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Letter to the Editor

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Comment on the Paper by Lemelin et al. Entitled "Elderly Patients with Metastatic Neuroendocrine Tumors Are Undertreated and Have Shorter Survival: The LyREMeNET Study"

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Dear Editor,

We read with great interest the recently published article by Lemelin et al. [1]. The management of elderly patients is a "hot" topic, not only in relation to neuroendocrine neoplasia (NEN) but also in other cancer settings [2]. Lemelin et al. [1] reported data on prognostic factors, treatment, and survival in NEN patients >70 years of age, comparing their outcome with that of younger patients and concluding that the former population is undertreated.

We agree with the authors that little information is available on the prognosis and on the risks of treating elderly populations. The widespread prejudice about life expectancy also prevents cancer specialists from offering the best possible treatment to patients in the older age group.

Lemelin et al. [1] reported that patients >70 years of age received somatostatin analogs as first-line treatment, which is consistent with the strategy used in the Clarinet and Promid trials [2–5]. At progression, only a small percentage (5.1%) received peptide receptor radionuclide therapy (PRRT) as second-line therapy. The median overall survival (mOS) in this population was 5.2 years compared to 9.6 years in younger patients.

In a paper recently published by our group, we provided an overview of the clinical characteristics and outcome of an elderly population (>70 years) with metastatic NEN [6]. The mOS of the group was 5.1 years, including those with G3 neuroendocrine carcinoma. In the subgroups receiving PRRT as first-line treatment, mOS survival was 6.5 (3.3 not reached) years, slightly higher than that reported by Lemelin et al. [1]. Five-year survival was 80.7% in patients treated with first-line PRRT, substantially higher than the 57.9% (range 41.2–71.5) and 58.3% (range 18.0–84.4) observed in patients with G1-G2 neuroendocrine tumors receiving first-line somatostatin analogs and chemotherapy, respectively ($p < 0.001$) (Table 1).

In the recently updated NETTER-1 trial, a mOS of 27.4 months was reported for the octreotide arm and had still not been reached in the ^{177}Lutetium-PRRT arm, suggesting a significant benefit in the quality of life of patients with progressive midgut neuroendocrine tumors [7, 8] In previous studies, mOS from the start of treatment was 46 months and 128 months from diagnosis compared with historical controls, revealing a survival benefit of 40–72 months from diagnosis. [9]

These findings highlight the impact of PRRT treatment on patient outcome; especially of older patients whose shorter life expectancy and comorbidities can affect access to this treatment in a second-or-further-line setting.

Table 1. OS in patients >70 years of age with metastatic NENs

Variables	Patients, *n*	Events, *n*	1-year OS (95% CI)	5-year OS (95% CI)	Median OS in years (95% CI)	*p* value log rank test
All patients	125	68	85.1 (77.4–90.3)	50.7 (40.3–60.3)	5.1 (3.4–6.6)	–
Grading and first-line treatment						
G1/G2 with PRRT	13	4	92.3 (56.6–98.8)	80.7 (40.9–95.0)	6.5 (3.3–NR)	<0.001
G1/G2 with SSA	55	28	94.5 (83.9–92.2)	57.9 (41.2–71.5)	5.7 (4.2–7.0)	
G1/G2 with CHT	8	4	87.5 (38.7–98.1)	58.3 (18.0–84.4)	5.9 (0.4–NR)	
G3 with CHT	18	13	68.7 (40.4–85.6)	20.8 (4.4–45.5)	1.5 (1.0–2.5)	
Grading						
G1/G2	79	39	93.5 (85.2–97.2)	59.2 (45.4–70.6)	5.9 (4.2–7.0)	<0.001
G3	28	19	69.9 (48.6–83.6)	35.4 (16.8–54.7)	1.7 (1.0–3.2)	

NEN, neuroendocrine neoplasia; OS, overall survival; G, grading; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogs; CHT, chemotherapy; NR: not reached.

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Another point is the lack of grading in one-third of the patients, which may influence the final analysis of OS. ^{18}F-fluorodeoxyglucose (^{18}FDG) positron-emission tomography/computed tomography (PET/CT) seems to be a promising prognostic tool [10]. In our case series, age and comorbidities did not worsen the outcome, perhaps because of the good tolerability shown by patients to the specific treatments administered. ^{18}FDG PET/CT and ECOG performance status remained independent prognostic factors. [6]. As previously reported, ^{18}FDG-PET/CT positivity could be a useful tool to detect patients with a poorer prognosis [10].

Prospective clinical trials are needed to confirm the real benefit of treatments in patients >70 years of age. Although PRRT in NEN patients appears to be well tolerated and also shows good efficacy in patients with Ki67 >10%, further prospective studies are warranted. In addition, the prognostic role of ^{18}FDG-PET/CT should be investigated and be taken into account when evaluating candidates for first-and-further-line treatment.

Disclosure Statement

The authors have no conflicts of interest to declare.

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