[⁶⁸Ga]Ga-tilmanocept PET/CT lymphoscintigraphy: a novel technique for sentinel lymph node imaging

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Published online: 6 November 2020

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Sentinel lymph node biopsy (SLNB) has been implemented in most Dutch Head and Neck Cancer institutions as a standard oncological care for staging the clinically negative neck in early-stage (cT1/2N0) oral squamous cell carcinoma (OSCC) [1]. As SLNB has shown to accurately stage the clinically negative neck in these patients, with a pooled sensitivity of 87% and negative predictive value of 94%, SLNB offers a reliable, less invasive alternative for elective neck dissection with overall lower morbidity rates, better quality-of-life, and lower healthcare costs [1–10].

Nevertheless, SLNB with conventional peritumorally administered ^{99m}Tc-labeled radiotracers has its predicaments in OSCC, arising from the limited resolution of conventional scintigraphy and SPECT/CT imaging. Especially in cases where sentinel lymph nodes (SLNs) are located in proximity of the primary tumor, the activity residing at the radiotracer injection site can conceal these adjacent SLNs and impede distinction between SLN and injection site. This so-called shine-through phenomenon is notably manifest in floor-of-mouth OSCC, resulting in a significant lower accuracy of SLNB in floor-of-mouth tumors (sensitivity 63%; NPV 90%) compared to other OSCC subsites (sensitivity 86%; NPV 95%) [1]. Such decline in diagnostic accuracy increases the risk of neglecting occult lymph node metastasis that will

inevitably develop into clinical manifestation of disease and consequently induce a poor oncological prognosis [11, 12].

Furthermore, on conventional scintigraphy and SPECT/CT imaging, distinguishing hotspots as either real SLN or higher echelon node (HEN) can pose a challenge. Consequently, in clinical practice, presumably an excessive amount of lymph nodes is harvested, as some will actually represent HENs. Extirpation of HENs may lead to unnecessary morbidity and risk of complications and may even hamper a complementary surgical treatment in case of metastatic involvement of SLNs [13].

In this issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, we present a promising novel imaging technique that may solve the clinical issues addressed: [⁶⁸Ga]Ga-tilmanocept PET/CT lymphoscintigraphy [14]. The superior spatial resolution of PET/CT lymphoscintigraphy, when compared to SPECT/CT using ^{99m}Tc-labeled radiotracers, enables identification of SLNs located close to the radiotracer injection site and improves anatomic localization of SLNs, which is of particular importance in the complex anatomy of the neck and its abundant lymph nodes. Hence, PET/CT lymphoscintigraphy using [⁶⁸Ga]Ga-tilmanocept might lead to a reduction of false-negative SLNB outcomes by diminishing the shine-through phenomenon. In addition, its high temporal resolution and ability to visualize lymphatic vessels could improve differentiation between true SLNs and HENs, thereby decreasing unnecessary HEN extirpation and reducing the risk of surgical complications and morbidity [14, 15].

Further merits of [⁶⁸Ga]Ga-tilmanocept PET/CT lymphoscintigraphy, relative to SPECT/CT with [^{99m}Tc]Tc radiotracers, include its potential to considerably shorten acquisition time with similar signal-to-noise ratios, as well as the concomitant opportunities provided by using a tri-modal agent (IRD-800CW-[⁶⁸Ga]Ga-[^{99m}Tc]Tc-tilmanocept) [16–19]. This tri-modal agent should facilitate high-resolution PET/CT lymphoscintigraphic images for preoperative SLN mapping and, the following day, intraoperative localization of SLNs with both the conventional portable gamma probe and

This article is part of the Topical Collection on Oncology - Head and Neck

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fluorescence imaging, without interference from ^{68}Ga 's positron emission due to its short half-life (68 min). Although high-energy handheld PET probes are available, designed for intraoperative localization of SLNs containing a positron-emitting isotope-labeled radiotracer (e.g., [^{89}Zr]Zr-nanocolloid), their use is not recommended due to their large size and limited sensitivity [20]. Therefore, intraoperative localization of SLNs should still depend on at least conventional gamma probe guidance, which remains feasible when combining [^{68}Ga]Ga and [$^{99\text{m}}\text{Tc}$]Tc radiotracers [14].

Finally, in contrast to other commonly used positron emitting isotopes (e.g., ^{11}C , ^{18}F , ^{89}Zr), production of ^{68}Ga does not require a nearby cyclotron, but can be obtained from a portable $^{68}\text{Ge}/^{68}\text{Ga}$ generator, allowing on-demand preparation of [^{68}Ga]Ga-tilmanocept in a standard hospital radiopharmacy [21–23].

Yet, the materialistic costs associated with [^{68}Ga]Ga-tilmanocept PET/CT lymphoscintigraphy may remain a hindrance for the global spread of this innovative technique. First of all, as labeling of ^{68}Ga with nanocolloids is unfeasible due to instability of their bond at physiological pH, this technique relies on using the more expensive tracer tilmanocept. Secondly, the additional costs for labeling tilmanocept with ^{68}Ga should be taken into account. The necessary commercial automated synthesis units are relatively expensive, although more economical options with minimal operator radiation exposure are available [23]. In addition, $^{68}\text{Ge}/^{68}\text{Ga}$ generators typically cost in excess of €50,000 and expire after 1 year. However, it should be emphasized that the interest in ^{68}Ga -labeled tracers (e.g., [^{68}Ga]Ga-DOTATOC, [^{68}Ga]Ga-PSMA) continues to increase. Accordingly, the costs per preparation decrease, while $^{68}\text{Ge}/^{68}\text{Ga}$ generators have already proven to provide a cost-effective alternative to radionuclides obtained from reactors and cyclotrons [23–25]. Finally, the operating costs for PET acquisition are still higher than scintigraphy and SPECT acquisition, despite the fact that the costs of purchasing and operating PET scanners have been halved over the past 10 years [25]. All considered, the costs for performing [^{68}Ga]Ga-tilmanocept PET/CT lymphoscintigraphy in our institution are estimated at €1,700 per patient, not including expenses for additional $^{99\text{m}}\text{Tc}$ and fluorescent labeling in light of future perspectives. In contrast, in our institution, costs for conventional lymphoscintigraphy including SPECT/CT using [$^{99\text{m}}\text{Tc}$]Tc nanocolloid are estimated at €1,200 per patient, when performed in a research setting.

In spite of these higher materialistic costs, [^{68}Ga]Ga-tilmanocept PET/CT lymphoscintigraphy may even be cost-effective, apart from its potential to raise the standard of care, especially when enabling a depletion of false-negative SLNB outcomes, considering that patients with regional failure (i.e., false negative) generally require comprehensive healthcare, including more extensive surgery and adjuvant radiotherapy, compared to patients who are correctly staged positive for

disease by SLNB [9, 11, 26]. Furthermore, the potential of [^{68}Ga]Ga-tilmanocept PET/CT lymphoscintigraphy to significantly decrease acquisition times for SLN imaging may substantially decline relative personnel costs [25]. Since [^{68}Ga]Ga-tilmanocept PET/CT lymphoscintigraphy may diminish unnecessary HEN extirpation, expenses for meticulous histopathological assessment (i.e., step-serial-sectioning, immunohistochemistry) of irrelevant HENs might also be avoided [27].

For now, [^{68}Ga]Ga-tilmanocept PET/CT lymphoscintigraphy for SLN mapping in early-stage OSCC is both promising and encouraging, although the number of studied patients requires a considerable increase before any definite conclusions can be drawn. Still, the first results are inspiring for future prospects, including adoption of a tri-modal agent for SLNB (IRD-800CW-[^{68}Ga]Ga-[$^{99\text{m}}\text{Tc}$]Tc-tilmanocept), implementation in other malignancies, and employing highly accurate targeted radiotherapy by PET/CT lymphoscintigraphic-guided nodal irradiation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Not applicable

Ethical approval Institutional Review Board approval was not required because the paper is an Editorial.

References

1. Den Toom IJ, Boeve K, Lobeek D, Bloemena E, Donswijk ML, de Keizer B, et al. Elective neck dissection or sentinel lymph node biopsy in early stage oral cavity cancer patients: the Dutch experience. *Cancers*. 2020;12:1783. <https://doi.org/10.3390/cancers12071783>.
2. Liu M, Wang SJ, Yang X, Peng H. Diagnostic efficacy of sentinel lymph node biopsy in early oral squamous cell carcinoma: a meta-analysis of 66 studies. *PLoS One*. 2017;12(1):e0170322.
3. Schilling C, Stoeckli SJ, Haerle SK, Broglie MA, Huber GF, Sorensen JA, et al. Sentinel European Node Trial (SENT): 3-year results of sentinel node biopsy in oral cancer. *Eur J Cancer*. 2015;51(18):2777–84. <https://doi.org/10.1016/j.ejca.2015.08.023>.
4. Flach GB, Bloemena E, Klop WM, van Es RJ, Schepman KP, Hoekstra OS, et al. Sentinel lymph node biopsy in clinically N0 T1-T2 staged oral cancer: the Dutch multicenter trial. *Oral Oncol*. 2014;50(10):1020–4. <https://doi.org/10.1016/j.oraloncology.2014.07.020>.
5. Schiefke F, Akdemir M, Weber A, Akdemir D, Singer S, Frerich B. Function, postoperative morbidity, and quality of life after cervical sentinel node biopsy and after selective neck dissection. *Head Neck*. 2009;31(4):503–12. <https://doi.org/10.1002/hed.21001>.
6. Murer K, Huber GF, Haile SR, Stoeckli SJ. Comparison of morbidity between sentinel node biopsy and elective neck dissection for treatment of the n0 neck in patients with oral squamous cell carcinoma. *Head Neck*. 2011;33(9):1260–4. <https://doi.org/10.1002/hed.21622>.

7. Govers TM, Schreuder WH, Klop WM, Grutters JP, Rovers MM, Merkx MA, et al. Quality of life after different procedures for regional control in oral cancer patients: cross-sectional survey. *Clin Otolaryngol*. 2016;41(3):228–33. <https://doi.org/10.1111/coa.12502>.
8. Govers TM, Takes RP, Baris Karakullukcu M, Hannink G, Merkx MA, Grutters JP, et al. Management of the N0 neck in early stage oral squamous cell cancer: a modeling study of the cost-effectiveness. *Oral Oncol*. 2013;49(8):771–7. <https://doi.org/10.1016/j.oraloncology.2013.05.001>.
9. Hemando J, Villarreal P, Álvarez-Marcos F, García-Consuegra L, Gallego L, Junquera L. Sentinel node biopsy versus elective neck dissection. Which is more cost-effective? A prospective observational study. *J Craniomaxillofac Surg*. 2016;44(5):550–6. <https://doi.org/10.1016/j.jcms.2016.01.017>.
10. Garrel R, Poissonnet G, Moyà Plana A, Fakhry N, Dolivet G, Lallemand B, et al. Equivalence randomized trial to compare treatment on the basis of sentinel node biopsy versus neck node dissection in operable T1-T2N0 oral and oropharyngeal cancer. *J Clin Oncol*. 2020;14:JCO2001661. <https://doi.org/10.1200/JCO.20.01661>.
11. D'Cruz AK, Vaish R, Kapre N, Dandekar M, Gupta S, Hawaldar R, et al. Head and neck disease management group. Elective versus therapeutic neck dissection in node-negative oral cancer. *N Engl J Med*. 2015;373(6):521–9. <https://doi.org/10.1056/NEJMoa1506007>.
12. de Bree R, Takes RP, Shah JP, Hamoir M, Kowalski LP, Robbins KT, et al. Elective neck dissection in oral squamous cell carcinoma: past, present and future. *Oral Oncol*. 2019;90:87–93. <https://doi.org/10.1016/j.oraloncology.2019.01.016>.
13. Heuveling DA, Flach GB, van Schie A, van Weert S, Karagozoglu KH, Bloemena E, et al. Visualization of the sentinel node in early-stage oral cancer: limited value of late static lymphoscintigraphy. *Nucl Med Commun*. 2012;33(10):1065–9. <https://doi.org/10.1097/MNM.0b013e3283571089>.
14. Mahieu R, Krijger GC, Ververs FFT, de Roos R, de Bree R, de Keizer B. [⁶⁸Ga]Ga-tilmanocept PET/CT lymphoscintigraphy for sentinel lymph node detection in early-stage oral cavity carcinoma. *Eur J Nucl Med Mol Imaging*. (Accepted for publication 29th September 2020).
15. Heuveling DA, van Schie A, Vugts DJ, Hendrikse NH, Yaqub M, Hoekstra OS, et al. Pilot study on the feasibility of PET/CT lymphoscintigraphy with ⁸⁹Zr-nanocolloidal albumin for sentinel node identification in oral cancer patients. *J Nucl Med*. 2013;54(4):585–9. <https://doi.org/10.2967/jnumed.112.115188>.
16. Rahmim A, Zaidi H. PET versus SPECT: strengths, limitations and challenges. *Nucl Med Commun*. 2008;29(3):193–207. <https://doi.org/10.1097/MNM.0b013e3282f3a515>.
17. Qin Z, Hoh CK, Hall DJ, Vera DR. A tri-modal molecular imaging agent for sentinel lymph node mapping. *Nucl Med Biol*. 2015;42(12):917–22. <https://doi.org/10.1016/j.nucmedbio.2015.07.011>.
18. Lee HJ, Barback CV, Hoh CK, Qin Z, Kader K, Hall DJ, et al. Fluorescence-based molecular imaging of porcine urinary bladder sentinel lymph nodes. *J Nucl Med*. 2017;58(4):547–53. <https://doi.org/10.2967/jnumed.116.178582>.
19. Anderson KM, Barback CV, Qin Z, Hall DJ, Hoh CK, Vera DR, et al. Molecular imaging of endometrial sentinel lymph nodes utilizing fluorescent-labeled Tilmanocept during robotic-assisted surgery in a porcine model. *PLoS One*. 2018;13(7):e0197842. <https://doi.org/10.1371/journal.pone.0197842>.
20. Heuveling DA, Karagozoglu KH, van Lingen A, Hoekstra OS, van Dongen GAMS, de Bree R. Feasibility of intraoperative detection of sentinel lymph nodes with ⁸⁹-zirconium-labelled nanocolloidal albumin PET-CT and a handheld high-energy gamma probe. *EJNMMI Res*. 2018;8(1):15. <https://doi.org/10.1186/s13550-018-0368-6>.
21. Kasbollah A, Eu P, Cowell S, Deb P. Review on production of ⁸⁹Zr in a medical cyclotron for PET radiopharmaceuticals. *J Nucl Med Technol*. 2013;41(1):35–41. <https://doi.org/10.2967/jnmt.112.111377>.
22. Martiniova L, Palatis L, Etchebehere E, Ravizzini G. Gallium-68 in medical imaging. *Curr Radiopharm*. 2016;9(3):187–207. <https://doi.org/10.2174/1874471009666161028150654>.
23. Heidari P, Szretter A, Rushford LE, Stevens M, Collier L, Sore J, et al. Design, construction and testing of a low-cost automated (⁶⁸)gallium-labeling synthesis unit for clinical use. *Am J Nucl Med Mol Imaging*. 2016;6(3):176–84.
24. Velikyan I. Prospective of ⁶⁸Ga-radiopharmaceutical development. *Theranostics*. 2013;4(1):47–80. <https://doi.org/10.7150/thno.7447>.
25. Hicks RJ, Hofman MS. Is there still a role for SPECT-CT in oncology in the PET-CT era? *Nat Rev Clin Oncol*. 2012;9(12):712–20. <https://doi.org/10.1038/nrclinonc.2012.188>.
26. Flach GB, Tenhagen M, de Bree R, Brakenhoff RH, van der Waal I, Bloemena E, et al. Outcome of patients with early stage oral cancer managed by an observation strategy towards the N0 neck using ultrasound guided fine needle aspiration cytology: no survival difference as compared to elective neck dissection. *Oral Oncol*. 2013;49(2):157–64. <https://doi.org/10.1016/j.oraloncology.2012.08.006>.
27. Dhawan I, Sandhu SV, Bhandari R, Sood N, Bhullar RK, Sethi N. Detection of cervical lymph node micrometastasis and isolated tumor cells in oral squamous cell carcinoma using immunohistochemistry and serial sectioning. *J Oral Maxillofac Pathol*. 2016;20(3):436–44.

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