RESEARCH

Unfavorable biological behavior and treatment response of neuroendocrine ovarian metastases of midgut neuroendocrine tumors

M C F Mulders[1], **Q G de Lussanet de la Sablonière**[2], **M L F van Velthuysen**[3], **E M Roes**[4], **J Hofland**[1] and **W W de Herder**[1]

[1]Department of Internal Medicine, ENETS Center of Excellence, Section of Endocrinology, Erasmus Medical Center and Erasmus Medical Center Cancer Institute, Rotterdam, The Netherlands
[2]Department of Radiology and Nuclear Medicine, Erasmus Medical Center, Rotterdam, The Netherlands
[3]Department of Pathology, Erasmus Medical Center, Rotterdam, The Netherlands
[4]Department of Gynecologic Oncology, Erasmus Medical Center Cancer Institute, Rotterdam, The Netherlands

Correspondence should be addressed to M C F Mulders: m.mulders@erasmusmc.nl

Abstract

Neuroendocrine ovarian metastases (NOM) predominantly derive from midgut neuroendocrine tumors (NETs) and develop in about 25% of women with advanced stage of this malignancy. Little is known of the growth rate and treatment response of NOM. We therefore evaluated the efficacy of different management options for patients with NOM, including peptide receptor radionuclide therapy (PRRT), somatostatin analogues (SSAs) and oophorectomy. Records were screened for patients with well-differentiated NOM of midgut origin that presented in our NET referral center between 1991 and 2022. Progression-free survival (PFS) and tumor growth rate (TGR) of ovarian and extra-ovarian metastases were determined using RECIST (response evaluation criteria in solid tumors) 1.1. In 12 available patients undergoing PRRT, NOM were associated with a shorter PFS than extra-ovarian metastases ($P = 0.003$). While PRRT induced a similar decrease in TGR for ovarian and extra-ovarian lesions in nine patients with available data (–2.3 vs –1.4, $P > 0.05$), only the TGR of NOM remained positive after PRRT. In 16 patients treated with SSAs, the TGR of NOM was almost three times that of extra-ovarian lesions during treatment (2.2 vs 0.8, $P = 0.011$). Oophorectomy was performed in 46 of the 61 included patients and was significantly associated with a prolonged OS (115 vs 38 months, $P < 0.001$). This association persisted after propensity score matching and correction for tumor grade and simultaneous tumor debulking. In conclusion, NOM have a higher TGR compared to extra-ovarian metastases, resulting in a shorter PFS after PRRT. Bilateral salpingo-oophorectomy should be considered for postmenopausal women with NOM undergoing surgery for metastatic midgut NETs.

Key Words
- neuroendocrine tumor
- ovary
- PRRT
- SSA
- tumor growth rate
- PFS
- OS

Endocrine-Related Cancer (2023) **30**, **e230035**

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms that predominantly arise from neuroendocrine cells of the embryonic gut and are subdivided into foregut, midgut and hindgut NETs (Hofland *et al.* 2020). NET incidence has increased 3.7- to 6.4-fold over the previous four decades, with the midgut

https://erc.bioscientifica.com
https://doi.org/10.1530/ERC-23-0035

or small intestine as a leading primary site in western countries (Fraenkel *et al.* 2014, Dasari *et al.* 2017, Das & Dasari 2021, White *et al.* 2022). Overall survival (OS) has substantially improved over this time period, particularly in patients with midgut NETs (White *et al.* 2022). About 34% of midgut NET patients present with metastases at the time of diagnosis and an additional 42% develop metastases during follow-up (Hallet *et al.* 2015). Physicians are therefore consulted by metastatic midgut NET patients with increasing frequency.

Ovarian metastases of NETs predominantly occur in midgut NET patients and are generally considered rare (Robboy *et al.* 1975, Strosberg *et al.* 2007). However, a recent study by Limbach and colleagues showed that these neuroendocrine ovarian metastases (NOM) occur in about 25% of female patients with a well-differentiated midgut primary tumor (Limbach *et al.* 2020). Only a few studies on patients with NOM have been published, and little is known of the treatment response of these metastases (Robboy *et al.* 1975, Strosberg *et al.* 2007, Zhang *et al.* 2018, Limbach *et al.* 2020). To the best of our knowledge, the study by Limbach and colleagues is the only one that evaluated the efficacy of any treatment modality in patients with NOM, in this case oophorectomy. Unfortunately, these authors compared 24 patients that underwent an oophorectomy to only three that did not. Moreover, endpoints like OS were not included in their analysis. Even though the effect of systemic therapy has not been described for NOM, a decreased response to chemotherapy is well known for ovarian metastases of colorectal cancer (Taylor *et al.* 1995, Goéré *et al.* 2008, Sekine *et al.* 2018). Hence, our study evaluated the efficacy of different management options for patients with NOM, including peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE, somatostatin analogues (SSAs) and oophorectomy.

Materials and methods

Patient selection

Electronic medical records were screened for all patients with NOM that presented in our NET referral center between 1991 and 2022. Primary inclusion criteria were either having histologically proven NOM or somatostatin receptor (SSTR) functional imaging suggesting the presence of NOM. Patients with neuroendocrine carcinomas and those with a non-midgut primary origin (including ovarian) were excluded. For this retrospective cohort study, the need for written informed consent was waived, and the study was approved by the medical ethical committee of the Erasmus MC.

Pathologic assessment

Diagnosis, tumor grade, Ki67 index and percentage of SSTR2a-positive tumor cells were revised by our expert NET pathologist (MLV) according to the 2022 WHO classification (Rindi *et al.* 2022). If available, primary tumor specimens and synchronous extra-ovarian metastases were also revised to allow for comparison of the Ki67 index and SSTR2a expression. Automated immunohistochemistry was performed on 4-µm-thick FFPE (formalin-fixed paraffin-embedded) sections using the Ventana Benchmark ULTRA (Ventana Medical Systems Inc., Tucson, AZ, USA) according to the protocol, using the rabbit MIB-1 antibody (clone 30-9, Ventana) at a dilution of 2.0 µg/mL for the Ki67 index and the rabbit polyclonal antibody (BioTrend, Köln, Germany) at a dilution of 1:25 for the SSTR2a expression.

Radiological assessment

Blinded for the patient's characteristics, an expert NET radiologist (QLS) determined the tumor size of ovarian and extra-ovarian NET lesions. Computed tomography (CT) scans were evaluated up to 30 months after treatment initiation, and assessment was stopped if both ovaries were removed, if the patient was lost to follow-up or if the patient died. All lesions were measured according to RECIST 1.1, and measurements were combined to determine the sum of largest diameters of both the ovarian and extra-ovarian lesions (Eisenhauer *et al.* 2009).

Outcomes

The primary endpoint was the difference in progression-free survival (PFS) after PRRT between ovarian and extra-ovarian lesions. PFS was defined as time from treatment initiation to morphological progression (progression defined as ≥20% growth, criteria adopted from RECIST 1.1 (Eisenhauer *et al.* 2009)). Secondary endpoints were tumor growth rate (TGR) and OS. TGR was defined as the percentage change in tumor volume over 1 month (%/month) and was calculated as described by Dromain and colleagues (Dromain *et al.* 2019). PFS and OS were censored if the patient was lost to follow-up. Patients' follow-up information was updated until November 2022.

https://erc.bioscientifica.com
https://doi.org/10.1530/ERC-23-0035

Treatment

PRRT treatment consisted of either four cycles of approximately 7.4 GBq ^{177}Lu-DOTATATE at an interval of 6–10 weeks or retreatment with two cycles of the same dose and interval, the exact protocol has been described previously (Brabander *et al.* 2017, Vaughan *et al.* 2018). Regarding patients on SSA treatment, only those on a stable dose of either octreotide LAR (30 mg/4 weeks) or lanreotide autogel (120 mg/4 weeks) were selected for TGR analysis.

Statistics

Data are presented as mean ± S.D. for normally distributed data, median and interquartile range for non-normally distributed data and frequency and percentage of cases for categorical data. A McNemar's or chi-square test was used for categorical data and, while a paired or unpaired *t*-test was used for normally distributed continuous data, a Wilcoxon signed rank or rank-sum test was utilized for non-normally distributed data. PFS and OS were analyzed with the Kaplan–Meier method and the log-rank test was used to compare differences between groups (Kaplan & Meier 1958). A multivariate Cox-proportional hazards analysis was utilized to calculate mortality hazard ratios. Only variables that significantly affected survival in the univariate analysis were included in the Cox model. The proportionality of hazards assumption was tested and not broken in any of the Cox regression models (Cox 1972).

To further evaluate of the effect of oophorectomy on OS, these analyses were repeated in a propensity score (PS)-matched cohort in order to optimize the post-weighting balance of covariates between groups (Austin 2009, 2013). Similar to previous work from our group (Refardt *et al.* 2020), a weight between 0 and 1 was assigned to all patients. This weight was based on a logistic regression model with oophorectomy as dependent variable and the covariates tumor grade, age, the presence of carcinoid syndrome and hepatic metastases at NOM diagnosis as independent variables. Utilizing caliper matching without replacement, PSs were used to match patients with oophorectomy to those without in a 1:1 ratio. With a caliper distance of absolute difference of 0.2, 13 patients who underwent an oophorectomy were matched to 13 who did not undergo this intervention. Unfortunately, we failed to find a match for 2 of the 15 patients who did not undergo an oophorectomy. Successful matching was indicated by the absence of statistical significance between the covariates.

A two-tailed *P*-value of <0.05 was considered significant. All data analyses were conducted in R Studio v4.1 or higher (https://www.R-project.org/).

Results

Study population

Ninety patients with suspected NOM were identified, of whom 61 met our inclusion criteria. While the PFS after PRRT could be determined in 12 patients, the TGR could be analyzed in 9 patients during PRRT treatment and in 16 on a regular dose of SSAs. Response to PRRT was measured after a full course of 29.4–30.6 GBq in eight PRRT patients, after retreatment with 14.9–15.3 GBq in three and after a submaximal initial dose of 15.2 GBq in one (treatment stopped due to RECIST progression of her NOM). A total of 46 out of the 61 included patients underwent an oophorectomy (Fig. 1). The majority (85.2%) of our cohort was postmenopausal (mean (SD) age at NOM diagnosis 64.4 (± 10.8) years), and 78% of patients had grade 1 tumors. Other relevant baseline characteristics are shown in Supplementary Table 1 (see section on supplementary materials given at the end of this article).

PFS

First, we determined the PFS of both ovarian and extra-ovarian metastases among the 12 patients who received PRRT with their NOM *in situ*. In our population and employing adopted RECIST v1.1 criteria, NOM were associated with a shorter PFS compared to extra-ovarian lesions ($P = 0.003$). While none of the extra-ovarian lesions progressed during a median follow-up of 11 months, the median PFS of the NOM was 15 months (Fig. 2). These findings were not altered when we performed the analysis with a PFS based solely on measurements of the solid component of NOM or after exclusion of patients who received submaximal PRRT activity.

TGR

We then examined the effect of treatment with PRRT and SSAs on the TGR (% of tumor growth per month) of ovarian and extra-ovarian metastases. For extra-ovarian metastases, PRRT induced a significant decrease in TGR, resulting in tumor regression (TGR 1.1 before and –0.3 after, $P = 0.020$). The TGR of NOM, on the other hand, remained

https://erc.bioscientifica.com
https://doi.org/10.1530/ERC-23-0035

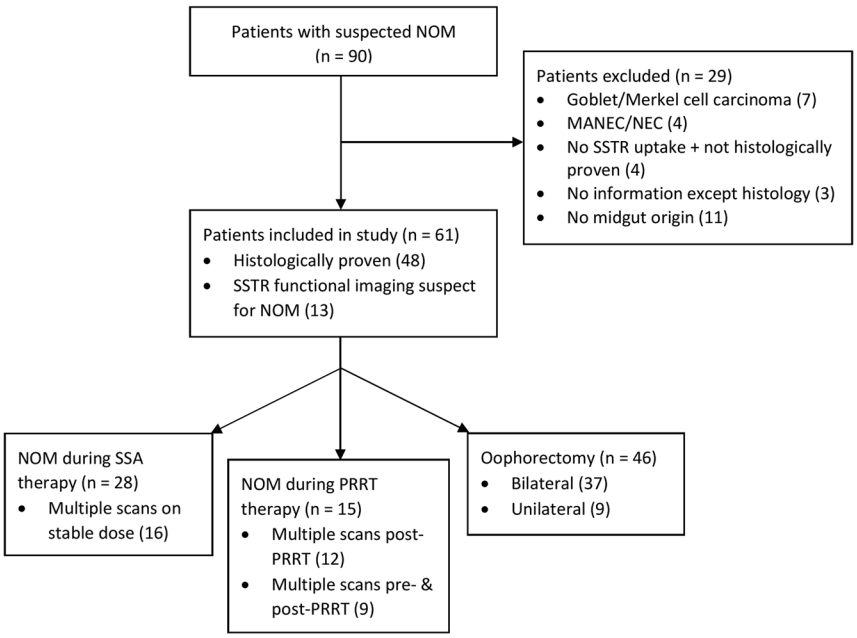

Figure 1
Flow diagram of patient selection. NOM, neuroendocrine ovarian metastases; MANEC, mixed adenoneuroendocrine carcinoma; NEC, neuroendocrine carcinoma; SSTR, somatostatin receptor; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analog.

positive after PRRT (TGR 2.6 before and 1.6 after, $P=0.426$) (Table 1, Fig. 3). When comparing the total change in TGR after PRRT, we observed a similar response of ovarian and extra-ovarian metastases (–2.3 and –1.4, $P=0.591$). In 16 patients treated with a stable dose of SSAs, the TGR of NOM was almost three times that of extra-ovarian lesions (2.2 vs 0.8, $P=0.011$) (Table 2). These findings were not altered when we performed the analyses with a TGR based solely on measurements of the solid component of NOM or after exclusion of patients who received submaximal PRRT activity.

Tumor characteristics

Next, we compared immunohistochemical characteristics of 19 NOM to their respective primary tumor and 7 to a simultaneously present extra-ovarian (lymph node, peritoneal or omental) metastasis. Both the Ki67 index and percentage of SSTR2a-positive tumor cells did not differ between NOM and the associated primary tumor ($P=0.975$ and 0.783, respectively); similar results were obtained when comparing ovarian and extra-ovarian metastases ($P=0.085$ and 0.855, respectively).

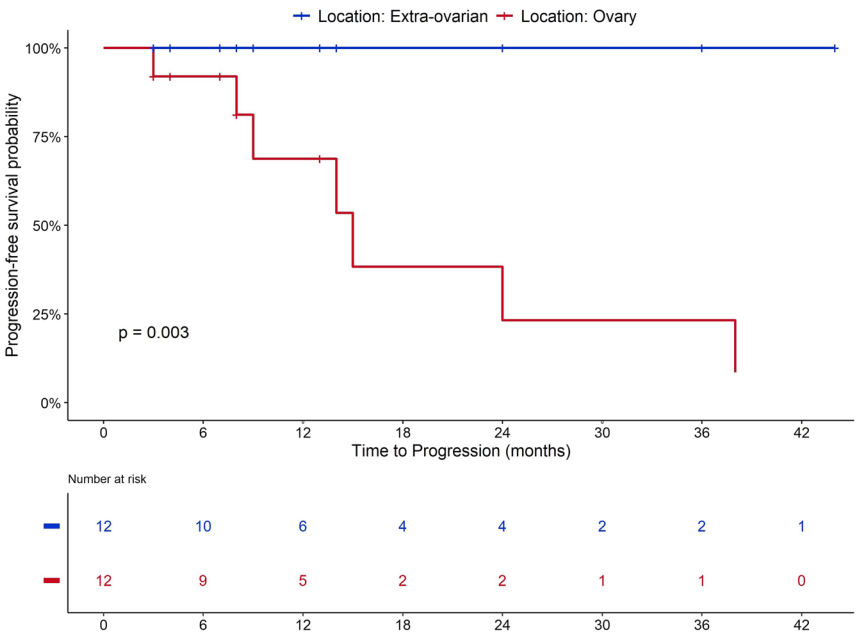

Figure 2
Outcome of patients treated with PRRT. Kaplan–Meier analysis showing time to progression of ovarian ($n=12$) and extra-ovarian metastases ($n=12$) after PRRT treatment. *P*-value indicates difference in PFS (log-rank test). PFS, progression-free survival; PRRT, peptide receptor nuclide therapy. A full color version of this figure is available at https://doi.org/10.1530/ERC-23-0035.

Oophorectomy

Finally, we analyzed the efficacy of oophorectomy as a treatment for patients with NOM. During follow-up, death occurred in 50% ($n = 23/46$) of patients who underwent an oophorectomy and in 60% ($n = 9/15$) of patients who did not undergo an oophorectomy. Median OS time was significantly higher in the oophorectomy group compared to the group of patients who did not undergo this surgical procedure (115 vs 38 months, $P < 0.001$) (Fig. 4).

Multivariate proportional hazards analysis confirmed that oophorectomy was associated with a reduced risk of overall mortality independent of tumor grade and simultaneous tumor debulking (hazard ratio 0.177 (95% CI 0.061–0.517), $P = 0.002$). Being diagnosed with a grade 2 tumor was the only other independent risk factor for mortality in our population with a hazard ratio of 3.130 (95% CI 1.160–8.443, $P = 0.024$).

PS matching led to two well-balanced cohorts of 13 patients; baseline characteristics did not differ between the two groups ($P > 0.05$) (Supplementary Table 1). Thirty-nine percent ($n = 5/13$) of patients who underwent an oophorectomy died, compared to 62% ($n = 8/13$) who did not undergo this surgical procedure. Median OS time in the oophorectomy group remained significantly increased at 121 months vs 53 months in the PS-matched control group ($P = 0.013$) (Fig. 4). A Cox-proportional hazards analysis re-confirmed that oophorectomy was associated with a prolonged OS (hazard ratio 0.062 (95% CI 0.007–0.531), $P = 0.011$).

Among the 37 patients who underwent a bilateral oophorectomy, 17 had a preoperative CT scan or ultrasound suspicious of bilateral disease, and unilateral disease was suspected in 12 patients. All of the patients with bilateral radiologic disease had bilateral disease at histologic examination. Interestingly, 83% of patients with unilateral disease on preoperative imaging in fact had bilateral disease at histologic examination when both ovaries were removed. Pre-oophorectomy imaging data could not be retrieved for analysis in 8/37 patients.

Table 1 Tumor growth rate pre- and post-PRRT treatment.

Variable	Pre-PRRT	Post-PRRT[a]	*P*
Patients included (*n*)	9	9	
TGR extra-ovarian lesions (median (IQR))	1.1 (0.6; 1.9)	−0.3 (−0.7; 0)	0.020[b]
TGR ovarian lesions (median (IQR))	2.6 (0.9; 4.1)	1.6 (0.4; 2.3)	0.426

[a]TGR measured from start PRRT until 30 months after start.
[b]Significant *P*-value (<0.05)
IQR, interquartile range; PRRT, peptide receptor radionuclide therapy; TGR, tumor growth rate, defined as percentage of tumor growth per month.

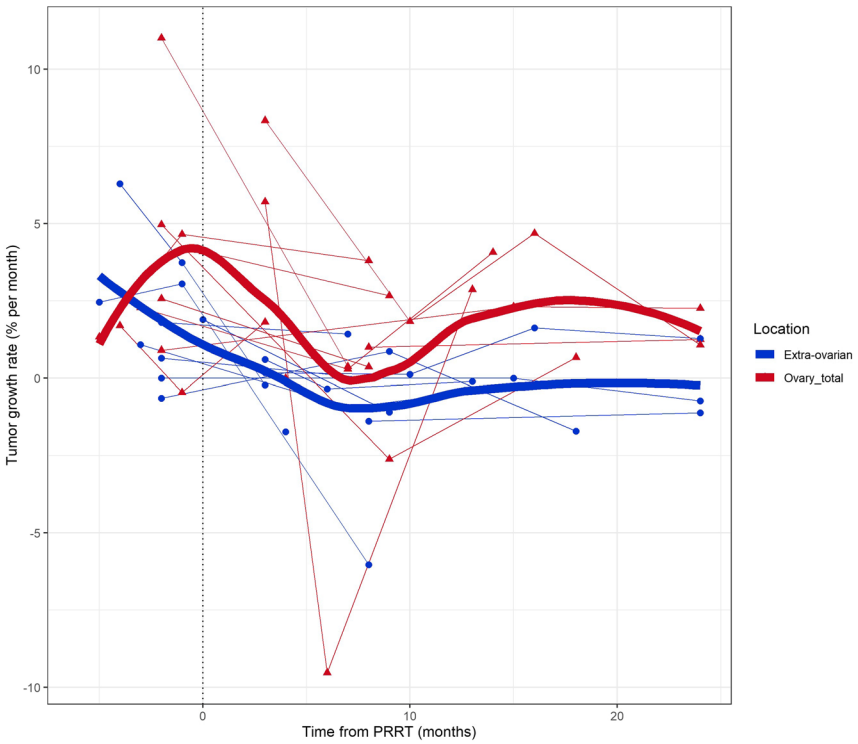

Figure 3
Tumor growth rate during PRRT treatment. Mean tumor growth grate for ovarian ($n = 12$) and extra-ovarian metastases ($n = 12$) determined with locally estimated scatterplot smoothing. PRRT, peptide receptor nuclide therapy. A full color version of this figure is available at https://doi.org/10.1530/ERC-23-0035.

Table 2 Treatment response of ovarian and extra-ovarian lesions.

Variable	Extra-ovarian lesions	Ovarian lesions	*P*
Patients included (n)	16	16	
TGR during SSA treatment[a] (median (IQR))	0.8 (–0.3; 1.8)	2.2 (0.7; 3.9)	0.011[c]
Patients included (*n*)	9	9	
Change in TGR after PRRT[b] (mean (s.d.))	–1.4 (1.7)	–2.3 (4.2)	0.591

[a]On stable dose of either octreotide (30 mg/4 weeks) or lanreotide (120 mg/4 weeks).
[b]TGR pre-PRRT compared to first TGR after PRRT.
[c]Significant *P*-value (<0.05).
IQR, interquartile range; SSA, somatostatin analog; TGR, tumor growth rate, defined as percentage of tumor growth per month.

Discussion

Main findings

The present study set out to evaluate the biological behavior and the efficacy of various treatment modalities for NOM. We found that NOM were associated with a shorter PFS after PRRT compared to extra-ovarian metastases. While PRRT induced a similar decrease in TGR for ovarian and extra-ovarian lesions, only the TGR of NOM remained positive after PRRT. In patients on a stable dose of SSAs, the TGR of NOM was almost three times that of extra-ovarian lesions during treatment. In our cohort, oophorectomy was associated with a prolonged OS. Lastly, we found that a large proportion of patients with unilateral disease on conventional imaging techniques demonstrated bilateral disease at histologic examination.

Interpretation of findings

Although NOM were associated with a shorter PFS after PRRT, we observed a similar decrease in TGR for ovarian and extra-ovarian lesions, which implies that NOM have a similar response to PRRT as extra-ovarian metastases. This finding is different from studies in colorectal cancer which have shown that ovarian metastases are less responsive to chemotherapy, naming them 'metastatic sanctuaries' (Taylor *et al.* 1995, Goéré *et al.* 2008, Sekine *et al.* 2018). The shorter PFS of NOM appears to be caused by their higher baseline TGR compared to extra-ovarian metastases, resulting in continued positive TGR of NOM after PRRT. To the best of our knowledge, this is the first study to analyze TGR in ovarian metastases. Whether this increased growth rate is specific for NETs or also pertains to ovarian metastases of other malignancies is unknown.

The question arises why NOM have a higher TGR than extra-ovarian metastases. We first explored the possibility that the cystic components of NOM, which were frequently present, were confounding the tumor size measurements. However, TGR and PFS calculated solely based on the solid component of these lesions did not differ from those based on the total size of the NOM. A more likely explanation is that NOM have a favorable micro-environment which results in an increased TGR. However, to the best of our knowledge, no studies have been published that have analyzed the interaction between ovarian NETs and their microenvironment. Additional research, e.g. *in vitro* work on potential ovarian mediators of tumor growth, is needed to explain this finding.

Another important finding was that oophorectomy was associated with a prolonged OS, independent of known predictors of survival. Therefore, ovarian metastases might be associated with an increased risk of mortality. This is in line with the findings in colorectal cancer, where oophorectomy significantly improves OS (Sekine *et al.* 2018). Interestingly, Limbach and colleagues did not find a difference in OS between well-differentiated NET patients with and without ovarian metastases (Limbach *et al.* 2020). A possible explanation for this result might be the fact that 89% of their patients with NOM had received an oophorectomy. For now, the mechanism that causes this survival benefit remains unknown. While the presence of ovarian metastases is linked to KRAS, SMAD4 and NTRK1 mutations in colorectal cancer (Ganesh *et al.* 2017), we do not expect the observed survival benefit to be mutation driven in our population, given the low mutational burden of NETs (Priestley *et al.* 2019).

Implications for practice

This study implies that patients with progressive disease based solely on progression of NOM likely will not benefit from PRRT. Performing an oophorectomy in these patients may delay the use of PRRT and consequently increase its effectiveness in treating the extra-ovarian disease. Similar to colorectal cancer, our results suggest that NOM are associated with significant morbidity and mortality. In contrast, an oophorectomy is generally considered a safe procedure (Asante *et al.* 2010), with probably even lower risks in a postmenopausal patient

https://erc.bioscientifica.com
https://doi.org/10.1530/ERC-23-0035

who requires concurrent abdominal surgery. Moreover, because a large proportion of patients with unilateral disease on conventional imaging techniques ended up having bilateral disease when both ovaries were removed, bilateral oophorectomy should be preferred over unilateral resection. Finally, in current practice, a hysterectomy is combined with an opportunistic salpingectomy, i.e. removal of the fallopian tubes in order to reduce the incidence of ovarian cancer. Given the vast benefits of this combined procedure (Naumann *et al.* 2021), we speculate

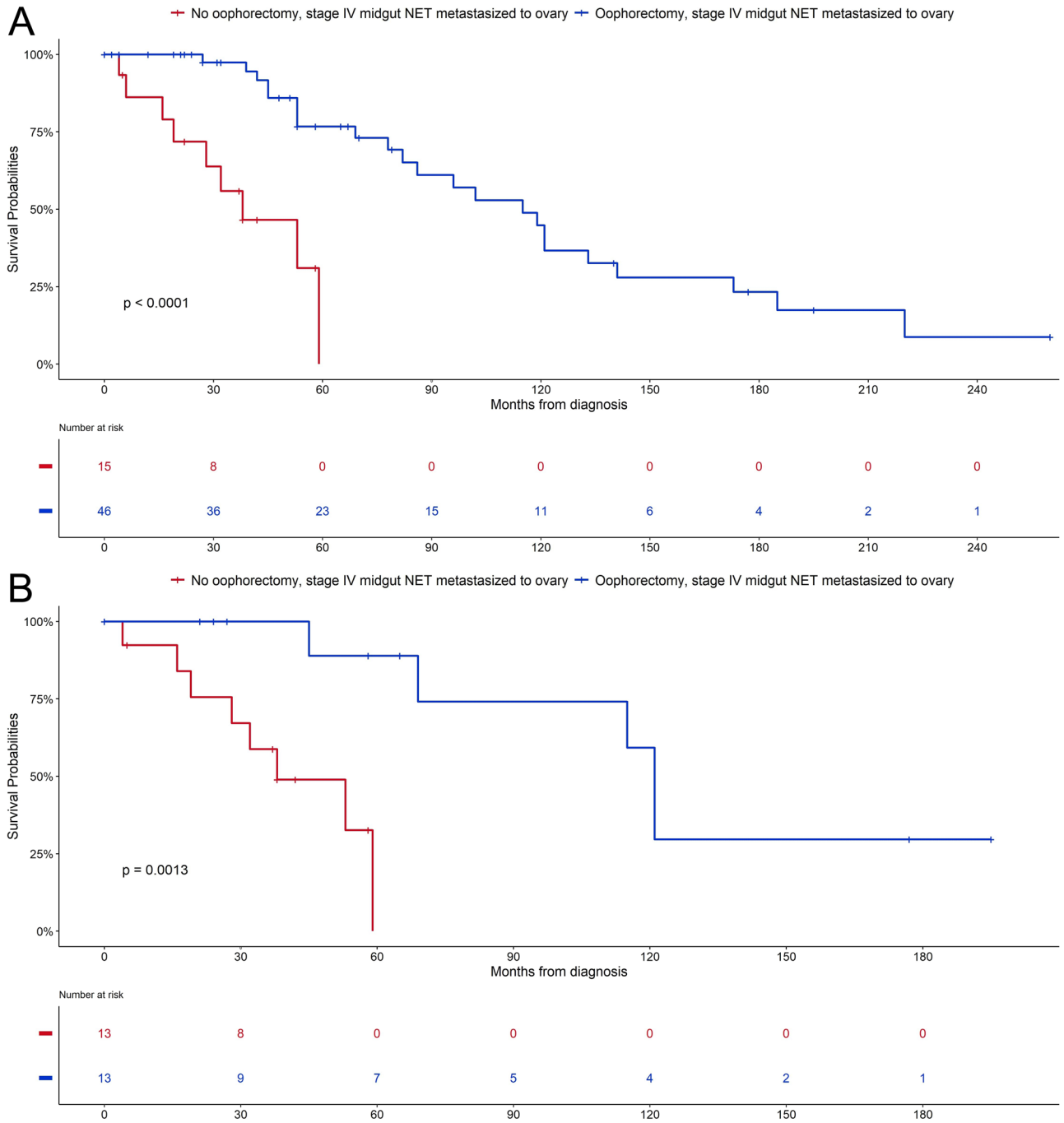

Figure 4

Overall survival of patients with and without oophorectomy. (A) Kaplan–Meier analysis showing overall survival of unmatched cohort (oophorectomy: $n = 46$, no oophorectomy: $n = 15$), (B) Kaplan–Meier analysis showing overall survival of propensity score-matched cohort (oophorectomy: $n = 13$, no oophorectomy: $n = 13$). *P*-value indicates difference in overall survival (log-rank test). NET, neuroendocrine tumor. A full color version of this figure is available at https://doi.org/10.1530/ERC-23-0035.

that a salpingo-oophorectomy should be preferred over an oophorectomy. We therefore conclude that prophylactic bilateral salpingo-oophorectomy should be considered for postmenopausal women with NOM undergoing abdominal surgery for metastatic midgut NETs.

Strengths and weaknesses

An inherent limitation in studies regarding specific subgroups of NET patients is their small sample size, which increases the possibility of type II errors. In our study, especially the results of the comparison of immunohistochemical characteristics need to be interpreted with caution, as these were regretfully only based on a small number of cases. This is, however, the largest cohort in which the effect of oophorectomy on patients with NOM has been described and the first to evaluate the efficacy of systemic treatment. Other studies either included a heterogeneous cohort of NOM with midgut, lung and/or unknown origin or even combined these patients with primary ovarian NETs, which have a different biologic behavior compared to NOM (Robboy *et al.* 1975, Strosberg *et al.* 2007, Zhang *et al.* 2018, Limbach *et al.* 2020). Another limitation of this study is its retrospective design. This non-randomized design is inherently subject to treatment-selection bias, as physicians may more frequently select patients whom they expect to live longer for operation. This bias was minimized by confirming the effect of oophorectomy on OS in a multivariate Cox-proportional hazards analysis as well as a PS-matched cohort, correcting for well-known factors that predict OS.

Conclusions

NOM have a higher TGR compared to extra-ovarian metastases, both during SSA treatment and after PRRT, resulting in a shorter PFS after PRRT. Prophylactic bilateral salpingo-oophorectomy should be considered for postmenopausal women with NOM undergoing abdominal surgery for metastatic midgut NETs.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/ERC-23-0035.

Declaration of interest

MM, QLS, MLV and EM have no potential conflict of interest. JH has received travel or speaker fees from Novartis, Ipsen and Advanced Accelerator Applications and is on the Advisory Board of Novartis. WWH has received travel or speaker fees from Novartis, Ipsen and Advanced Accelerator Applications and research funds from Ipsen and is on the Advisory Boards of Novartis and of Ipsen.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Author contribution statement

MM collected data from electronic patient records, carried out the formal data analysis and wrote the original draft of the manuscript. QLS performed the radiologic assessment of the treatment response. MLV performed the central pathology review. WWH carried out the conceptualization of the study and MM, EM and JH participated in the study conceptualization. QLS, MLV, EM, JH and WW critically reviewed and edited the manuscript. All authors reviewed the results and approved the final version of the manuscript.

References

Asante A, Whiteman MK, Kulkarni A, Cox S, Marchbanks PA & Jamieson DJ 2010 Elective oophorectomy in the United States: trends and in-hospital complications, 1998–2006. *Obstetrics and Gynecology* **116** 1088–1095. (https://doi.org/10.1097/AOG.0b013e3181f5ec9d)

Austin PC 2009 Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Statistics in Medicine* **28** 3083–3107. (https://doi.org/10.1002/sim.3697)

Austin PC 2013 The performance of different propensity score methods for estimating marginal hazard ratios. *Statistics in Medicine* **32** 2837–2849. (https://doi.org/10.1002/sim.5705)

Brabander T, van der Zwan WA, Teunissen JJM, Kam BLR, Feelders RA, de Herder WW, van Eijck CHJ, Franssen GJH, Krenning EP & Kwekkeboom DJ 2017 Long-term efficacy, survival, and safety of [(177)Lu-DOTA(0),Tyr(3)]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. *Clinical Cancer Research* **23** 4617–4624. (https://doi.org/10.1158/1078-0432.CCR-16-2743)

Cox DR 1972 Regression models and life tables (with discussion). *Journal of the Royal Statistical Society: Series B* **34** 187–202. (https://doi.org/10.1111/j.2517-6161.1972.tb00899.x)

Das S & Dasari A 2021 Epidemiology, incidence, and prevalence of neuroendocrine neoplasms: are there global differences? *Current Oncology Reports* **23** 43. (https://doi.org/10.1007/s11912-021-01029-7)

Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T & Yao JC 2017 Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncology* **3** 1335–1342. (https://doi.org/10.1001/jamaoncol.2017.0589)

Dromain C, Pavel ME, Ruszniewski P, Langley A, Massien C, Baudin E, Caplin ME & CLARINET Study Group 2019 Tumor growth rate as a metric of progression, response, and prognosis in pancreatic and intestinal neuroendocrine tumors. *BMC Cancer* **19** 66. (https://doi.org/10.1186/s12885-018-5257-x)

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al.* 2009 New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline, version 1.1. *European Journal of Cancer* **45** 228–247. (https://doi.org/10.1016/j.ejca.2008.10.026)

Fraenkel M, Kim M, Faggiano A, de Herder WW, Valk GD & Knowledge NETwork 2014 Incidence of gastroenteropancreatic neuroendocrine tumours: a systematic review of the literature. *Endocrine-Related Cancer* **21** R153–R163. (https://doi.org/10.1530/ERC-13-0125)

Ganesh K, Shah RH, Vakiani E, Nash GM, Skottowe HP, Yaeger R, Cercek A, Lincoln A, Tran C, Segal NH, *et al.* 2017 Clinical and genetic determinants of ovarian metastases from colorectal cancer. *Cancer* **123** 1134–1143. (https://doi.org/10.1002/cncr.30424)

Goéré D, Daveau C, Elias D, Boige V, Tomasic G, Bonnet S, Pocard M, Dromain C, Ducreux M, Lasser P, *et al.* 2008 The differential response to chemotherapy of ovarian metastases from colorectal carcinoma. *European Journal of Surgical Oncology* **34** 1335–1339. (https://doi.org/10.1016/j.ejso.2008.03.010)

Hallet J, Law CH, Cukier M, Saskin R, Liu N & Singh S 2015 Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer* **121** 589–597. (https://doi.org/10.1002/cncr.29099)

Hofland J, Kaltsas G & de Herder WW 2020 Advances in the diagnosis and management of well-differentiated neuroendocrine neoplasms. *Endocrine Reviews* **41** 371–403. (https://doi.org/10.1210/endrev/bnz004)

Kaplan EL & Meier P 1958 Non-parametric estimation from incomplete observations. *Journal of the American Statistical Association* **53** 457–481. (https://doi.org/10.1080/01621459.1958.10501452)

Limbach KE, Pommier SJ, Dewey E, Leon E & Pommier RF 2020 Neuroendocrine metastases to the ovaries are significantly associated with small bowel neuroendocrine tumors and carcinomatosis. *American Journal of Surgery* **219** 795–799. (https://doi.org/10.1016/j.amjsurg.2020.02.040)

Naumann RW, Hughes BN, Brown J, Drury LK & Herzog TJ 2021 The impact of opportunistic salpingectomy on ovarian cancer mortality and healthcare costs: a call for universal insurance coverage. *American Journal of Obstetrics and Gynecology* **225** 397.e1–397.e6. (https://doi.org/10.1016/j.ajog.2021.03.032)

Priestley P, Baber J, Lolkema MP, Steeghs N, de Bruijn E, Shale C, Duyvesteyn K, Haidari S, van Hoeck A, Onstenk W, *et al.* 2019 Pan-cancer whole-genome analyses of metastatic solid tumours. *Nature* **575** 210–216. (https://doi.org/10.1038/s41586-019-1689-y)

Refardt J, Zandee WT, Brabander T, Feelders RA, Franssen GJH, Hofland LJ, Christ E, de Herder WW & Hofland J 2020 Inferior outcome of neuroendocrine tumor patients negative on somatostatin receptor imaging. *Endocrine-Related Cancer* **27** 615–624. (https://doi.org/10.1530/ERC-20-0340)

Rindi G, Mete O, Uccella S, Basturk O, La Rosa S, Brosens LAA, Ezzat S, de Herder WW, Klimstra DS, Papotti M, *et al.* 2022 Overview of the 2022 WHO classification of neuroendocrine neoplasms. *Endocrine Pathology* **33** 115–154. (https://doi.org/10.1007/s12022-022-09708-2)

Robboy SJ, Norris HJ & Scully RE 1975 Insular carcinoid primary in the ovary. A clinicopathologic analysis of 48 cases. *Cancer* **36** 404–418. (https://doi.org/10.1002/1097-0142(197508)36:2<404::aid-cncr2820360216>3.0.co;2-0)

Sekine K, Hamaguchi T, Shoji H, Takashima A, Honma Y, Iwasa S, Kato K, Takahashi K, Kato T, Kanemitsu Y, *et al.* 2018 Retrospective analyses of systemic chemotherapy and cytoreductive surgery for patients with ovarian metastases from colorectal cancer: a single-center experience. *Oncology* **95** 220–228. (https://doi.org/10.1159/000489665)

Strosberg J, Nasir A, Cragun J, Gardner N & Kvols L 2007 Metastatic carcinoid tumor to the ovary: a clinicopathologic analysis of seventeen cases. *Gynecologic Oncology* **106** 65–68. (https://doi.org/10.1016/j.ygyno.2007.02.034)

Taylor AE, Nicolson VM & Cunningham D 1995 Ovarian metastases from primary gastrointestinal malignancies: the Royal Marsden Hospital experience and implications for adjuvant treatment. *British Journal of Cancer* **71** 92–96. (https://doi.org/10.1038/bjc.1995.18)

Vaughan E, Machta J, Walker M, Toumpanakis C, Caplin M & Navalkissoor S 2018 Retreatment with peptide receptor radionuclide therapy in patients with progressing neuroendocrine tumours: efficacy and prognostic factors for response. *British Journal of Radiology* **91** 20180041. (https://doi.org/10.1259/bjr.20180041)

White BE, Rous B, Chandrakumaran K, Wong K, Bouvier C, Van Hemelrijck M, George G, Russell B, Srirajaskanthan R & Ramage JK 2022 Incidence and survival of neuroendocrine neoplasia in England 1995–2018: A retrospective, population-based study. *Lancet Regional Health. Europe* **23** 100510. (https://doi.org/10.1016/j.lanepe.2022.100510)

Zhang X, Jones A, Jenkins SM & Huang Y 2018 Ki67 proliferative index in carcinoid tumors involving ovary. *Endocrine Pathology* **29** 43–48. (https://doi.org/10.1007/s12022-017-9510-7)

Received 19 April 2023
Accepted 3 May 2023
Available online 3 May 2023
Version of Record published 26 June 2023