

DRAFT**Patient-Centered Pathways of Care for Molecular-Targeted Radiopharmaceutical Therapies (MTRTs)**

Introduction

Cancer treatment is ever-changing with more options and combinations of therapy each year. Molecular-Targeted Radiopharmaceutical Therapies (MTRT) are an area of ongoing and anticipated exciting growth and importance with several agents in clinical use, new agents in clinical trials, as well as many others under testing and development.

Theranostics is an innovative and rapidly evolving novel type of MTRT which merges molecular-targeted diagnostic imaging agents with molecular-targeted radiopharmaceutical therapy. The term “theranostics” is a somewhat broader term linking a diagnostic and therapeutic process, including diagnostic laboratory tests and a therapeutic agent, neither necessarily radioactive. The term “radiotheranostics” can be applied for greater specificity. The molecular imaging scan, which may be performed with the same radiopharmaceutical as used in the therapy or with a diagnostic radiopharmaceutical with similar biodistribution characteristics as the targeted radiopharmaceutical therapeutic agent is used, to detect, locate, and characterize tumors, as well as to quantify tumor tracer uptake and the uptake into normal tissues. Thus, the diagnostic portion of the MTRT pair is used to qualify the patient for radiopharmaceutical therapy, typically by establishing selective diagnostic radiopharmaceutical uptake in tumors and lower, acceptable, tracer uptake into normal tissues.

The approach of MTRT can also be more rigorously applied using image quantitation to predict energy deposition of the therapeutic radiopharmaceutical to tumors and normal structures. The image quantitation of the diagnostic image predicts the therapeutic delivery (radiation dose) of internally targeted radiation energy to tumors and normal tissues through scaling of the quantitated image. In this context, the “diagnostic dose” of the MTRT pair may be used to calculate a “therapeutic dose” to adjust the administered activity, and thus predict radiation absorbed dose, of the therapeutic agent. With this detailed quantitation approach including dosimetry, MTRT offers true personalized, precision medicine, tailoring the treatment to the individual characteristics of each tumor and the normal tissues within each patient.

Selecting the best-suited patients for MTRT and the optimal administered activity and targeted radiation dose for each patient through the quantitation of the diagnostic portion of the MTRT enables the possibility of an improved and most efficacious radiopharmaceutical treatment compared to more conventional approaches of “one dose fits all” targeted radiopharmaceutical therapies. In reality, MTRT is not a new concept. Radioiodine as I-131 has been used for the diagnosis and treatment of thyroid cancer since the 1940’s. In addition, FDA-approved radioimmunotherapies like I-131 Tositumomab and combined In-111/Y-90 ibritumomab have been used as theranostic agents for lymphoma where the

37 biodistribution and the dosimetric information from the In-111 tracer images have been used in some
38 approaches to more precisely guide MTRT.

39 Examples of established, new, and emerging MTRT have or are about to dramatically amplify the
40 importance and use of this treatment technique in the coming years. Examples include:

41

- 42 ● FDA-approved Samarium (Sm-153) Lexidronam for bone pain of metastatic cancer, informed by
43 a Tc99m or NaF bone scan
- 44 ● FDA approved Lutetium labeled somatostatin analog (Lu-177 DOTATATE) therapy for
45 neuroendocrine tumors and other tumors expressing somatostatin receptors—informed by
46 somatostatin imaging (i.e., Ga-68 DOTATATE)
- 47 ● FDA-approved Ra-223 therapy for metastatic prostate cancer, and other cancers, in bones,
48 informed by a Tc99m MDP SPECT or NaF PET bone scan
- 49 ● FDA approved iobenguane I-131 (I-131 MIBG) for adult and pediatric patients (12 years and
50 older) with iobenguane scan-positive, unresectable, locally advanced or metastatic
51 pheochromocytoma or paraganglioma who require systemic anticancer therapy, with the
52 administered activity informed by a dosimetry scan with the same agent.
- 53 ● Lutetium labeled prostate specific membrane antigen targeting peptide (Lu-177- PSMA)
54 therapies for metastatic or treatment-resistant prostate cancer, informed by Ga-68 or F-18
55 PSMA targeting imaging agents
- 56 ● Investigational I-131 labeled antibodies to leukemia targets such as CD-45, informed by
57 dosimetry using a diagnostic dose of I-131 labeled antibodies Investigational Alpha emitting
58 therapeutics targeting a variety of targets including PSMA, informed by a PSMA targeted
59 imaging study.

60

61

62 **Treatment Pathways:**

63 This path of care guidance seeks to identify an early consensus on the steps in the emerging process of
64 care for cancer patients receiving MTRT and to identify optimal workflows to support safe, high-quality
65 care by qualified professionals. These recommendations are based on the consensus of the Theranostics
66 Work Group comprised of members from the Society of Nuclear Medicine and Molecular Imaging
67 (SNMMI) and the American Society for Radiation Oncology (ASTRO). Additionally, this guidance and the
68 format of this document draws from aspects of the Patient-Centered Oncology Practice Standards of the
69 National Committee of Quality Assurance¹(NCQA) and the National Academy of Medicine, formerly
70 known as the Institute of Medicine, workshop on patient-centered cancer treatment planning². It should
71 be noted that this field is rapidly evolving, and pathways of care will vary by disease, by risks/benefits of
72 MTRT, and by local technical capabilities, many of which will certainly change with time.

¹ Patient-centered oncology practice. National Committee for Quality Assurance. 2015.

<http://store.ncqa.org/index.php/catalog/product/view/id/2329/s/patient-centered-oncology-practice-standard>

² Balogh EP, Ganz PA, Murphy SB, Nass SJ, Ferrell BR, Stovall E. Patient-centered cancer treatment planning: improving the quality of oncology care. Summary of an institute of medicine workshop. *Oncologist*, 2011. 16(12):1800–1805

73 Care Teams:

74 Selection of patients for MTRT begins with a clear understanding of the patient’s cancer and the range
75 of therapeutic options (both non-radiopharmaceutical and MTRT), generally by an oncologist (radiation
76 or medical). Furthermore, understanding both the diagnostic and therapeutic use of
77 radiopharmaceuticals is essential. Appropriate oncologic follow-up and imaging are also critical parts of
78 therapeutic assessment of patients with cancer. This is most often, best achieved with a multi-
79 disciplinary approach, similar to other models for cancer care. There are several unique aspects of an
80 MTRT care team because MTRT involves qualitative and quantitative nuclear imaging and administration
81 of therapeutic amounts of radioactivity.

82 First, the care team must include physicians designated as authorized users of radioactivity. In the
83 United States, the Nuclear Regulatory Commission (NRC) or certain individual states (“Agreement
84 States” <https://www.nrc.gov/about-nrc/state-tribal/agreement-states.html>[https://www.nrc.gov/about-](https://www.nrc.gov/about-nrc/state-tribal/agreement-states.html)
85 [nrc/state-tribal/agreement-states.html](https://www.nrc.gov/about-nrc/state-tribal/agreement-states.html))³ in conjunction with the NRC regulates granting of authorized
86 user status to individuals with board certification in certain specialties or through a current alternative
87 pathway. Authorized users have authority to administer radioactivity and are responsible for ensuring
88 that radioactive materials are handled and used safely and in accordance with NRC regulations.
89 Regulations may differ in other countries. The Theranostics Work Group supports these NRC regulations
90 as important for the safety of patients and staff as well as for the optimal care of patients, especially as
91 the field evolves to more precision, patient-specific, therapeutic dosing.

92 Second, molecular imaging plays an important role in determining if a suitable therapeutic target is
93 present and the extent of radiotracer uptake in tumor and normal tissues. Quantitative imaging, with or
94 without patient specific dosimetry, may be required to determine if there is sufficient diagnostic
95 radiopharmaceutical tumor targeting compared to normal tissues to consider a patient a suitable
96 candidate for therapy.

97 Finally, members of the care team must have expertise in the care and follow-up of cancer patients
98 treated with radiation and its side effects. This unique constellation of expertise described will most
99 often involve a team of physicians with relevant training to deliver the best care to cancer patients,
100 though in some settings, a single physician may have the requisite training and experience. The NRC
101 requirements for administering therapeutic radiopharmaceuticals are noted in an appendix to this
102 document, but do not address the diagnostic portion of requisite training nor the important clinical care
103 aspects of patients receiving radiotherapeutic agents.

104 Patient Selection

105 Patients who are possible candidates for MTRT can be identified in several ways. Typically, patients will
106 be referred by an oncologist (surgical, medical or radiation) or subspecialty surgeon (urologist,
107 otolaryngologists etc.), interventionalist or nuclear medicine physician to centers that have expertise in
108 MTRT. In the era of freely available information regarding patient care programs, individual physicians in
109 a range of specialties may be quite knowledgeable regarding use of MTRT and some patients may
110 choose to be directly evaluated by such physicians in their practice.

111 For newly-approved radiopharmaceutical agents, it is essential for the qualified treating physician, most
112 commonly a nuclear medicine physician or radiation oncologist, hereafter referred to as the radiation
113 medicine physicians (RMPs), to reach out to the medical and patient communities to educate them
114 about the patient selection criteria for each new agent and its indications and contraindications. This
115 may be best accomplished through participation of RMPs in educational symposia, tumor boards,
116 didactic sessions and grand rounds of referring physicians. Similarly, outreach to patient support groups
117 to inform them about the availability of relevant new agents and their role in the disease management
118 is critical.

119 It is important for RMPs to discuss the methods to identify patients, selection criteria, and indications
120 for MTRT. In addition, education on the results of clinical studies demonstrating efficacy of the therapy
121 and potential side effects should be discussed. Management of side effects as well as contraindications
122 to the agents should be highlighted with referring physicians. Additional considerations should include a
123 brief review of practical aspects of treatment including radiation safety precautions, administration in
124 inpatient versus outpatient settings, duration of therapy, and post therapy radiation protection
125 guidelines to help both referring physicians and their patients in the initial discussions prior to the
126 referral.

127 **Track and coordinate referrals**

128 Appropriate referral is crucial for optimal utilization of the MTRT. Referrals for patients will often come
129 from a variety of sources. Qualified RMPs may see patients primarily, to direct their diagnostic and
130 potential cancer therapy pathways. However, very commonly, endocrinologists, medical oncologists,
131 surgeons (including urologists), and primary care physicians may refer patients to the RMP. Additionally,
132 referral from one RMP to another who has particular expertise or interest in MTRT, or a specific disease
133 site, is not uncommon. Patient work-up by the RMP for staging and appropriateness of MTRT or
134 alternatively collaborating with medical and surgical colleagues is essential because decision making in
135 oncology requires detailed knowledge of the specific pathology, molecular features, prognosis and
136 extent of disease. Confirmation of these clinical and pathologic features for integration into oncologic
137 and therapeutic care decisions is critical in the pathway of care. As an example, in neuroendocrine
138 tumors (NET), patient symptoms often antedate the diagnosis of the functioning NET by years. After a
139 diagnosis is established, the RMP physician must determine that the patient meets the required criteria
140 for treatment with MTRT versus other therapeutic options.

141 Proper referral should begin with a clinic visit for consultation followed by evaluation (including
142 recommended diagnostic tests) and finally oncologic decision making for therapy. In the case where a
143 single RMP is the sole provider of MTRT, referring physicians may communicate directly with the RMP
144 for a consult which can be scheduled by appropriate office staff. If a group of RMPs are providers,
145 referral may be directed to the RMP based on an assigned clinic day or specific subspecialty treatment
146 expertise (i.e., prostate cancer versus liver vs. neuroendocrine). A central staff coordinator to coordinate
147 MTRT consultations may be helpful. The referring physician and central staff coordination should triage
148 and coordinate visits considering the clinical status of the patient, so that the consult appointment
149 timing can be appropriately assigned and expedited in urgent cases where a patient may be
150 symptomatic and/or have rapidly progressing disease. Telemedicine may play a growing role in this
151 evaluative process. Very commonly, detailed data (often from outside sources) are necessary for a clinic
152 visit to fulfill goals of a meaningful evaluation. For institutions with a centralized electronic medical

153 record, internally referred patients' records are readily available. For external referrals, a full summary
154 of clinical history, imaging, laboratory and pathology reports should ideally be available at the time of
155 consult. Direct review of the pathology and imaging data by the RMP and his/her team are strongly
156 encouraged, in addition to the reports. Consults may be scheduled based on the timeline to obtain the
157 necessary records if needed.

158 **Initial consultation with qualified treating physician**

159 The clinical consultation is a crucial step in proper evaluation of a patient for MTRT. As with any other
160 medical condition and decision making for therapy, a full evaluation of the patient is necessary. Given
161 the molecular targeting required for most radiopharmaceuticals, an imaging study demonstrating that
162 there is tumor target present and that there is not excessive targeting to normal tissues will generally be
163 a pre-requisite for a decision toward MTRT. This will often occur prior to the consultation but may be
164 ordered as part of the oncologic work-up and decision-making process as well. Repeat studies may be
165 needed to confirm and assess the current status of disease for ultimate decision-making. This review
166 would be performed by a physician well-qualified and credentialed in interpreting theranostic imaging
167 studies. Targeting to all tumors in an individual must be assessed in case tumor biology is heterogeneous
168 as well as uptake in normal tissues. Additionally, it will be important to consider other treatments
169 previously given for the disease, if any, with particular attention toward those that could potentially
170 impact the radiopharmaceutical therapy such as prior external beam radiotherapy, brachytherapy, prior
171 chemotherapy, prior radiopharmaceutical treatments, or prior surgeries. Additionally, prior, and current
172 drugs need to be noted and considered for therapy impact.

173 A full review of the medical and surgical history with attention to tolerance and response to previous
174 therapy, allergies and medications is similarly necessary in this regard. A focused physical exam is
175 essential to assess appropriateness of the radiopharmaceutical for this patient as well as their
176 performance status and comorbidities. The RMP will review all relevant medical documentation and
177 imaging related to the patient's disease and current state. A detailed evaluation of all imaging studies,
178 not just of the theranostic imaging study, is paramount to determine eligibility for MTRT. The imaging
179 review should include, for theranostic agents, substantial targeting of all visible/viable lesions on cross
180 sectional imaging with the imaging radiopharmaceutical and also evaluation of any unexpected
181 distribution of the radiopharmaceutical in normal organs and tumors that could increase the risk of
182 adverse effects of MTRT. A direct review of the pathology, the relevant imaging studies, and a discussion
183 in a multidisciplinary clinic/tumor board setting is commonly advised, especially for more complex
184 patients, to discuss and prioritize the different therapy options and potentially to review these options
185 with the referring physician and other oncology specialists including interventional oncologists and
186 surgeons.

187 After completing this evaluation, the treating physician or team will decide whether to recommend the
188 MTRT for the patient. The RMP will explain to the patient (and family as appropriate) her/his
189 recommendation and rationale for MTRT. The advantages and disadvantages of proceeding as advised,
190 will be reviewed. If treatment is recommended, the potential side effects and complications, the
191 management of the side effects and complications should they occur, the practical aspects and logistics
192 of the radiopharmaceutical treatment and the radiation protection issues for the patient and those with
193 whom the patient lives, as well as radiation safety processes during transport, will be reviewed. After
194 full consideration of these issues, the patient will decide if he/she wishes to proceed with treatment. If

195 proceeding with treatment, an informed consent document is obtained and entered into the medical
196 record.

197 **MTRT Planning**

198 After a decision to proceed with treatment, specific imaging (currently termed companion diagnostic
199 imaging in nuclear medicine and simulation in radiation oncology) for a more comprehensive
200 assessment in close proximity before the time of treatment of disease is desirable. This molecular
201 imaging procedure can serve two purposes. The first is to verify targetable disease. The second purpose
202 of molecular imaging may be to perform more complex and often multi time point imaging to predict
203 radiation dosimetry from the MTRT. This series of scans, is in effect a “simulation” or dosimetric series
204 of quantitative images. The RMP will decide if imaging procedures adequately define the location and
205 extent of the target tissue, and ideally quantify potential uptake and distribution patterns (normal and
206 tumor) and provide input data for calculation of absorbed dose in the internal dosimetry process.
207 Quantitative assessment of tumor targeting as well as normal tissue uptake and predicted exposure is
208 preferred. While an earlier study may be used to determine patient eligibility and hence suffice in some
209 circumstances, it is more ideal to have pre-treatment scans for dosimetry calculation and potential
210 optimization. At a minimum, a qualitative assessment of target uptake and normal tissue has been
211 historically used, although the benefits of more complete quantitative dosimetry are increasingly well-
212 supported.

213

214 Ideally imaging should be performed as a baseline for treatment planning with the specific tracer
215 /theranostic that establishes targetable disease as close as possible to the treatment date. In addition,
216 conventional cross-sectional imaging may be useful at baseline for future response assessment and
217 assessment of currently targetable lesions. For example, in patients with neuroendocrine tumors, a
218 positive Ga-68 DOTATATE/DOTATOC scan prior to Lu-177 DOTATATE is a requisite although a CT scan or
219 MR of the liver may also be obtained prior to the MTRT. This baseline imaging will be important to both
220 compare post-treatment imaging for disease status and response to therapy as well as to assess the
221 concordance of lesion activity on the DOTATATE scans with tumors identified on the CT or MR. In certain
222 therapies, serial scanning after MTRT delivery may be performed to establish a basis for dosimetry, such
223 as radioiodine (RAI), I-131 MIBG, and I-131 anti-CD-20 antibody therapy (as applied in Australia and New
224 Zealand). However, some of the approved therapies do not currently “require” dosimetry-based dosing
225 and are given as fixed doses. For example, ²²³Ra Dichloride dosing is currently based on body weight, and
226 Lu-177 DOTATATE is administered as a fixed dose of radiopharmaceutical under the current FDA
227 approved label, though dosimetry can be used in some settings to more precisely adjust the radiation
228 absorbed dose. The opportunity to improve and optimize MTRT using more rigorous dosimetry is
229 promising.

230

231 If dosimetry is performed, it should be done by qualified personnel (generally a medical physicist). In
232 some instances, physicians with suitable training in delivering therapeutic radiopharmaceuticals using
233 FDA cleared software may perform some dosimetric calculations.

234

235 The skills of someone performing dosimetry calculations, or the team involved, should include: camera
236 QC/QA, calibration, proper image reconstruction with data correction, as well as specific training in the
237 specific methods of dosimetry for each MTRT agent. Some software may be FDA approved, but software

238 use typically requires certain assumptions and quality assurance would be important to ensure
239 consistency with the software use. Quality assurance throughout this process is important, and
240 collaboration of the radiopharmacy and physics is needed. One possible demonstration of qualification
241 of a medical physicist includes certification or being named on an NRC or Agreement State license or
242 permit as an authorized medical physicist (AMP). The AMP must have specialty board certification
243 recognized by the NRC or an Agreement State and meet the additional requirements in paragraph (c) of
244 section §35.51 or equivalent Agreement State regulations. (see appendix)

245
246 Dosimetry calculations can include estimates of radiation absorbed dose to blood and lungs for thyroid
247 cancer or to the whole body or major organs for radioimmunotherapy or peptide therapy, for example.
248 However, engagement of a physicist is likely needed for dosimetry calculations and estimations. A
249 detailed technical worksheet for imaging should be used so that all serial imaging can be performed
250 similarly. If regions of interest (ROI) or Volumes of Interest (VOI) are used for dosimetric calculation, the
251 ROI/VOI's should be delineated by the RMP in conjunction with the medical physicist and potentially
252 with collaboration of other technical staff. The medical physicist will calculate the target dose and a
253 therapeutic limit for dose may be calculated based on critical organ dosimetry, commonly termed an
254 organ at risk (OAR) or "Maximum Tolerated Dose" (MTD) for that organ. It should be noted that the
255 dose deposition from a therapy may in some instances be established from imaging of the patient after
256 therapy. For example, SPECT imaging post Lu-177 DOTATATE imaging may be used to verify absorbed
257 dose to organs and tumors. Such analyses, though not yet standard, will require qualified personnel to
258 make the dosimetric determinations and may be particularly important for future dosing considerations
259 and optimization.

260
261 The RMP will select the appropriate therapeutic dose using the best evidence to support the treatment
262 decision. Ideally, this will increasingly be based on predicted absorbed doses (rather than administered
263 activity) to optimize therapeutic index and provide personalized precision medicine as well as
264 assessments of predicted radiosensitivity of a specific patient. It is recognized, however, that if the
265 therapeutic index of a MTRT is high, that dosimetry may not be as necessary for safe deployment of that
266 therapy.

267 Once imaging has established tumor targeting and dosimetry-based dose estimates are known, the
268 physician should decide the final radiopharmaceutical administered activity to be administered. Based
269 on the patient history, patient biological status (such as platelet count, marrow involvement with tumor,
270 extent of prior radiation and prior chemotherapy, prior stem cell transplant), physical exam, lab values,
271 imaging, and preliminary dosimetry (if available or required), as well as information from the initial
272 consultation (referenced above in section 3), the RMP will determine the individualized
273 radiopharmaceutical prescription for the administered activity. Ideally, the prescription may specify the
274 intended absorbed dose to a volume of interest and must specify the activity to be administered. Route
275 of administration, chemical form, and other relevant characteristics of the intended therapy should also
276 be contained in the written and signed prescription. The prescription should comply with relevant
277 regulatory requirements of a Written Directive as required by the NRC (10 CFR 35.40) or equivalent
278 Agreement State regulation in the US. For treatments that are fixed activities or based on weight, the
279 administered activity should be calculated accordingly. The patient weight used for dosing should be
280 determined as closely as possible to the date of administration of therapy and preferably within at least
281 one week of treatment by direct measurement of the patient's weight, as opposed to the patient's

282 statement of their weight. To assure radiation safety for the patient’s family and the public, a clear
283 understanding of the patient’s living arrangements and transportation methods are required as a part of
284 an informed therapeutic decision, with written radiation safety instructions.

285 Coordination of MTRT with multidisciplinary physicians involved in the patient’s care, with special
286 attention to previous or planned systemic, radiation, chemo, biological, or surgical therapies is also
287 important. It will be necessary to consider both additive and synergistic interactions of the therapies
288 both pre-administration and potentially post-administration in any plan of care. These may impact both
289 anti-tumor effect and toxicity. Ideally, the RMP will communicate with the multidisciplinary team prior
290 to each planned dose/cycle of MTRT, especially if the patient’s clinical status changes and/or a dose
291 reduction or delay in treatment is being considered.

292 Further, the RMP will, typically in consultation with the appropriately qualified medical physicist and/or
293 radiation safety officer, carefully consider the radiation safety issues that may be associated with
294 circulating or deposited radionuclides with respect to other medical procedures such as blood tests,
295 dialysis, surgical interventions, etc. Some theranostic procedures may require special consideration in
296 the event of patient death and residual radioactivity. For MTRTs with a longer half-life, premature death
297 has potential to cause radiation contamination from the patient’s remains, and the multidisciplinary
298 team must be cautious to avoid potential subsequent health effects caused by repeated or long-term
299 exposure of employees in crematoriums in the United States.³

300 Caution is in order when MTRT is staged/integrated with other therapies. Generally, localized radiation
301 therapy given concurrently or recently prior to the MTRT is not limiting if it did not include substantial
302 portions of active bone marrow, the lungs or the target organ(s) for the MTRT. However, concurrent
303 chemotherapy or recent prior chemotherapy within 6 weeks is likely to lead to overlapping side effects
304 and therefore must be assessed individually for timing of the therapeutic radionuclides, particularly with
305 respect to overlapping bone marrow toxicity. There may also be unique interactions between certain
306 non-chemotherapy systemic drugs and MTRT agents. For example, a recent phase II randomized trial
307 showed increased fracture risk with the combination of Ra-223 and abiraterone for asymptomatic or
308 mildly symptomatic castration resistant prostate cancer (Lancet Oncol 20: 408-419; 2019). Lu-177
309 DOTATATE is not currently recommended to be co-administered with chemotherapies. Co-
310 administration of MTRT with ongoing immune oncologic agents is also being evaluated in trials for
311 specific indications and is not yet standardized for any radiopharmaceutical. In such cases, MTRT may
312 be given only after discontinuing the systemic therapy, and there may be a recommended ‘washout
313 period’ before and after MTRT therapy. For example, Lu-177 DOTATATE patients should be scheduled so
314 that their treatment with long acting somatostatin analogs is at least 4 weeks prior to the MTRT based
315 on current recommendations.

316

317 Once the optimal patient-specific schedule is determined and the dose to be administered is calculated,
318 the MTRT dose order may then be placed. Generally, orders require about 1-3 weeks advance notice to
319 vendors for obtaining the dose for a desired date. This should be taken into consideration while
320 planning the date of treatment. The day and time of treatment will need to be coordinated based on the
321 institution’s treatment schedule for other MTRT, availability of staff and the RMP authorized user, as

³ Yu, N. [Radiation Contamination Following Cremation of a Deceased Patient Treated With a Radiopharmaceutical](#) *JAMA*. 2019;321(8):803-804. doi:10.1001/jama.2018.21673

322 well as the patient's convenience. Coordination of imaging for treatment planning processes is also
323 important.

324 **MTRT Delivery**

325 The radiopharmaceuticals to be administered may be prepared within an institution or, more
326 commonly, are ordered from an external licensed radiopharmacy. In either case, the authorized treating
327 physician (RMP) will provide a written order (prescription and written directive) to initiate the therapy
328 administration process. In addition to providing clarity as to the clinical aspects of the intended MTRT
329 delivery, the written directive must adhere to institutional and national and/or state regulatory
330 requirements. Furthermore, the RMP, in cooperation with the radiation safety officer, qualified medical
331 physicist, and MTRT team, will assure that the physical location of the administration provides an
332 acceptable and safe clinical environment and is consistent with appropriate radiation safety practice.
333 These details of radiation safety are MTRT specific and may require substantial preparation and
334 coordination for waste disposal following administration. The attention to the specifics required for safe
335 delivery and after care for each radiopharmaceutical is paramount.

336 Following treatment, the RMP, in conjunction with the medical physicist or radiation safety officer, will
337 review post-administration radiation safety procedures with the patient.

338 In most circumstances, the planned administered activity of the radiopharmaceutical will be verified by
339 measurement at the time and place of administration. A licensed radiopharmacist at the administering
340 facility or the RMP will personally supervise the confirmatory measurement and verify that the activity
341 to be administered is consistent with the prescription/written directive and that the stated activity,
342 isotope and chemical form as provided by the radiopharmacy is as prescribed. A nuclear medicine
343 technologist or medical physicist can verify activity in addition to the verification of the RMP or
344 radiopharmacist.

345 The RPT will be administered by the RMP or a certified nuclear medicine technologist designee under
346 the personal supervision of the RMP with careful attention to the integrity of the infusion catheters so
347 as to eliminate the risk of extravasation of a MTRT dose. The RMP may be assisted by appropriately
348 trained staff, e.g., nursing, nuclear medicine technologist and/or medical physics staff. Syringes, vials
349 and other delivery equipment will be assayed for residual radioactivity to assess the extent of
350 radiopharmaceutical retained and thus delivered to the patient. Institutional and/or regulatory
351 requirements may also specify post-administration patient, staff and/or environmental surveys. The
352 RMP with the MTRT team, will assure the appropriate administration of any adjunctive medications
353 used with the radiopharmaceutical therapy. The RMP must be immediately available to treat adverse
354 reactions.

355 The patient will be given written post-treatment instructions, including a description of the
356 radiopharmaceutical, relevant safety precautions (which may also require physics calculations), advice
357 as to side effects, emergency contacts, and plan of follow-up care.

358 In some cases, additional post-administration dosimetry imaging will be indicated. The dosimetry
359 procedures will be planned by the relevant expert in dosimetry, which often will be a medical physicist
360 in collaboration with the RMP. The RMP will instruct the patient in this regard and facilitate scheduling

361 of these potential imaging procedures. The dosimetry calculations will be performed by the qualified
362 professional, sometimes the RMP but often a medical physicist and reviewed by the RMP.

363 The RMP will complete a treatment summary and other appropriate regulatory documentation
364 requirements and enter them into the medical record. Additionally, the RMP and team will coordinate
365 follow-up care for assessment of response and to assess side effects and potential need for any
366 supportive therapies such as colony stimulating factors or transfusions. Appointments for follow-up
367 imaging and laboratory tests as well as potential follow-up with other health care providers (PCP,
368 medical oncologist, etc.) as appropriate will also be coordinated. It is likely that telemedicine will play an
369 increasing role in follow up care, complementing lab studies.

370 Typically, the RMP will review all (or at least selected) cases in a systematic quality control program
371 which can include chart rounds, tumor board or quality assurance meetings as well as M&M conference
372 if indicated.

373 **Routine follow-ups with treating radiation medicine physician**

374 Consideration of the timing and future need to assess response and potential sequelae following
375 therapy are the next steps in the pathway of care. This will most commonly involve follow-up clinic visits
376 with the treating RMP as well as additional imaging assessment. It is noted that some approved
377 therapies such as Ra-223 and Lu-177 DOTATATE include a planned number of cycles as a course of
378 therapy. In some instances, dosing may have to be reduced, delayed or cancelled based on toxicities,
379 disease progression, comorbidities or overall performance status. In some cases, consideration of other
380 radiation therapies or systemic therapies will be discussed. Additional clinical assessments are needed
381 for these follow up therapies, to assure the patient remains suitably eligible for MTRT, when the patient
382 will be eligible, and if any dose modifications are required. Possible multidisciplinary coordination for
383 consideration of other therapies may be planned.

384 Tumor response assessment should be performed using appropriate and validated methods. Treatment
385 response may be evaluated with conventional imaging including CT, MRI, bone scan and FDG PET/CT
386 scans. Receptor based imaging such as Ga-68-DOTATATE/DOTATOC PET/CT is not well established for
387 assessing treatment response but may be better suited to identifying tumor progression. In addition,
388 biomarkers such as PSA or LDH may be appropriate for response assessment for some types of cancer.
389 The response assessment and strategies for further disease management should be discussed within the
390 MTRT team as well as with the multidisciplinary oncology care team. The RMP should remain active in
391 the multidisciplinary care coordination of the treated patient.

392
393 MTRT toxicity assessment and management will be performed by the treating RMP and members of the
394 team. In some instances, where patients live far from the site of MTRT, a close working relationship
395 with a local RMP if possible as well as the local referring physician, may allow for review of toxicity data
396 such as blood counts, from a satellite facility. More modern approaches such as telemedicine can also
397 be considered if patients are very remote from the treatment site with little local expertise in radiation
398 toxicity assessment, coupled with local lab testing near the patient. Toxicity assessments include
399 potential acute and late toxicities; hence long-term follow-up is recommended to recognize and manage
400 late radiation toxicities. The assessment will be tailored to the particular radiotherapeutic agent and the
401 individual patient. Toxicity management may involve further diagnostic testing, medical management,
402 and/or referral to other medical specialists as indicated.

403

404 Consideration of re-treatment (i.e. after completion of the initial course of MTRT) may be an area of
405 ongoing research for many agents and is likely to become a common consideration in the future. The
406 decision regarding re-treatment should involve assessment of previous absorbed dose by normal tissues
407 from prior treatments and any toxicities from prior treatments. It should also involve prediction of
408 potential absorbed dose from the planned treatment and prediction of associated cumulative risks of re-
409 treatment. The prior tumor response assessment will also be important for consideration of re-
410 treatment (i.e., a previously poorly responsive tumor will be less likely to gain benefit) as well as the
411 possible evolution of tumor lesions which do not accumulate the MTRT agent. The use of individual
412 dosimetry is expected to be highly valuable in this setting as it may allow for dose escalations.

413

414 Multidisciplinary care coordination is a key component of the patient-centered path of care for all
415 cancer treatments. This is particularly important for patients receiving newly approved MTRTs. The RMP
416 should establish clear lines of communication among team members and provide clinical follow-up for
417 response assessment, toxicity assessment and management. Coordination within a multidisciplinary
418 care environment and coordination of longitudinal management with other oncology providers is an
419 essential part of an optimal path of care.

420

421 **Conclusions**

422

423 A patient-centered path of care is a critical step in establishing MTRT as a standard therapy for our
424 cancer patients. While I-131 therapy has been reliably delivered for the past 70 years, there is
425 unquestionably an exponential increase in the numbers of relevant radiotherapeutic compounds that
426 are, and could be, important treatment options for many patients with both solid and hematologic
427 malignancies. This expected increase in therapy options will require enhanced coordination by radiation
428 medicine physicians with diverse expertise in quantitative imaging, dosimetric calculation, radiation
429 quality assurance and safety as well as oncology care and radiation induced sequelae and response
430 assessment. Teams of qualified professionals including nuclear medicine physicians, radiation
431 oncologists, medical physicists, radiopharmacists, nuclear medicine technologists, nurse practitioners,
432 physician's assistants, and nurses are needed to provide the highest quality care possible. The essential
433 role of this evolving MTRT Team within the framework of multidisciplinary oncology care with other
434 oncology specialists is a cornerstone of this recommended path of care. This consensus guidance
435 provides emerging pathways to optimally deliver this therapy within the complex milieu of cancer
436 therapy and recognizes that while the expertise required is clear, the precise makeup of the teams may
437 vary based on individual institutional capabilities. Given the heterogeneity of how radiopharmaceuticals
438 are delivered by various radiation medicine physicians in medical centers across the country, we believe
439 this path of care guidance is timely and needed to help shape clinical practice for a rapidly evolving
440 treatment.

441

442 Appendix

443 The training and experience requirements for a physician to become an Authorized User (AU) for
444 radionuclides are delineated in Title 10 of the *Code of Federal Regulations* (CFR), Part 35.390. In general,
445 radiation medicine physicians who are Board certified by their respective Boards (with an AU pathway or
446 “grandfather” status) as well as other physicians who pursue an available “alternative pathway” can
447 become AUs.

448 In addition, the physician AU must be identified as an AU on:

- 449 (i) A Commission or Agreement State license that authorizes the medical use of byproduct
450 material;
- 451 (ii) A permit issued by a Commission master material licensee that is authorized to permit the
452 medical use of byproduct material;
- 453 (iii) A permit issued by a Commission or Agreement State specific licensee of broad scope that
454 is authorized to permit the medical use of byproduct material; or
- 455 (iv) A permit issued by a Commission master material license broad scope permittee that is
456 authorized to permit the medical use of byproduct material.

457
458 The NRC defines Radiation Safety Officer as an individual who:

459

460 (1) Meets the requirements in §§ 35.50(a) or (c)(1) and 35.59; or

461 (2) Is identified as a Radiation Safety Officer on—

462 (i) A specific medical use license issued by the Commission or Agreement State; or

463 (ii) A medical use permit issued by a Commission master material licensee.⁴

464

465 The NRC or an Agreement State define the authorized medical physicist in paragraph (c) of section
466 §35.51 or equivalent Agreement State regulations

467

468 *A Qualified Medical Physicist is an individual who is competent to practice independently in one or more*
469 *of the subfields in medical physics. The American College of Radiology (ACR) considers certification,*
470 *continuing education, and experience in the appropriate subfield(s) to demonstrate that an individual is*
471 *competent to practice one or more of the subfields in medical physics and to be a Qualified Medical*
472 *Physicist. The ACR strongly recommends that the individual be certified in the appropriate subfield(s) by*
473 *the American Board of Radiology (ABR), the Canadian College of Physics in Medicine, or by the American*
474 *Board of Medical Physics (ABMP). In addition, the Qualified Medical Physicist must meet any*
475 *qualifications imposed by the state and/or local radiation control agency. The qualifications and training*
476 *for individual performing dosimetry are evolving and the SNMMI, ASTRO and other organizations will*
477 *continue to work to assure adequate training, experience and demonstration of quality are assured as*
478 *the sophistication of dosimetry increases.*

479

⁴ NRC Regulations (10 CFR) > Part Index > § 35.2 Definitions. <https://www.nrc.gov/reading-rm/doc-collections/cfr/part035/part035-0002.html>
Ref 10/1/19