Modifying the poor prognosis associated with FDG-avid NET with peptide receptor chemoradionuclide therapy (PRCRT)

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To The Editor,

Applying conventional diagnostic imaging paradigms, a negative FDG PET/CT in a patient with biopsy proven metastatic neuroendocrine tumour (NET) would be considered a false negative study. With molecular imaging, however, we have emerged from using imaging to merely detect and measure the size of lesions to increasingly using it to characterise disease phenotype, which was formerly the domain of pathology. We therefore read with interest the recent publication by Bahri et al.[1] confirming powerful prognostic utility of FDG PET/CT in patients with metastatic NET, which was superior even to conventional pathological factors such as histologic grade or Ki,67. These data substantiate earlier data by Binderup et al.[2] and Garin et al.[3]. These findings highlight the ability of PET/CT to reproducibly characterise all sites of disease in a given patient, minimising the sampling error inherent with histopathologic sampling of a random site of disease[4].

In their prospective study, Bahri et al.[1] demonstrated a median overall survival of 15 months for FDG-positive NET compared to 119.5 months for FDG-negative NET. The authors also explored the additional value of somatostatin receptor (SSTR) imaging. In keeping with concept that patient outcomes are related to the degree of tumor differentiation, patients with positive SSTR imaging had a better prognosis than those without but, even so, FDG also retained its prognostic utility within this group.

The adverse prognosis associated with FDG-avidity need not necessarily be the fate of such patients. We have recently published data regarding the efficacy of peptide receptor radionuclide chemoradiotherapy (PRCRT) with Lutetium-177 DOTATATE combined with 5-fluouracil in a cohort of 52 patients with FDG-avid NET[5]. Despite the anticipated poor prognosis of this cohort, we demonstrated an unexpectedly long progression free survival (PFS) of 48 months, while median overall survival (OS) had not been reached at the time of publication. We have since updated the OS data of this cohort after a median follow-up of 58 months, still with no patients lost to follow-up. Median OS from the commencement of PRCRT was 55 months (Kaplan-Meier survival analysis based on log-rank test). In response to the data presented by Bahri et al. we have further performed sub-analysis in patients with SUVmax ≥ 4.5 (n=44) or tumour / normal tissue (T/NT) ratio of ≥ 2.5 (n=23), groups by defined to have a relative risk for death of 6.2 and 23, respectively. Median survival of these subgroups in our cohort was the same as for our overall group.

These remarkable results attest to the superior efficacy of PRCRT compared to conventional therapeutic strategies since we can assume that the majority of patients in the study by Bahri et al. did not have access to this therapeutic modality due to lack of regulatory approval for PRRT in France, where their study was undertaken. Additionally, our results have a lead-time bias which is disadvantageous to our analysis, as survival in our study was not measured from diagnosis but rather from the time of PRCRT in a population who were previously treated with conventional therapeutic regimens including at least one line of chemotherapy in 67%. Thus, our median survival of 55 months is remarkable in comparison to 15 months defined by Bahri et al, suggesting that PRCRT prolongs survival by years in many patients with FDG-avid metastatic NET.

In addition to the encouraging results for the cohort, 4 patients have no evidence of disease after follow-up of 30 – 97 months, indicating that a small proportion of patients can be cured. Two achieved a complete response with PRCRT alone, while the other 2 were rendered disease-free following surgery; one to excise the primary site following complete regression of metastatic disease, and another in whom a R0 resection was achieved of residual primary and metastatic disease after major disease
regression[6]. Importantly, the resected residual disease in both patients was of significantly lower grade than that documented prior to treatment. Furthermore, 27% of patients in our cohort ultimately achieved a complete metabolic responses on FDG PET/CT despite presence of residual disease on SSTR PET/CT. In these patients, it appears PRCRT is able to convert the disease phenotype from an aggressive to an indolent phenotype. PRCRT is remarkably well tolerated as we and other have previously described [5, 7, 8]. However, there is a risk of long-term toxicity. With longer follow-up in our cohort, there have been 2 cases of myelodysplasia, although both patients remain alive with 44 and 79 months of follow-up. This risk must be weighed against the risk of death from the patients underlying NET and suggests that the risk-benefit ratio is likely to be highest for patients with higher grades of NET. Whilst the optimal sequences is available therapies remains uncertain, we believe that the most sensible approach is to use the most efficacious and least toxic therapy upfront. For metastatic FDG-avid ENETS G2 our results recommend that PRCRT is the first line therapeutic modality of choice, and we have recently changed our multi-disciplinary neuroendocrine service guidelines to reflect this.

There is further room to optimise delivery of PRCRT by refinement in patient selection and delivery of therapy[9], including use of Yttrium-90 in patients with larger volume disease and newer chemotherapeutic combinations such as capecitabine and temozolomide for pancreatic NET[10]. We are hopeful that these refinements will further improve patient outcomes.
References


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