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EDITORIAL

# $^{177}$Lu-PSMA for advanced prostate cancer: are we ready to play big?

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Prostate cancer is the second most common cancer among men [1, 2]. Although patients with localized prostate cancer receive treatment with curative intent, a significant proportion of patients will nonetheless progress to advanced metastatic disease [1, 3]. The interest in Lutetium-177 labeled, prostate specific membrane antigen ($^{177}$Lu-PSMA) targeted radioligand therapy for the treatment of advanced prostate cancer is growing: it generally appears well-tolerated and has a potential low toxicity as well as a beneficial efficacy profile [4–8]. Nevertheless, empirical evidence of clinical effectiveness is still limited to a number of retrospective studies and at best a phase II trial [7, 9]. Ongoing trials registered on ClinicalTrials.gov include three phase I and five phase II studies. In May 2018, the first phase III study, so-called VISION (ClinicalTrials.gov: NCT03511664), started, investigating $^{177}$Lu-PSMA treatment safety and effectiveness against the current standard treatments for patients with progressive PSMA-positive, castration-resistant, post-chemotherapy metastatic prostate cancer [3, 6, 10]. The primary endpoint is survival and the first data of this study are expected in 2021 [3].

When trials prove positive, the demand for $^{177}$Lu-PSMA therapy is might dramatically increase at short notice. Global supply must anticipate; however, a precise forecast of the expected therapeutic isotope production capacity for the next 10 years is not yet available. To date, most of $^{177}$Lu is produced in Europe, in six nuclear reactors, one of which is located in Petten, the Netherlands [11, 12]. Two of these facilities (aged over 45 years) require renovation or new construction investments in the coming 15 years [11]. The Dutch demand for $^{177}$Lu is expected to increase with 7% per year, which will lead to shortages within 5 years [11]. In the Netherlands alone, with an estimated number of 4500 eligible patients per year and an anticipated 4–6 $^{177}$Lu-PSMA treatment cycles per patient, this means that a number of 18,000–27,000 $^{177}$Lu-PSMA treatments need to be accommodated per year. This would be a volume increase without parallel in the history of nuclear medicine, and it is at best questionable whether existing production facilities can produce the $^{177}$Lu necessary.

However, the hitherto inconceivable patient volume is just one of a multitude of issues that need to be dealt with. Other obstacles are the lack of empirical evidence of clinical effectiveness, the limited hospital capacity (e.g., appropriate facilities, resources, and staffing), and appropriate regulations that limit the introduction of radioligand therapy in today's healthcare systems [13]. $^{177}$Lu-PSMA is a radiopharmaceutical agent with a mechanism of action that is far more a form of radiation therapy than a conventional pharmaceutical treatment. Nonetheless, it is strongly regulated like a conventional pharmaceutical, while it differs markedly from conventional oncological therapies. This in turn has a number of strong implications for its clinical introduction. Thus far, no directives have yet been developed for $^{177}$Lu-PSMA's introduction into routine care. Along the lines of implementation challenges, we here propose an agenda to promote optimal introduction and implementation of $^{177}$Lu-PSMA.

The implementation of $^{177}$Lu-PSMA into routine care, like other new treatments, typically is multifaceted [14]. It includes provider behavior and preference, care organization, and environmental, ethical, and policy considerations [15–17]. The Non-adoption, Abandonment, Scale-up, Spread and Sustainability (NASSS) framework of new medical technologies and services points to the fundamental elements/aspects

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of implementation processes of complex technologies in healthcare in seven domains: (1) the clinical condition, (2) technology, (3) value proposition, (4) the adopter system (patient, lay caregivers, technology user, and other staff), (5) the organization, (6) the wider institutional and social context, and (7) the embedding and adaptation of these domains over time [15]. Figure 1 visualizes these domains with their components. Conceptualizing and identifying potential challenges as well as requirements of $^{177}$Lu-PSMA will advance the understanding of its implementation processes [15, 16].

Current literature on $^{177}$Lu-PSMA mainly focuses on its expected clinical efficacy and safety (the first and second NASSS domains) [4, 6, 8, 18]. Based on the NASSS framework, we propose four implementation domains: (1) value proposition, (2) organizational readiness, (3) operational readiness, and (4) environmental management.

1. Value proposition

The ultimate value proposition of $^{177}$Lu-PSMA in the treatment of advanced prostate cancer has not yet been determined. Randomized controlled trials are running to generate evidence of $^{177}$Lu-PSMA's clinical effectiveness and safety compared to present-day treatments, such as chemotherapy, radiotherapy, and androgen blockade. The innovation also lacks evidence in different settings, such as different patient populations, cotreatment, dosage cycles, and dosage intensities [18]. Hence, the optimal valuing methods of $^{177}$Lu-PSMA's expected benefits still have to be determined for short- and long-term cost-effectiveness analyses. These evaluations are becoming imperative in setting reimbursement in most countries [19] and are vital to ensure quality, efficiency, and access to specific healthcare interventions. Decision analytic modelling can quantify the (clinical) benefit and costs upfront and therefore raises information to effectively guide research budget and treatment development [20–22]. This approach can also predict the potential impact of $^{177}$Lu-PSMA on the present-day treatments and the allocation of scarce resources in healthcare systems.

2. Operational readiness

The introduction of new technical developments in cancer treatment possibly disrupts standard treatment strategies and therefore calls for organizational renewal [14, 23]. The operational requirements and technical complexities of $^{177}$Lu-PSMA also have implications for the overall organization of hospital care. The true cost of implementing $^{177}$Lu-PSMA depends upon the final costs of the overall therapy (an important part of which, as with most novel oncology drugs, will be determined by the price setting by the manufacturer) as well as the location of therapy delivery. Potential users should assess the extent to which it can be successfully used or carried out within the nuclear medicine department as well as the hospital at large [16]. To illustrate, the delivery of $^{177}$Lu-PSMA is resource intensive: it requires a radiolabeled intravenous preparation and careful handling and specialist staff together with quality control and post-administration observation [4]. Although in some countries, outpatient administration of radionuclide therapy is allowed, most countries, certainly within Europe, legally prescribe hospitalization for administration [24]. Such hospitalization requires dedicated radiation protection facilities, in which patient rooms are required to have dedicated sanitary facilities and shielded walls [13].

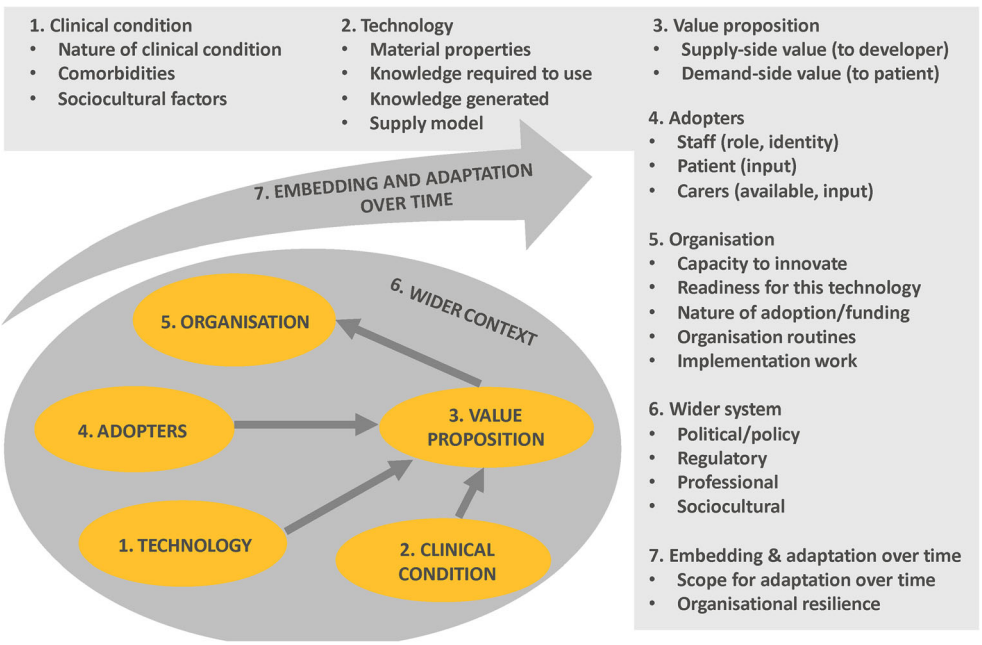


**Fig. 1** The Non-adoption, Abandonment, Scale-up, Spread and Sustainability framework of new medical technologies and services (adapted from Greenhalgh et al. [15])

Radiological drainage saturates in large storage tanks that are often located in the basement of the hospital before being discharged into the wastewater system. After treatment, each space is assessed for remaining radioactivity and decontaminated if needed. Therefore, especially new and/or expanding users will be faced with substantial investments and the adjustment of current management protocols and procedures [25].

3. Organizational readiness

Introducing $^{177}$Lu-PSMA into practice on a large scale calls for considerable expansion of teaching of radiation-related subjects in the medical curriculum and the appropriate staffing policy for providing this treatment. Users have to manage all aspects of both PET/CT and $^{177}$Lu-PSMA, including specific clinical knowledge and in- and outpatient consultation by nuclear medicine staff (e.g., nuclear medicine physicians, technologists, nurses) [2]. This also requires appropriate team interactions and professional training [2, 25]. Ultimately, the need for highly trained staff calls for a review of the current medical training for nuclear medicine physicians, as this is oftentimes embedded in the general medical training for radiologists. The clinical role of many nuclear medicine physicians will change from a purely diagnostic role to a mixed diagnostic and therapeutic role. This will likely have an effect on staff attendance at tumor board meetings and collaboration within the team of clinical specialists.

Furthermore, patient follow-up after $^{177}$Lu-PSMA treatment varies between hospitals. Some nuclear medicine physicians check on patients themselves; in other hospitals, follow-up is managed by medical oncologists or others. The number of patients for whom follow-up is needed will markedly increase, especially for nuclear medicine physicians who carry out this task.

4. Environmental management

It is critical that hospitals consciously pay attention to the ecological responsibility and safety of $^{177}$Lu-PSMA [24]. The processing of hazardous medical disposal and the emission of metabolized substance activity, including appropriate storage space, requires radiation protection regarding public and environmental exposure [26]. This responsibility demands resource and waste management guidelines both at individual and housekeeping levels for each operational phase of the hospital. At national level, each country will have to set specific radiation protection standards given that each radioactive substance requires specific management processes [13]. Compliance will be undoubtedly demanding.

Based on the four domains discussed, we propose the following research directions to facilitate $^{177}$Lu-PSMA's implementation into routine care:

1. Empirical evidence of the clinical effectiveness and safety of $^{177}$Lu-PSMA for the treatment of advanced prostate cancer and the identification of patient categories that benefit most;
2. The ideal positioning and provision method of $^{177}$Lu-PSMA in the management pathway of advanced prostate cancer to optimize clinical and patient outcomes;
3. How potential benefits and setbacks of $^{177}$Lu-PSMA implementation could differ from different medical products, in specific contexts, across indication groups and other demographic factors;
4. Optimal methods for valuing the potential benefits of $^{177}$Lu-PSMA to support its short- and long-term cost-effectiveness analyses;
5. How $^{177}$Lu-PSMA will affect the current pathways of prostate cancer care;
6. Treatment perceptions and level of acceptance by patients, nuclear medicine physicians, and referral physicians;
7. The optimal hospital operational and organizational structure and process to sustainably practice $^{177}$Lu-PSMA;
8. Policies and practices to sustainably manage $^{177}$Lu-PSMA and help to omit unintended adverse consequences that could arise from it;
9. The societal impact (e.g., academic infrastructure, economic, environmental aspects) of $^{177}$Lu-PSMA at both national and international levels.

These directions may guide and stimulate further research into the implementation of $^{177}$Lu-PSMA. The substantial investments and complexities may lead to $^{177}$Lu-PSMA being offered in a limited number of hospitals. $^{77}$Lu-PSMA therefore also reflects the general trend of specialized prostate cancer care [2, 27]. Implementation challenges are locally, nationally, and globally oriented and therefore require interactions between policymakers, healthcare providers, technology developers, and civil society organizations [14, 28]. Thus introducing $^{177}$Lu-PSMA into routine care sustainably requires multifaceted efforts from a holistic systemic perspective. Timely addressing implications in specific settings will likely avoid setbacks and may pave the way for a bright future of nuclear medicine therapy.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

**Informed consent** Not applicable.

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