The ProPSMA Randomized Trial: A Landmark Study with Many Lessons

Sir,

^{68}Gallium-prostate-specific membrane antigen (^{68}Ga-PSMA) positron emission tomography–computed tomography (PET-CT) has been shown to be a highly sensitive and specific technique for imaging prostate cancer in the last few years. While there are multitudes of studies showing superiority of ^{68}Ga-PSMA PET-CT over presently recommended standard conventional imaging (contrast CT of the chest, abdomen, and pelvis plus bone scan) for staging of high-risk prostate cancer, the scientific level of evidence remains low. Many of these studies are retrospective, few are multicenter, and none randomized.[1] In fact, the latest National Comprehensive Cancer Network (NCCN) guidelines in prostate cancer (version 2. 2020) still recommend the use of CT plus bone scan for staging high-risk prostate cancer.[2] The use of PET-CT is recommended only in certain circumstances, that too ^{11}C-choline and ^{18}F-fluciclovine PET-CT, both of which have been shown to be inferior to ^{68}Ga-PSMA PET-CT.[3,4] Fortunately, this is likely to change after a recent landmark randomized trial by Hofman *et al*., published in Lancet.[5]

This prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA) study was a prospective, multicenter, two-armed, randomized trial with crossover,[6] where the primary outcome was accuracy of first-line imaging (^{68}Ga-PSMA-111 PET-CT versus conventional imaging with CT plus bone scan with single-photon emission computerized tomography [SPECT]-CT) for detection of pelvic nodal and distant site of metastasis. Total 302 patients with high-risk prostate cancer were randomized into conventional imaging (n = 152) and ^{68}Ga-PSMA PET-CT (n = 150) arms. ^{68}Ga-PSMA PET-CT showed significantly higher accuracy (92% vs. 65%, $P < 0.0001$), sensitivity (85% vs. 38%), and specificity (98% vs. 91%). In subgroup analysis, ^{68}Ga-PSMA PET-CT was superior to conventional imaging for detecting pelvic nodal (91% vs. 59%) and distant metastasis (95% vs. 74%). It was also seen that ^{68}Ga-PSMA PET-CT conferred significantly more management changes than conventional imaging (41% vs. 23%, $P = 0.008$). Two additional significant findings were less equivocal lesions (7% vs. 23%) and lower radiation dose (8.4 mSv vs. 19.2 mSv, $P < 0.001$) with ^{68}Ga-PSMA PET-CT than conventional imaging. The latter was because of universal use of SPECT-CT for bone scan in this study, which leads to raised radiation burden in conventional imaging arm[7] but, at the same time, made it more comparable. The authors concluded ^{68}Ga-PSMA PET-CT to be a suitable replacement for current standard of care conventional imaging with superior accuracy in staging high-risk prostate cancer. This high-quality Category 1 evidence will definitely be reflected in NCCN guidelines for prostate cancer when they are modified or updated next.

Another, in my opinion more important, lesson to be learned from this study is that nuclear medicine physicians should come to the forefront and start generating high-quality evidence with randomized trials in imaging rather than waiting for our oncology colleagues to do the same. While the traditional, single-center, retrospective, and prospective studies routinely performed by us do provide important and significant scientific information, they fall short as a level of evidence when framing management guidelines. It is time that our observations in reporting rooms become part of general clinical discourse, with the help of well-thought-out, simple, and meticulously performed multicenter randomized trials. Indian nuclear medicine community, with its advanced molecular imaging resources and huge patient load, can lead the path, probably in liaison with national societies. I hope that this study by Hofman *et al*.[5] is a beginning that inspires and not just an aberration.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Punit Sharma

Department of Nuclear Medicine and PET-CT, Apollo Gleneagles Hospitals, Kolkata, West Bengal, India

Address for correspondence: *Dr. Punit Sharma, Department of Nuclear Medicine and PET-CT, Apollo Gleneagles Hospitals, 58, Canal Circular Road, Kolkata - 700 054, West Bengal, India.*
E-mail: dr_punitsharma@yahoo.com

Received: 21-07-2020
Accepted: 31-07-2020
Published: 21-10-2020

References

1. Morigi JJ, Anderson J, de Nunzio C, Fanti S. PSMA PET/CT and staging high risk prostate cancer: A non-systematic review of high clinical impact literature. Minerva Urol Nefrol 2020;(published online ahead of print Jun 16).
2. NCCN Guidelines, Prostate cancer Version 2.2020. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx. [Last accessed on 2020 Jul 21].
3. Jilg CA, Drendel V, Rischke HC, Beck TI, Reichel K, Krönig M, *et al*. Detection rate of 18F-choline PET/CT and 68Ga-PSMA-HBED-CC PET/CT for prostate cancer lymph node metastases with direct link from PET to histopathology: Dependence on the size of tumor deposits in lymph nodes. J Nucl Med 2019;60:971-7.
4. Calais J, Ceci F, Eiber M, Hope TA, Hofman MS, Rischpler C, *et al*. 18F-fluciclovine PET-CT and 68Ga-PSMA-11 PET-CT in

patients with early biochemical recurrence after prostatectomy: A prospective, single-centre, single-arm, comparative imaging trial. Lancet Oncol 2019;20:1286-94.

5. Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, *et al*. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): A prospective, randomised, multicentre study. Lancet 2020;395:1208-16.
6. Hofman MS, Murphy DG, Williams SG, Nzenza T, Herschtal A, Lourenco RA, *et al*. A prospective randomized multicentre study of the impact of gallium-68 prostate-specific membrane antigen (PSMA) PET/CT imaging for staging high-risk prostate cancer prior to curative-intent surgery or radiotherapy (proPSMA study): Clinical trial protocol. BJU Int 2018;122:783-93.
7. Sharma P, Sharma S, Ballal S, Bal C, Malhotra A, Kumar R. SPECT-CT in routine clinical practice: Increase in patient radiation dose compared with SPECT alone. Nucl Med Commun 2012;33:926-32.

Access this article online

Quick Response Code:

Website: www.ijnm.in

DOI: 10.4103/ijnm.IJNM_162_20

How to cite this article: Sharma P. The ProPSMA randomized trial: A landmark study with many lessons. Indian J Nucl Med 2020;35:377-8.