The theranostic use of prostate-specific membrane antigen (PSMA) appears to be promising in patients with high-grade glioma. This study investigated $[^{177}\text{Lu}]$Lu-PSMA therapy as an individual treatment approach with a focus on intratherapeutic dosimetry.

**Methods:** Three patients were treated with a median of 6.03 GBq (interquartile range [IQR], 5.74–6.10) of $[^{177}\text{Lu}]$Lu-PSMA. Intratherapeutic dosimetry was performed using a hybrid scenario with planar whole-body scintigraphy at 2, 24, and 48 h after injection and SPECT/CT at 48 h after injection. Additive whole-body scintigraphy at 8 d after injection was performed on 1 patient. **Results:** The median doses were 0.56 Gy (IQR, 0.36–1.25 Gy) to tumor, 0.27 Gy (IQR, 0.16–0.57 Gy) to risk organs, 2.13 Gy (IQR, 1.55–2.89 Gy) to kidneys, and 0.76 Gy (IQR, 0.70–1.20 Gy) to salivary glands. Whole-body exposure was 0.11 Gy (IQR, 0.06–0.18 Gy). **Conclusion:** Because the intratherapeutic tumor dose is lower than that used in external radiation oncology, the effectiveness of treatment is questionable.

**Key Words:** $[^{68}\text{Ga}]$Ga-PSMA; $[^{177}\text{Lu}]$Lu-PSMA; glioma; PET/MRI; theranostics

**J Nucl Med 2023; 64:892–895**

DOI: 10.2967/jnumed.122.264850

The overall prognosis for high-grade glioma (HGG) patients is dismal, and treatment options are limited (1). In patients with prostate cancer, the use of prostate-specific membrane antigen (PSMA)–based isotopes has already been established as a theranostic approach (2). Although PSMA shows high expression levels in prostate cancer cells, it has also been found in other tumors, such as in HGG (3–5). Compared with low-grade gliomas, HGGs have presented generally higher PSMA uptake on PET (6,7). The expression was present in de novo HGG as well as in recurrent disease, and worsened survival has been reported for patients with high PSMA levels in recurrence and for patients with increasing vascular PSMA expression during the course of the disease (8).

To date, only a few case reports have been published analyzing the possible use of radiolabeled PSMA as a theranostic approach for HGG. Two case reports have been published presenting promising results for $[^{177}\text{Lu}]$Lu-PSMA in the treatment of HGG (9,10). On the basis of these results, we investigated $[^{177}\text{Lu}]$Lu-PSMA therapy as an individual treatment approach in 3 patients with HGG. A special focus was placed on intratherapeutic dosimetry.

**MATERIALS AND METHODS**

A detailed version of the methods can be found in the supplemental materials (available at http://jnmt.snmjournals.org).
According to the European Association of Nuclear Medicine guideline on selecting eligible patients with metastatic castration-resistant prostate cancer (11) for treatment with \[^{[177}Lu\]Lu-PSMA, only 3 of 20 patients with HGG who underwent \[^{[68}Ga\]Ga-PSMA PET/MRI at our institution were suitable for treatment. Following the recommendation of the interdisciplinary tumor board and in accordance with the European Association of Nuclear Medicine guideline (11,12), they were scheduled for 2 cycles of \[^{[177}Lu\]Lu-PSMA therapy with a median treatment activity of 6.03 GBq (interquartile range [IQR], 5.74–6.10 GBq).

Intratherapeutic imaging was performed, including planar whole-body scintigrams at 2, 24, and 48 h after injection and SPECT/low-dose CT of the head, thorax, abdomen, and pelvis at 48 h after injection. In accordance with Kunikowska et al. (9), 1 patient received a prolonged protocol for the second treatment cycle, including an additional whole-body scintigram at 8 d after injection. The dosimetry data were analyzed using a hybrid scenario applying both the whole-body scintigraphy data and the SPECT/CT data (13–15).

### RESULTS

#### Treatment with \[^{[177}Lu\]Lu-PSMA

Although all 20 patients showed increased tracer uptake in tumors on \[^{[68}Ga\]Ga-PSMA PET/MRI (supplemental results), only 3 of 20 patients were eligible for the treatment (12). No early treatment-related toxicities were detected.

Because 1 patient with underlying myelodysplastic syndrome presented chronic thrombocytopenia between the first and second treatment cycles (Common Terminology Criteria for Adverse Events, version 5.0, definition II) (12), we reduced the dose to 5 GBq for his second treatment cycle.

Because of an increasing deterioration in the health status of 2 of 3 patients, only 1 patient underwent early follow-up PET/MRI at 6 wk after the second treatment cycle; the results showed spatial tumor growth and an increasing tumor SUV\(_{\text{max}}\) (Fig. 1).

The short follow-up period, with only 1 patient undergoing follow-up PET/MRI, makes it difficult to draw conclusions about the possible risk of late-term side effects.

#### Dosimetry

The median tumor dose was 0.56 Gy (IQR, 0.36–1.25 Gy). The median doses were 0.27 Gy (IQR, 0.16–0.57 Gy) to the liver, 2.13 Gy (IQR, 1.55–2.89 Gy) to the kidneys, 0.76 Gy (IQR, 0.70–1.20 Gy) to the salivary glands, and 0.11 Gy (IQR, 0.06–0.18 Gy) to the whole body. The results are detailed in Table 1. The prolonged protocol, applied to 1 patient, resulted in an increased tumor dose (Table 2; Fig. 2). For this patient, the intratumoral dose distribution is presented in Supplemental Figure 1.

### DISCUSSION

In this study, we demonstrated that only a minority of patients with HGG were eligible for treatment with \[^{[177}Lu\]Lu-PSMA (12) and that the achieved tumor dose was lower than in a previous case report (9) and too low for a sufficient therapeutic effect. The number of patients in our study was small, but because the tumor target doses in all patients were consistently too low, an early interpretation of the study results seems necessary.

The intratherapeutic tumor dose of 0.56 Gy in our study was only 1/25th of the first encouraging results of Kunikowska et al. (9). The standard cumulative tumor dose for external-beam radiation is 60 Gy (16) and, thus, much higher than the achieved tumor doses both in our patients and in the case report by Kunikowska et al. (9). Although overall survival is significantly prolonged after radiochemotherapy, the outcome remains poor (17). The dose recommendation of the European Association of Nuclear Medicine guideline for radionuclide therapy (11) is based on observational studies. An increase in tumor dose by increasing the applied dose per cycle would be conceivable in principle but only in an experimental approach. There is no clear upper limit at which it can be ensured that the harm to the patient outweighs any possible benefit. Overall, it is debatable whether the achieved doses of internal radionuclide therapy can be sufficient for a relevant treatment effect.

---

**TABLE 1**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment cycle</th>
<th>Activity (GBq)</th>
<th>Tumor (Gy)</th>
<th>Liver (Gy)</th>
<th>Kidneys (Gy)</th>
<th>Salivary glands (Gy)</th>
<th>Whole body (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>6.023</td>
<td>1.06</td>
<td>0.33</td>
<td>2.64</td>
<td>0.83</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5.052</td>
<td>0.36*</td>
<td>0.16*</td>
<td>1.55*</td>
<td>0.62*</td>
<td>0.06*</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>6.09</td>
<td>0.35</td>
<td>0.42</td>
<td>1.91</td>
<td>0.73</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5.969</td>
<td>1.83</td>
<td>1.0</td>
<td>3.65</td>
<td>2.31</td>
<td>0.23</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>6.045</td>
<td>0.59</td>
<td>0.16</td>
<td>2.34</td>
<td>0.72</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>6.148</td>
<td>0.53</td>
<td>0.21</td>
<td>1.53</td>
<td>0.79</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Whole-body scintigraphy was usable only 24 and 48 h after injection.

MPRAGE = magnetization-prepared rapid gradient echo.

---

**TABLE 2**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Tumor (Gy)</th>
<th>Liver (Gy)</th>
<th>Kidneys (Gy)</th>
<th>Salivary glands (Gy)</th>
<th>Whole body (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>0.53</td>
<td>0.21</td>
<td>1.53</td>
<td>0.79</td>
<td>0.07</td>
</tr>
<tr>
<td>Prolonged</td>
<td>0.84</td>
<td>0.25</td>
<td>2.05</td>
<td>0.91</td>
<td>0.09</td>
</tr>
</tbody>
</table>
PSMA and [225Ac]Ac-PSMA may be advantageous. [177Lu]Lu, the higher energy levels of a-emitters in combination with PSMA-based therapy. In addition to the use of [177Lu]Lu-PSMA in HGG patients, a cocktail of [177Lu]Lu-PSMA and respectively time-activity curves for target lesion and organs at risk (E). cps = counts per second.

Because PSMA is expressed mainly in endothelial cells, it is assumed that PSMA-based tracers are bound mainly in the angiogenetic part of the tumor. This might lead to an insufficient radiation distribution within the tumor.

In principle, treatment with [177Lu]Lu-PSMA may offer radiotherapeutic treatment when the limits of external radiation are reached. Our study showed that organs of risk did not receive hazardous radiation. Temozolomide has increased the survival rate by radiosensitization to external radiation and may also improve the treatment effect in combination with PSMA-based therapy. In addition to the use of a-emitter, there have been a few studies on the use of a-emitters in HGG patients. Compared with the the higher energy levels of a-emitters may be more effective. Nevertheless, the shorter tissue penetration of a-emitters may become a limiting factor in the case of endothelial expression of PSMA in HGG. The wider range and crossfire effects of a-emitters may be an advantage over a-emitters in HGG. As already discussed for other tumor entities, a cocktail of [177Lu]Lu-PSMA and [225Ac]Ac-PSMA may be advantageous.

**REFERENCES**


**CONCLUSION**

Despite promising initial case reports, the intratherapeutic tumor dose levels in our study fell well below expectations, and the therapeutic efficiency remains questionable.

**DISCLOSURE**

No other potential conflict of interest relevant to this article was reported.

**KEY POINTS**

**QUESTION:** Does [177Lu]Lu-PSMA therapy in HGG reach a sufficient tumor dose?

**PERTINENT FINDINGS:** This was a cohort study with a limited number of patients with HGG who underwent [177Lu]Lu-PSMA therapy. The study presents an intratherapeutic reached tumor dose well short of expectations, with a median of 0.56 Gy.

**IMPLICATIONS FOR PATIENT CARE:** The treatment effect is questionable.

**REFERENCE**

FIGURE 2. Regions of interest for dosimetry of tumor, salivary glands, liver, and kidneys in anterior whole-body scintigrams (A–D) in 1 patient at 2 h (A), 24 h (B), 48 h (C), and 192 h (D) after injection of 6.148 GBq of [177Lu]Lu-PSMA and respective time–activity curves for target lesion and organs at risk (E). cps = counts per second.


