Targeted precision neuroendocrine neoplasms (NEN) surgery may represent an innovative, yet promising, development of surgical procedures to achieve a radical resection of the primary tumour (by intra-operative confirmation of tumour-free margins) and to improve the identification of small sized lesions (that might otherwise be missed by either pre-operative functional imaging, ultrasound or manual palpation during surgery). From a practical point of view, radioguided surgery (RGS) requires a close collaboration between the nuclear medicine and the surgical teams, so that a small amount of radiopharmaceutical is intravenously injected in the patient right before surgery. The tumour lesions’ emitted radiation is then detected by a hand-held probe by the surgeon intra-operatively.

RGS is routinely and successfully used in breast (1) and melanoma (2) patients as well as for localization of hyper-functioning parathyroid glands (3).

Previous reports of the employment of RGS in NEN first employed 99Tcm-labelled somatostatin analogues (SA) (4,5). However, the development of beta-emitting SA for PET/CT imaging (SA-PET/CT) of well differentiated NEN tumours rendered pure scintigraphy imaging obsolete. The higher accuracy of SA-PET/CT was reported in many papers (6,7) and their theranostic potential (by labelling SA compounds with beta-minus isotopes for target treatment) also contributed to their increasing use (8).

In 2015, a prospective study on a relatively small cohort (n=14) of gastroentero-pancreatic (GEP)-NEN patients with positive pre-operative 68Ga-DOTATATE PET/CT was performed to assess the added value of 68Ga-DOTATATE RGS (5 mCi of radiopharmaceutical were administered at start of surgery in the operating room) (9). The authors reported that 68Ga-DOTATATE RGS had the highest correct identification by pathology for gastric and small bowel NEN, including mesenteric lymph nodes, correctly identifying more than 80% of lesions. The reported concordance between surgeon’s palpation and RGS was almost perfect, with only 3/35 (8.6%) lesions detected by RGS-only (9). It is interesting to notice, however, that the 3 above mentioned lesions were all at ileal level and millimetric in size, suggesting that the setting in which RGS might show a higher added value is definitely the identification of small mid-gut lesions. In fact, surgeons usually use manual palpation or intra-operative ultrasound to identify small ileal NEN lesions but their correct detection can be challenged, even in case of experienced surgeons, by their often millimetric size and multiple localizations in the same patient.

The intraoperative assessment of MEN patients, that are expected to develop multiple NEN lesions, is another potentially interesting setting in which RGS might prove additional value. Moreover, already surgically treated patients might be candidates for RGS to improve the identification of still viable tumour cells within surgical scar tissue, multiple adhesions or altered-anatomy regions.

In a previous report by Kaemmerer et al. (10) (9 NEN patients with mostly mid-gut primary tumour, stage 4), RGS detected 94% of the whole lesions as compared to pre-surgical PET/CT (69%) and surgical palpation (50%).

Considering the high background activity of the spleen, the adrenals and, to a lesser extent, the liver, RGD seems
not appropriate to identify small pancreatic tail NEN or liver secondary lesions (9,10).

The paper by El Lakis et al. recently published on *JAMA Surgery* 2019 (11), described a prospective cohort of 44 NEN patients (59% with a genetic predisposition to develop NEN) who underwent 68Ga-DOTATATE RGS (5 mCi were administered intravenously at the time of the operation). The authors reported a high RGS accuracy for true NEN lesions detection (with the more frequent disease sites being the nodes, followed by pancreas, small bowel, liver and adrenal/paraganglioma). The tumour-to-background (TBR) threshold of 2.5 yielded the highest sensitivity (90%). They also found that the best intra-abdominal organ for TBR optimization was the omentum (easily accessible, showing a homogeneous/minimal uptake and rarely involved with NEN carcinomatosis). Overall, 5/39 (13%) lesions were detected by RGS-only as compared to pre-surgical PET/CT, intraoperative ultrasound and palpation. Last but not least, the radiation exposure to the operating room personnel was reported to be negligible. The authors concluded that RGS is safe and can provide additional value in NEN lesions’ detection when the TBR (using the omentum as background) is above 2.5.

Overall, the results portrayed on the accuracy and safety of 68Ga-DOTATATE RGS in NEN are very promising, however, several issues still need to be investigated. First of all, since the estimated number of additional lesions detected by RGS-only seems to be approximately 10% across studies, the identification of the patients’ subset who might benefit more from the procedures seems mandatory. From the published, preliminary studies it seems that mid-gut NET patients with an indication to elective surgery, patients with known NEN secondary lesions and suspected/unidentified ileal primary or patients with genetic predisposition to develop NEN might be the ideal candidates. Secondly, a more in-depth analysis should clarify whether the performance of RGS increases the number of radical resections, to what extent the performance of RGS impacts the surgical procedure itself and survival. Finally, considering the high prevalence of pancreatic NEN primary and small liver NEN lesions, a deeper evaluation of the possibility to identify lesions close to/within high background parenchymas (e.g., spleen, adrenal glands and kidneys) should be further investigated.

**Acknowledgments**

None.

**Footnote**

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**References**


