.565–8.748	0.003
Necrosis						
No	1	–	<0.001	1	–	–
Yes	14.035	3.918–50.274		4.095	1.020–16.433	0.047

[a] PanNET: pancreatic neuroendocrine tumor.

Of those 22 patients, 19 had a NF-PanNET with a Ki67 proliferative index equal or higher than 3% but lower than 10%. None of the patients with a NF-PanNET < 1 cm had G2 tumor. When considering only patients with NF-PanNET > 25 mm (n = 104), on bivariate linear regression analysis, the association between NF-PanNET size and Ki67 proliferative index was no longer statistically significant (β = 0.022, 95% C.I. -0.034–0.043, P = 0.821).

Lymph node metastases were found in 70 patients (30%), whereas 135 patients (57%) had no nodal involvement. In the remaining 30 cases (13%), no lymph nodes were examined (Nx). In patients submitted to enucleation (n = 34), a lymph node sampling was performed in 16 cases (47%) and lymph node involvement was found in none of them. On multivariate linear regression analysis performed considering only patients without distant metastases and with at least one resected lymph node, the presence of a G2 NF-PanNET was the only independent predictor of nodal involvement (OR: 3.672, P < 0.001) (Table S-1).

At a median follow-up of 60 months (IQR 24–86 months), 32 patients (14%) had a recurrence and 9 patients (28%) eventually died of disease. At multivariable analysis, only tumor dimension >25 mm (P = 0.009), the presence of perineural (P = 0.027) and microvascular (P = 0.007) invasion were indipendent predictors of DFS (Table 5). In particular, patients with a tumor size ≤ 25 mm had a significantly better DFS compared to patients with larger tumors (P < 0.0001) (Fig. 1).

4. Discussion

This study demonstrated that increasing age is not related with larger or more aggressive NF-PanNET, whereas the tumor size is strictly associated with Ki67 proliferative index.

NF-PanNET are rare tumors mainly characterized by a wide biological heterogeneity. The genetic landscape of these tumors has been recently analyzed [18], but many aspects of their natural history are far to be defined. The early detection of lesions with malignant potential allow them to be early treated and usually to prevent the development of cancer. In several malignancies this mechanism is well known. One example is represented by colon cancer in which the adenoma-carcinoma sequence has been very well defined [19]. Similarly, as regard of pancreatic malignancies, intraductal papillary mucinous neoplasm (IPMN) is thought to progress from an adenomatous stage to IPMN with dysplasia, IPMN with carcinoma in-situ and eventually invasive IPMN. Consistently, patients with malignant IPMN are usually older than their benign counterparts [20]. In the last decade, a dramatic increase in the diagnosis of small, asymptomatic NF-PanNET has been observed [3]. Although a conservative management of these lesions is now suggested by the main international guidelines [21], concerns about a “wait and watch” attitude in young patients have not been overcome. In the present study, the size and aggressiveness of NF-PanNET, as determined by evaluation of Ki67 index, were not in relation with the age of the patient. Patients affected by NF-PanNET had a median age of 61 years, which is consistent with other larger epidemiological series. Dasari et al. [1] reported better outcomes for patients affected by PanNET when they were younger than 60 years, but these results are biased by the absence of a disease-specific survival analysis. Several reports analyzed the impact of NF-PanNET size on the prognosis of these neoplasms, but these studies did not observe significant differences in terms of age between patients with small NF-PanNET compared to other patients affected by larger tumors [4–6].

The results provided by the current analysis may have an important implication related to the absence of a significant correlation between age and tumor aggressiveness. In the largest, single-institutional, experience published so far on comparing surgical versus observational treatment of small NF-PanNET, it was reported that patients in the surgical group were 4 years younger than those conservatively managed [10]. Similar results were found in another study by Lee et al. [8] as the median age of nonoperative group was 67 years compared to 60 years in the operative group. Patients

Table 5
Univariate and multivariate analysis of predictors of disease free survival (DFS).

Variable	Univariate			Multivariate		
	HR	95% C.I.	*P*	OR	95% C.I.	*P*
Gender						
Male	1	–	0.714			
Female	0.875	0.429–1.787				
Age						
≤60 years	1	–	0.451			
>60 years	1.313	0.647–2.664				
Tumor size, mm	1.020	1.011–1.028	<0.001			
PanNET[a] largest diameter						
≤25 mm	1	–	<0.001	1	–	0.009
>25 mm	6.734	2.759–16.432		3.368	1.357–8.356	
Grade						
G1	1	–	<0.001			
G2	4.654	2.162–10.019				
Ki67 index						
≤5%	1	–	<0.001			
>5%	5.356	2.585–11.096				
R status						
R0	1	–	0.112			
R1	2.071	0.844–5.085				
N stage						
N0	1	–	<0.001			
N1	5.202	2.444–11.069				
Perineural invasion						
No	1	–	<0.001	1	–	0.027
Yes	8.224	4.041–16.735		2.519	1.108–5.724	
Microvascular invasion						
No	1		<0.00	1	–	0.007
Yes	10.744	4.616–25.066		3.935	1.463–10.583	
Necrosis						
No	1	–	<0.001			
Yes	5.647	2.405–13.260				

[a] PanNET: pancreatic neuroendocrine tumor.

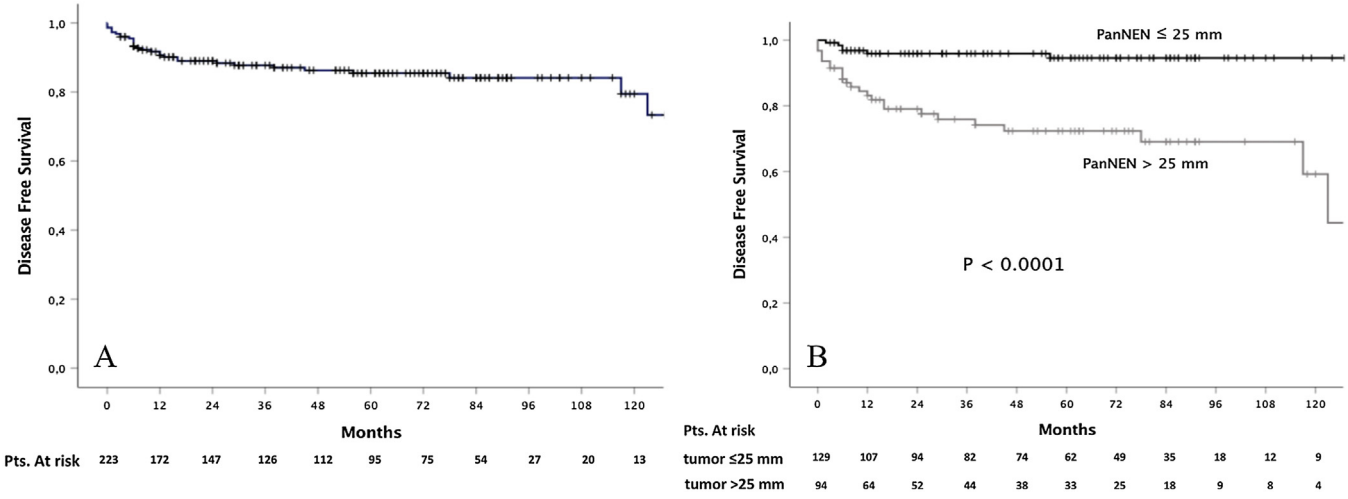

Fig. 1. Disease-free survival (DFS) of patients affected by NF-PanNET and submitted to a curative resection (R0-R1) (A). Comparison of DFS between patients who has a NF-PanNET ≤ 25 mm ($n = 129$) and those who has a NF-PanNET > 25 mm ($n = 94$) ($P < 0.0001$).

who were surgically treated were even younger in another study in which the authors suggest that for small NF-PanNET the exact tumor size should be factored into management decisions along with other variables including patient age [11].

The current findings may mitigate some concerns about a non-operative management of small, NF-PanNET when they occur in young or middle-aged adults. In this setting, younger age should not be a mandatory condition for routinely submitting patients with small NF-PanNET to surgery, as a long-life expectancy is probably unlikely to increase the risk of malignant transformation.

Of note, a strong correlation between NF-PanNET size and Ki67 proliferative index was demonstrated in the current experience. This result is consistent with previous reports. In particular, Bettini et al. [4] observed that patients with NF-PanNET less or equal

than 2 cm in size had a median Ki67 value of 1% compared to 2% in those who had a median NF-PanNET size between 2 and 4 cm and a Ki67 of 3% in those with a median NF-PanNET size >4 cm. Similarly, Kuo et al. [3], analyzing population-based data from 18 registries throughout the United States, found that patients with PanNET larger than 2 cm had a higher incidence of moderately or poorly differentiated forms compared with patients who had a PanNET less or equal than 2 cm. Recently, a large multi-institutional series on surgical resected NF-PanNET less than 2 cm in size, reported that only less than 20% of the examined population had a G2 tumor and 0.5% had a G3 carcinoma [7]. When analyzing this relationship after excluding patients with PanNET-G1 > 2.5 cm, a significant association between these two variables was not confirmed again. It is reasonable to speculate that in NF-PanNET larger than 2.5 cm both tumor size and grading independently play a role on prognosis and natural history of the neoplasm.

Indeed, tumor size was strongly associated with the risk of recurrence whereas the presence of a G2-tumor could accurately predict the presence of nodal metastases. Lymph node involvement is a powerful prognostic factor for PanNET [22], but its presence is often difficult to predict before surgery. In this series, when considering also patients with distant metastases, no correlation was found between nodal involvement and Ki67 proliferative index. However, the presence of a G2-PanNET was identified as the only preoperatively retrievable factor independently associated to lymph node metastases in patients affected by NF-PanNET G1-G2 without liver metastases thus demonstrating that in the presence of a tumor grade higher than G1, a proper lymphadenectomy should be always performed.

The present study has several limitations to be recognized. First of all, only patients who were operated were included. Therefore, a possible bias related to the selection of patients with more aggressive tumors could have been introduced. Secondly, the median age reported in the study could not reflect the real one, as older patients are generally more likely to undergo clinical and radiological examinations incidentally discovering small NF-PanNET. Thirdly, the results found in this retrospective study should be necessarily evaluated in a prospective trial with long follow-up to confirm that an observational approach is safe also in young patients. Finally, although in the present experience no differences were seen between radiological and histological diameter, a possible discrepancy between these two measurements has been previously reported [7]. Of note, several tumor size cut offs have been previously proposed: at this regard, it is likely that a precise tumor size cut off cannot be the only criterion considered in order to identify NF-PanNET with an aggressive behavior.

In conclusion, no correlations exist between age and NF-PanNET size or Ki67 proliferative index. Therefore, an a priori aggressive attitude is not justified in young patients. On the other hand, Ki67 proliferative index is significantly associated with NF-PanNET size that is an independent predictor of the presence of a G2 tumor when larger than 2.5 cm.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2019.01.008.

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