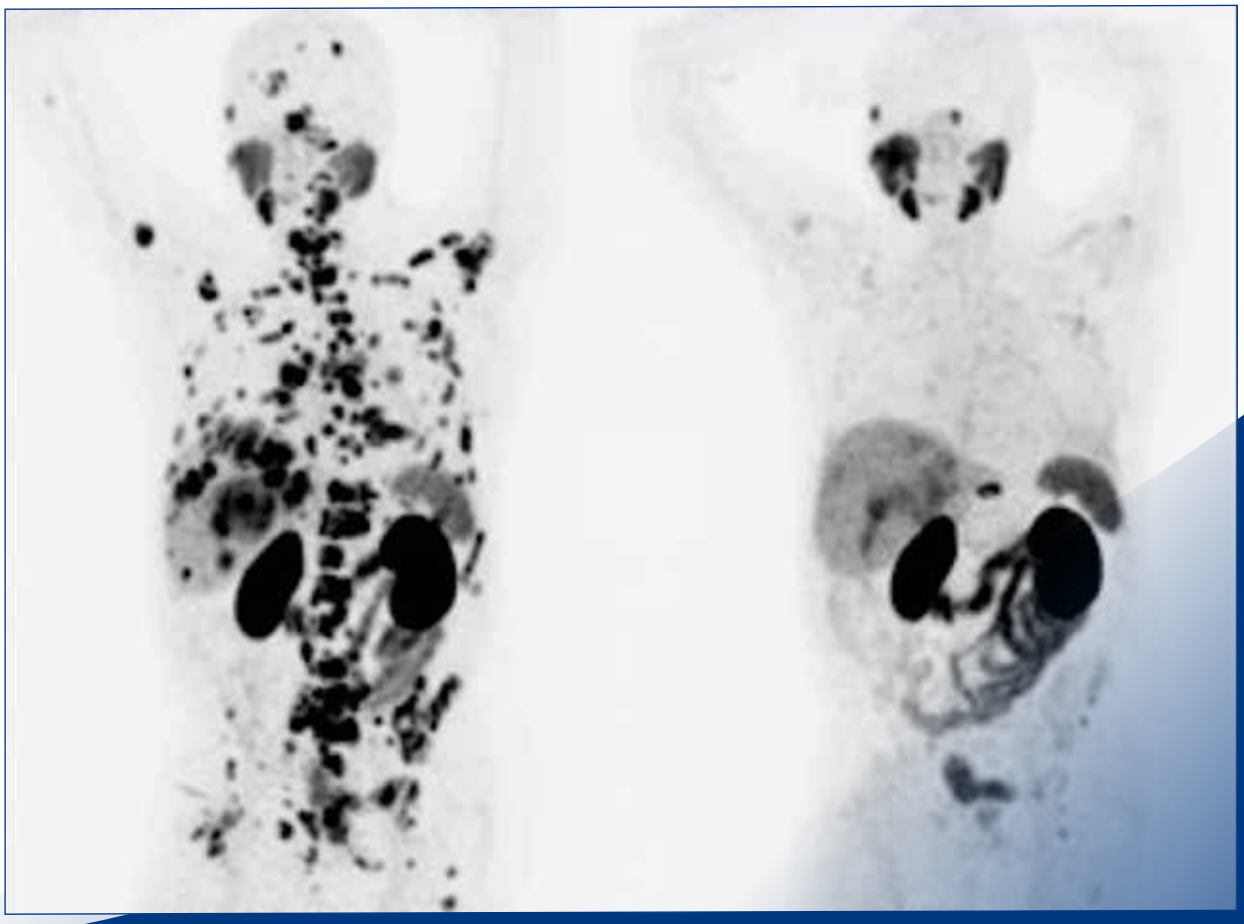
tijdschrift voor
NUCLEAIRE GENEESKUNDE



Themanummer 2023

Radionuclidentherapie

45e jaargang 2023 nummer 2 issn 1381 - 4842

GE HealthCare

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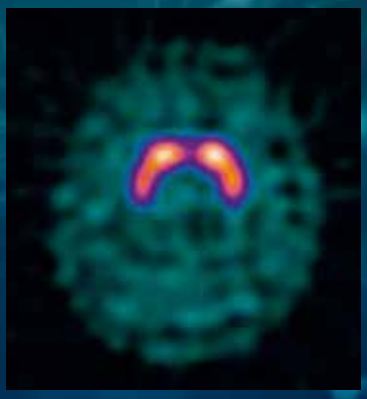
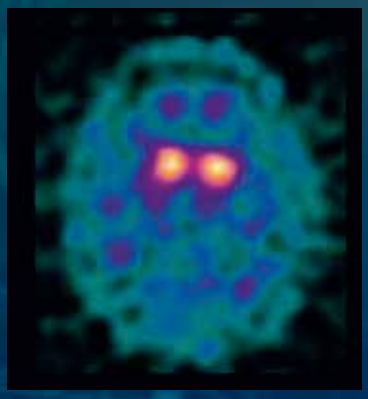


NORMAL SCAN
No evidence of striatal neurodegeneration



ABNORMAL SCAN
Visual evidence of striatal neurodegeneration

Images courtesy of Birmingham City Hospital, UK

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PRESENTATIE Flacon met enkelvoudige dosis van 185 MBq of 370 MBq joflupaan (^{123}I) op referentietijd. **INDICATIES** Dit geneesmiddel is uitsluitend voor diagnostisch gebruik. DaTSCAN wordt toegepast voor het aantonen van een verlies aan functionele dopaminerge zenuwuiteinden in het striatum: - Bij volwassen patiënten met een klinisch onduidelijk Parkinsonistisch syndroom, bijvoorbeeld patiënten met de eerste symptomen, teneinde essentiële tremor te helpen onderscheiden van Parkinsonistische syndromen die verwant zijn aan de idiopathische ziekte van Parkinson, multipel systeematrofie en progressieve supranucleaire palsy. Het is niet mogelijk om met behulp van DaTSCAN onderscheid te maken tussen de ziekte van Parkinson, multipel systeematrofie en progressieve supranucleaire palsy. - Als hulpmiddel bij volwassen patiënten bij het differentiëren van waarschijnlijke dementie met Lewy-body's van de ziekte van Alzheimer. DaTSCAN kan geen onderscheid maken tussen dementie met Lewy-body's en dementie bij de ziekte van Parkinson.
DOSERING EN WIJZE VAN TOEDIENING De klinische werkzaamheid van het middel is aangetoond binnen het gebied van 111 tot 185 MBq. Dien geen hogere dosis toe dan 185 MBq en gebruik het middel niet wanneer de activiteit kleiner is dan 110 MBq. Patiënten moeten een passende schildklierblokkerende behandeling krijgen voor de injectie om de opname door de schildklier van radioactief jodium te beperken, bijvoorbeeld door orale inname van ongeveer 120 mg kaliumjodide 1 tot 4 uur voor de injectie van DaTSCAN. Er zijn geen officiële onderzoeken gedaan bij patiënten met significante nier- of leverfunctiestoornis; er zijn geen gegevens beschikbaar. De veiligheid en werkzaamheid van DaTSCAN bij kinderen van 0 tot 18 jaar zijn niet vastgesteld; er zijn geen gegevens beschikbaar. DaTSCAN dient onverdund en intraveneus te worden toegediend. Om de mogelijkheid van het optreden van pijn op de plaats van injectie tijdens de toediening te verminderen, wordt aanbevolen langzaam te injecteren (niet minder dan 15 tot 20 seconden) via een ader in de arm. SPECT imaging dient plaats te vinden tussen drie en zes uur na de injectie. **CONTRAINDICATIES** Zwangerschap en overgevoeligheid voor het werkzame bestanddeel of voor één van de hulpstoffen. **WAARSCHUWINGEN EN VOORZORGEN BIJ GEBRUIK** Bij het optreden van overgevoeligheidsreacties dient de toediening van het geneesmiddel onmiddellijk worden gestopt en, indien nodig, intraveneuze behandeling te worden gestart. Reanimatiegeneesmiddelen en uitrusting (bijv. endotracheale buis en ventilator) dienen snel beschikbaar te zijn.
Voor elke patiënt moet de blootstelling aan ioniserende straling worden gerechtvaardigd op basis van waarschijnlijk voordeel. De toegediende activiteit moet dusdanig zijn dat de resulterende dosis zo laag is als redelijkerwijs mogelijk is waarbij de benodigde diagnostische resultaten in het oog worden gehouden. Er zijn geen officiële studies uitgevoerd met patiënten met een aanzienlijk verminderde nier- of leverfunctie. Vanwege het ontbreken van data wordt DaTSCAN niet aanbevolen voor patiënten met een matige tot ernstig verminderde nier- of leverfunctie. Dit geneesmiddel bevat 39,5 g/l (5% volume) ethanol (alcohol), tot maximaal 197 mg per dosis, equivalent aan 5 ml bier of 2 ml wijn. Schadelijk voor alcoholisten. Hiermee dient rekening gehouden te worden bij risicogroepen zoals patiënten met leverziekte of epilepsie. *Interpretatie van DaTSCAN-beelden:* DaTSCAN-beelden worden visueel geïnterpreteerd op basis van het uiterlijk van de striata. Als aanvulling kan visuele interpretatie worden ondersteund door semi-kwantitatieve beoordeling met behulp van CE-gemarkeerde software, waarbij de volgende voorzorgsmaatregelen moeten worden genomen bij het gebruik van semi-kwantitatieve methoden: - Semi-kwantificering mag alleen worden gebruikt als aanvulling op visuele beoordeling; - Er mag alleen software met CE-markering worden gebruikt; - Gebruikers moeten door de fabrikant worden getraind in het gebruik van software met CE-markering en de EANM-praktijkrichtlijnen volgen voor beeldacquisitie, reconstructie en beoordeling; - Lezers moeten de scan visueel interpreteren en vervolgens de semi-kwantitatieve analyse uitvoeren volgens de instructies van de fabrikant, inclusief kwaliteitscontroles voor het kwantificeringsproces. **INTERACTIES** Joflupaan bindt aan de dopamine transporter. Geneesmiddelen die met een hoge affiniteit binden aan de dopamine transporter kunnen daardoor een DaTSCAN diagnose beïnvloeden. Hieronder worden gerekend amfetamine, benzatropine, buproprion, cocaïne, mazindol, methylfenidaat, fentermine en sertraline. Van de volgende geneesmiddelen is aangetoond dat ze gedurende klinische studies niet interfereren met de DaTSCAN beeldvorming: amantidine, benzhexol, budipine, levodopa, metoprolol, primidon, propranolol and selegiline. Dopamine agonisten en antagonisten die actief zijn op de post-synaptische dopamine receptoren zullen naar verwachting de beeldvorming niet beïnvloeden en kunnen daarom, indien gewenst, gebruikt blijven worden. Pergolide is een van de geneesmiddelen waarvan met dierstudies is aangetoond dat ze de DaTSCAN beeldvorming niet beïnvloeden. **VRUCHTBAARHEID, ZWANGERSCHAP EN BORSTVOEDING** Gecontraïndiceerd bij zwangerschap. Waar het nodig is radioactieve geneesmiddelen aan een vrouw in de vruchtbare leeftijd toe te dienen, dient altijd navraag te worden gedaan naar een eventuele zwangerschap.
Van iedere vrouw die over tijd is, moet worden aangenomen dat ze zwanger is totdat het tegendeel is aangetoond. In geval van onzekerheid is het van belang de blootstelling aan straling tot een minimum te beperken, terwijl een bevredigende beeldvorming wordt bereikt. Men dient te overwegen of alternatieve methoden, waarbij geen ioniserende straling vrijkomt, in aanmerking komen. Indien men ervan uitgaat dat toediening noodzakelijk is, dient het geven van borstvoeding gedurende 3 dagen onderbroken en door flesvoeding vervangen te worden. **BIJWERKINGEN** De volgende bijwerkingen worden voor DaTSCAN erkend: Bijwerking die vaak voorkomt is hoofdpijn. Bijwerkingen die soms voorkomen zijn vertigo, verhoogde eetlust, duizeligheid, formicatie (paresthesie), dysgeusie, misselijkheid, droge mond en pijn op de injectieplaats (intense pijn of brandend gevoel na toediening in kleine aderen). Overgevoeligheid komt voor met een onbekende frequentie, evenals erythema, pruritus, uitslag, urticaria, hyperhidrose, kortademigheid, braken, gedaalde bloeddruk en warm voelen. **DOSIMETRIE** De effectieve dosis (E) als gevolg van de toediening van 185 MBq DaTSCAN-injectie is 4,63 mSv (voor een individu van 70 kg).
HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN GE Healthcare B.V., De Rondom 8, NL-5612 AP Eindhoven, Nederland.
AFLEVERSTATUS Geneesmiddel op medisch voorschrift (U.R).
NUMMERS VAN DE VERGUNNING VOOR HET IN HANDEL BRENGEN EU/1/00/135/001 (2,5 ml), EU/1/00/135/002 (5 ml). **DATUM** SPC gedateerd jan 2021; verkorte bijsluiter gedateerd 5 maart 2021

Beroepsbeoefenaren in de gezondheidszorg worden verzocht alle vermoedelijke bijwerkingen te melden via: Nederlands Bijwerkingen Centrum Lareb, website: www.lareb.nl. Bijwerkingen kunnen ook direct worden gerapporteerd aan GE Healthcare B.V.: Benelux.PVcomplaint@ge.com of Tel. (+31) 040 2991000.

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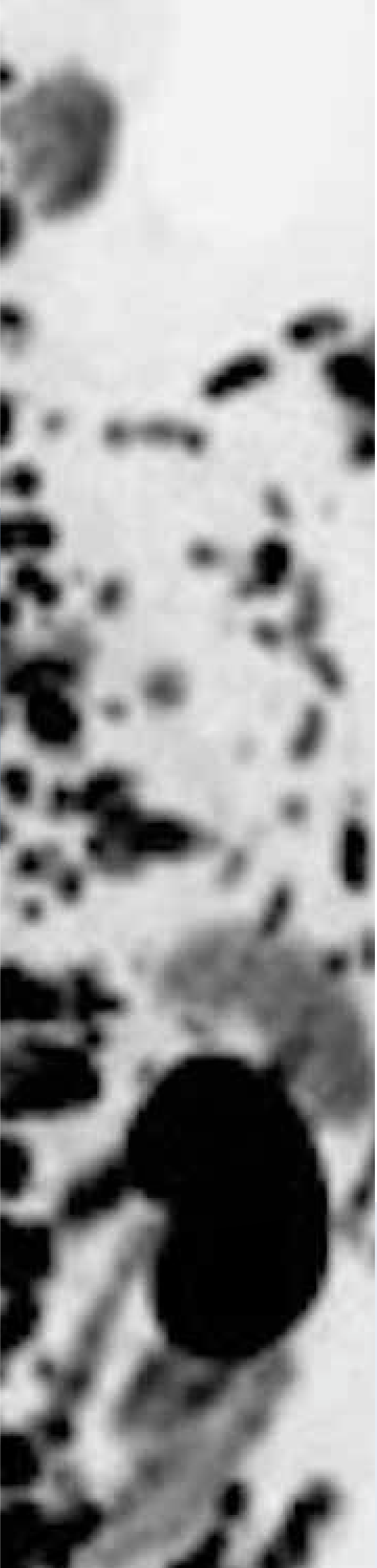

INHOUD

Snelle translatie van diagnostiek naar therapie in de Nucleaire Geneeskunde, zijn we er klaar voor?

Radionuclide behandelingen zijn inmiddels niet meer weg te denken uit de nucleair geneeskundige praktijk. Elk jaar wordt in Nederland een toenemend aantal patiënten op afdelingen nucleaire geneeskunde behandeld. Was dit vroeger vaak beperkt tot behandelingen van benigne en maligne schildklieraandoeningen, uitgevoerd in de grotere ziekenhuizen, inmiddels is er een scala aan therapeutische mogelijkheden, uitgevoerd in vrijwel alle ziekenhuizen van Nederland. Diagnostiek en behandeling zijn daarbij nauw met elkaar verbonden, populair 'thera(g)nostics' genoemd. In dit nummer van het Tijdschrift voor Nucleaire Geneeskunde geven verschillende collega's een overzicht van de huidige mogelijkheden. Het illustreert niet alleen de snelle ontwikkelingen van de laatste jaren, maar ook de expertise die op het gebied van radionuclide therapie in Nederland aanwezig is. De focus ligt in dit themanummer dan ook op de mogelijkheden van radionuclide therapie, maar ook de uitdagingen waar we met elkaar voor staan mogen niet onbenoemd blijven.

Het opschalen van vooral de lutetium-177 radionuclide behandelingen gaat momenteel gepaard met grote uitdagingen. Bijna dagelijks is te merken dat de keten van radionuclide productie en levering nog niet op orde is. Dit maakt de eigen productie van radiofarmaca zeer kwetsbaar, waardoor de beschikbaarheid voor (kanker)patiënten onder druk komt te staan. Los van de relevante wet- en regelgeving blijft het daarbij de vraag of eigen productie van radiofarmaca voor radionuclide behandelingen (in een ziekenhuis setting) op de korte en lange termijn wenselijk is? Het is een discussie over maatschappelijke kosten, (brede) beschikbaarheid en kwaliteit, maar ook over (academische) taakstelling en benodigde investeringen. De recente problemen met de levering van lutetium-177 zetten die discussie verder op scherp.

De uitvoering van radionuclide behandelingen dient plaats te vinden op een verpleegafdeling die daarvoor speciaal geütiliseerd is. Een voorzichtige schatting leert dan enkele duizenden patiënten in Nederland jaarlijks in aanmerking komen voor radionuclide behandelingen, waarbij de volledige therapie meestal bestaat uit vier tot zes behandelingen. Bij een schatting van ca. 25.000 toekomstige behandelingen per jaar en 50 behandelcentra in Nederland betekent dit nog altijd 500 behandelingen per centrum. Die benodigde capaciteit van tenminste 50 behandelcentra met gemiddeld 2 bedden per centrum is op dit moment niet in Nederland aanwezig. Significante investeringen ten aanzien van benodigde infrastructuur zullen nodig blijken om lange wachtlijsten te voorkomen. Kunnen we die infrastructuur op tijd realiseren? Hoe worden de investeringen gefinancierd?
De huidige (en toekomstige) verpleegafdelingen voor radionuclide behandelingen zijn bovendien niet overal integraal onderdeel van de afdeling Nucleaire geneeskunde.
Hoe wordt een verpleegafdeling voor radionuclide therapie optimaal georganiseerd? Zouden differentianten nucleaire geneeskunde een rol op zich kunnen nemen als zaalarts, wellicht als onderdeel van de opleiding? Hoe zijn de financiële stromen geregeld en wie treedt op als hoofdbehandelaar? Deze vragen beperken zich niet tot de organisatie zelf, maar zijn ook medisch inhoudelijk van aard. Bij voorkeur treedt de nucleair geneeskundige bij verwijzing op als hoofdbehandelaar. Volgens de meest gebruikte definitie van het hoofdbehandelaarschap stelt de hoofdbehandelaar de indicatie voor de behandeling, informeert de hoofdbehandelaar de patiënt over de behandeling, voert de hoofdbehandelaar de behandeling uit, en verzorgt de hoofdbehandelaar de noodzakelijke

nazorg en follow-up. Het is in ieder geval gebruikelijk dat de eigenlijke behandelaar (als hoofd- of medebehandelaar) zelf de indicatie stelt en de patiënt van informatie voorziet, voordat de behandeling uitgevoerd wordt. Voor nucleair geneeskundigen zou dat betekenen dat zij in toenemende mate poliklinische afspraken met patiënten hebben, voor de behandeling, maar ook gedurende een follow-up periode na de behandeling. Is de infrastructuur daarvoor aanwezig? Zijn nucleair geneeskundigen voldoende medisch geschoold om patiënten gedurende de behandelperiode te begeleiden?

Sinds de integratie van de opleidingen Radiologie en Nucleaire geneeskunde is de uitgebreide stage van een jaar interne geneeskunde geen verplicht onderdeel meer van de opleiding tot nucleair geneeskundige/radioloog. Hierdoor ontstond ruimte voor verdieping in de radiologische aspecten van ons vak. Door de voortschrijdende integratie met Radiologie ontstaan nieuwe mogelijkheden. Niet alleen is de radiologische diagnostiek vaak complementair aan de nucleaire diagnostiek, de radiologische diagnostiek is door de integratie ook gemakkelijker beschikbaar voor onze eigen patiënten. Tegelijk is de focus van de opleiding daarbij meer komen te liggen op de diagnostiek, in een periode waarin juist radionuclide therapie een vlucht heeft genomen. Differentianten nucleaire geneeskunde worden gedurende hun differentiatie geschoold in beide aspecten van ons vak, maar de vraag blijft of dit voldoende is voor het uitvoeren van radionuclide therapie in de volle breedte? Analoog aan de Interventie Radiologie is het denkbaar dat een fellowship nucleaire geneeskunde invulling zou kunnen geven aan deze kennislacune?

Nog veel onbeantwoorde vragen. Hoe dan ook zullen we gezamenlijk oplossingen vinden, de ontwikkelingen gaan namelijk onverminderd door. De vraag voor bijvoorbeeld PSMA-behandelingen is nu al groot, terwijl de farmaceutische industrie momenteel meerdere grote gerandomiseerde fase III studies uitvoert in eerdere lijnen van de behandeling van prostaatkanker. Bij positieve resultaten zal het indicatiegebied daarmee verder verbreden en de vraag verder vergroten. Bovendien onderzoekt de farmaceutische industrie momenteel multipele kandidaat radiofarmaca voor een scala aan indicaties, ondersteunt door investeringen in de productie van medische isotopen (e.g. PALLAS, SHINE) en de verwerking van medische isotopen door leveranciers. Een en ander verder versterkt door innovatie op het gebied van beeldvormende technieken die met sterk verbeterde accuratesse bijdragen aan selectie van de juiste patiënten en het opstellen van een behandelplan voor elke individuele patiënt, in overeenstemming met de huidige eisen.

Behalve de snelle ontwikkelingen op het gebied van systemische radionuclide behandelingen, is er ook een toenemende interesse in lokaal toegepaste radionuclide behandelingen. Te denken valt aan intra-arteriële toepassingen (e.g. radio-embolisatie), maar ook intra-tumorale toepassingen, intra-peritoneaal of cutaan. Deze radionuclide behandelingen kenmerken zich door het gebruik van (zeer) hoge lokale doseringen en beperkte (systemische) toxiciteit, maar zijn vaak ook beperkt qua indicatiegebied vanwege de lokale toepassing. Omdat de effectieve halveringstijd alleen bepaald wordt door de fysische halveringstijd en niet door de biologische halveringstijd (vanwege de permanente retentie lokaal), is het opstellen van een persoonlijk behandelplan, gebaseerd op dosimetrie, gemakkelijker te realiseren. Daarmee kunnen dit type radionuclide behandelingen ten aanzien van dosimetrie het pad effenen voor systemische radionuclide behandelingen.

Dosimetrie is voor alle radionuclide behandelingen van groot belang. Omdat het aantal radionuclide behandelingen toeneemt, in eerdere fasen van ziekten, in combinatie met andere behandelingen, en gefractioneerd, neemt de druk op verbetering van dosimetrie toe. Dosimetrie op basis van kwantitatieve beeldvorming moet leiden tot een goede selectie van patiënten, een individueel behandelplan naar analogie van de uitwendige radiotherapie, en een accurate analyse van de therapie tijdens of na de behandeling. De ontwikkelingen op

het gebied van dosimetrie software hebben dit veld de laatste jaren een significante boost gegeven.

Het moge duidelijk zijn: Radionuclide behandelingen zijn booming. Nucleaire Geneeskunde heeft een trackrecord op het gebied van snelle translatie van innovatieve diagnostische en therapeutische modaliteiten. Multidisciplinaire samenwerking, niet in de minste plaats met onze collega radiologen, zal leiden tot succesvolle implementatie van de huidige radionuclide behandelingen en de innovatie van de toekomstige radionuclide behandelingen faciliteren. Onze industriële partners en partners uit de publieke sector zijn daarbij onontbeerlijk voor succes, maar ook samenwerking tussen de ziekenhuizen in Nederland zal cruciaal blijken voor implementatie, standaardisatie en innovatie.

Prof. dr. Marnix G.E.H. Lam
Gasthoofdredacteur

Bijschrift coverfoto:
[^{68}Ga]Ga-PSMA-11 vóór (links) en na (rechts) 2 cycles van 7,4 GBq [^{177}Lu]Lu-PSMA-I&Y in een patiënt met gemetastaseerd castratie-resistent prostaatcarcinoom. Het beeld komt uit het artikel "Lutetium-177 PSMA for prostate cancer; current developments and challenges" van E.C.A. van der Sar et al.

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Palliative radionuclide therapy for bone metastases with strontium-89-chloride and samarium-153-EDTMP

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Department of Nuclear Medicine, Meander Medical Centre, Amersfoort

Abstract
A considerable proportion of patients with cancer will develop bone metastases. Bone metastases frequently cause severe bone pain and seriously affect quality of life. Palliative treatment of patients with bone pain from multiple bone metastases using radiopharmaceuticals such as [^{89}Sr]$SrCl_2$ and [^{153}Sm]Sm-EDMTP can be a safe and easily accessible option to effectively relieve bone pain.

Introduction

Cancer incidence is on the rise, with over 124.000 cases alone being diagnosed in 2022 in the Netherlands according to the statistics of the Integral Cancer Center in the Netherlands (IKNL). A considerable proportion of patients with advanced prostate, breast or lung carcinoma will develop bone metastases. Bone metastases are an indicator of progressive disease with bad prognosis, frequently causing severe bone pain and affecting quality of life (1,2).

The aim of treating bone metastases with bone seeking radiopharmaceuticals is purely palliative (except Radium-223). The treatment options are diverse and depend on the disease condition. A common treatment sequence is nonsteroidal analgesics to opioids often combined with radiotherapy, surgery, chemotherapy, hormone treatment, bisphosphonates and radionuclide therapy (3). External beam radiotherapy is preferred for localized pain and limited metastases (4). For patients with multiple or diffuse metastases, or when other treatments do not respond, treatment with bone seeking radiopharmaceuticals is a good alternative, given that metastases are osteoblastic (which can be confirmed with bone scintigraphy). This is mostly the case for prostate cancer metastases, but bone seeking radiopharmaceuticals can also target metastases from many other types of tumors that have a mix of osteoblastic and osteoclastic components (5). On top of allowing systemic treatment, other advantages of treatment with bone seeking radiopharmaceuticals are its repeatability, ease of administration as well as the potential to be combined with other therapies for enhanced effectiveness.

There are different radionuclides that can be used. The most common are the beta-emitting strontium-89-chloride (^{89}Sr-Cl) and samarium-153-EDTMP ([^{153}Sm]Sm-EDMTP) as well as the alpha-emitting radium-223-chloride ([^{223}Ra]$RaCl_2$). In the past, rhenium-188 hydroxyethylidene diphosphonate and rhenium-186-hydroxyethylidene disphosphonate ([^{188}Re]Re-HEDP and [^{186}Re]Re-HEDP) were also used, but these radiopharmaceuticals are now out of production for this indication. After injection, the radionuclides target all osteoblastic bone lesions simultaneously. Pain relief commences in days or weeks, lasting for months (6). Pain reduction is achieved by destruction of malignant and immune cells, leading to a decrease of cytokines and growth factors that lessen periosteal swelling (5). The related treatment toxicity is mainly (reversible) myelosuppression, thrombocytopenia in particular, and depends on the administered dose and type of radionuclide (3).

This review presents insights into the clinical results of using the beta-emitting strontium-89-chloride ([^{89}Sr]$SrCl_2$) and samarium-153-EDTMP ([^{153}Sm]Sm-EDMTP) (approved in Europe and the US) for treatment of bone metastases, including effectiveness for pain relief for different primary tumors and side effects derived from this treatment.

Characteristics and Production

Summary characteristics of both radionuclides are presented in table 1.

Strontium-89-chloride

^{89}Sr was the first radionuclide to receive US Food and Drug Administration approval for the palliation of bone pain. The isotope ^{89}Sr has a half-life of 50.57 days and undergoes decay into stable yttrium-89, emitting mostly high energy beta-particles (Emax = 1.46 MeV). A very small negligible proportion of gamma rays is emitted (910 keV) as well as a small amount

Table 1. Summary characteristics of both radionuclides.

Radionuclide	Half-life (days)	Energy (beta max) (mEv)	Emission	Range in soft tissue (mm)
strontium-89	50.57	1.46	Beta	8.0
samarium-153	1.93	0.71	Beta/Gamma	3.0

of bremsstrahlung. Because of the small proportion of gamma and bremsstrahlung it is safe to administer in an outpatient setting.

Strontium is a calcimimetic agent and thus behaves similar to calcium. After intravenous injection strontium migrates to the bone and is actively taken up by the bone matrix. The high energy beta particles are responsible for the therapeutic effect. The maximum range in soft-tissue is 8 mm (7).

^{89}Sr is produced through neutron activation, irradiating a sample of stable strontium-88 (^{88}Sr) with neutrons in a nuclear reactor. This transforms some of the ^{88}Sr into ^{89}Sr through neutron capture and subsequent beta decay. The resulting ^{89}Sr is separated and purified to the desired level of radioactivity. Finally, it is incorporated with a chloride solution to make it ready for intravenous delivery to the patient (8).

Samarium-153-EDTMP

^{153}Sm was approved in the USA and Europe for the treatment of pain from bone metastases in the late 1990s. ^{153}Sm has desirable characteristics, with a combined radiation of beta and gamma emissions while decaying to stable europium-153. Beta emissions occur at 640, 710 and 810 keV with an average beta particle energy of 233 keV. Its gamma-ray emission of 103 keV allows to assess patient biodistribution and dosimetry after injection via SPECT imaging. The beta particle of [^{153}Sm]Sm-EDMTP has a maximum range of 3.0 mm in soft tissue and 1.7 mm in bone. It has a half-life of 46.3 hours (1.93 days) (9).

[^{153}Sm]Sm-EDMTP has good selective skeletal localization, low blood levels, and low soft tissue retention, including the liver. Accumulation in non-osseous tissue other than the bladder/urine is low. A study by Brenner et al. found a mean bone uptake of 47.7±11.2% at 24 hours, soft-tissue retention at 24 hours was 12.7±4.7%, and urinary excretion 39.5±13.8% at 24h after injection of 37 MBq/kg [^{153}Sm]Sm-EDMTP (10).

^{153}Sm is commonly prepared by neutron irradiation of enriched $^{152}Sm_2O_3$ in a nuclear reactor, which is then chelated with ethylenediaminetetramethylene phosphonic acid (EDTMP) (11).

Clinical Results

Strontium-89-chloride

A standard fixed dose of 150 MBq is recommended by the European Association of Nuclear Medicine (EANM) Guidelines following many investigations (3). [^{89}Sr]$SrCl_2$ is administered intravenously and a slow infusion is recommended to avoid a 'flushing sensation' (3). Good response rates have been reported in clinical trials ranging from 57 to 96% (table 2).

Pain relief in studies is usually reported as either complete or partial pain reduction. Different scales are used to measure pain relief, including numerous numerical weighting systems, ten-point Visual Analogue Scale (VAS), RTOG (Radiation Therapy Oncology Group) pain scoring system or subjectively assessed by the oncologist. In a large meta-analysis from 2012 an overall response rate of 70% (95% CI: 65-75%) was reported (12). Delay in the start of response is usually between 4 days and 28 days, with a response duration of up to 15 months (6).

Additionally, a few studies have shown an improvement of quality of life after radionuclide treatment with [^{89}Sr]$SrCl_2$ (13–15). It has to be noted that naturally, improvement in quality of life generally follows pain relief (16). Although showing acceptable response rates regarding pain relief, another recent meta-analysis (17) showed no benefits in overall survival rates or symptomatic 'skeletal related event (e.g. pathological fractures)' (SRE)-free survival in metastatic castration-resistant prostate cancer (mCRPC).

Retreatment with [^{89}Sr]$SrCl_2$ is possible and safe, though the response to retreatment tends to be significantly worse compared to first treatment (rate of patients with at least good response decreased from 60% to 48%) (18).

Table 2. Summary of efficacy studies on strontium-89-chloride. Pain relief is reported as the response rate of patients with either complete or partial pain reduction.

Reference	Year	Nr. Patients	Diagnosis	Dosage	Pain Relief
Lewington (19)	1991	26	Prostate	150 MBq	75%
Pons (20)	1997	76	Prostate / Breast	148 MBq	89% Prostate 92% Breast
Kasalicky (21)	1998	118	Prostate / Breast / Other	148 MBq	96%
Fuster (22)	2000	40	Breast	148 MBq	92%
Kraeber-Bodere (14)	2000	94	Prostate	150 MBq	78%
Dafermou (18)	2001	527	Prostate	148 MBq	60%
Turner (16)	2001	93	Prostate	150 MBq	63%
Sciuto (23)	2001	25	Breast	148 MBq	84%
Ashayeri (24)	2002	41	Prostate / Breast	150 MBq	81%
Zorga (25)	2003	33	Prostate / Breast / Other	148 MBq	88%
Baczyk (13)	2003	70	Prostate	148 MBq	88%
Oosterhof (26)	2003	203	Prostate	148 MBq	78%
Gunawardana (27)	2004	13	Prostate	148 MBq	57%
Liepe (28)	2007	15	Prostate / Breast	148 MBq	73%
Zenda (29)	2014	54	Prostate / Breast / Other	2 MBq/kg	71%
Furubayashi (30)	2014	18	Prostate	2 MBq/kg to a maximum of 141 MBq per patient.	72%
Ye (31)	2018	246	Prostate / Breast / Lung	2.2 MBq/kg	75% Lung 95% Prostate and Breast

Samarium-153-EDTMP

[^{153}Sm]Sm-EDMTP has been widely used since its approval in the late 1990s. The optimal dosage of 37 MBq/kg has been investigated thoroughly in the past which has been shown to be effective and safe (32,33). Therefore, a dose of 37 MBq/kg is now the recommended dose by the EANM guidelines.

Response rates are comparable to [^{89}Sr]$SrCl_2$ ranging from 57%-90% (table 3). In a large meta-analysis, an overall response rate of 70% (95% CI: 63-96%) was found for [^{153}Sm]Sm-EDMTP, similar to ^{89}Sr-Cl.

Given its much shorter half-life, [^{153}Sm]Sm-EDMTP onset of response after treatment is faster than [^{89}Sr]$SrCl_2$, and pain relief is typically noted rapidly within 5 to 10 days and with a duration up to 4 months (6). Patients who need quick pain relief due to a fast-progressing disease and pain can benefit more from treatment with a short-lived isotope such as [^{153}Sm]Sm-EDMTP. In the case of a good first response, repeated treatment may be desirable and has been shown to improve duration of pain response (6,16,34).

Side Effects

Many of the above mentioned studies reported the observed side effects of [^{89}Sr]$SrCl_2$ and [^{153}Sm]Sm-EDMTP. The most common side effects are pain

Table 3. Summary of efficacy studies on samarium-153-EDTMP. Pain relief is reported as the response rate of patients with either complete or partial pain reduction.

Reference	Year	Nr. Patients	Diagnosis	Dosage	Pain Relief
Turner (16)	1991	23	Prostate / Breast / Other	Absorbed dose to bone marrow was fixed at 2 Gy	61%
Collins (35)	1993	52	Prostate	18.5–111 MBq/kg	67%
Resche (33)	1997	114	Prostate / Breast / Other	18.5–37 MBq/kg	70%
Serafini (32)	1998	118	Prostate / Breast / Other	18.5–37 MBq/kg	57-65%
Tian (36)	1999	105	Prostate / Breast / Other	37 MBq/kg	Only complete pain relief reported (25%)
Dolezal (37)	2000	33	Prostate / Breast / Other	37 MBq/kg	71%
Sapienza (38)	2004	73	Prostate / Breast	37 MBq/kg	90% (decrease in pain score by more than 25%)
Etchebehere (39)	2004	58	Prostate / Breast / Other	37–59.2 MBq/kg	78% (decrease in pain score by more than 25%)
Sartor (40)	2004	152	Prostate	37 MBq/kg	65%
Tripathi (41)	2006	84	Prostate / Breast / Other	37 MBq/kg	73%
Ripamonti (42)	2007	13	Prostate	40 MBq/kg	77%
Liepe (28)	2007	15	Prostate / Breast	37 MBq/kg	73%
Gallichio (43)	2014	21	Breast / Lung	37 MBq/kg	86%
Correa-Gonzalez (44)	2014	277	Prostate / Breast / Other	37 MBq/kg	74% Prostate 67% Breast 67-80% Other
Thapa (45)	2015	16	Prostate / Other	37 MBq/kg	75%
Elzahry (46)	2017	110	Prostate / Breast	1.1 GBq	94%

flare and (low grade) hematological side effects such as thrombopenia and leukopenia.

The flare phenomenon involves an increase in pain symptoms and typically occurs within 72 hours after the start of the treatment and it is observed in approximately 10% of patients. In the majority of patients the pain symptoms are self-limiting and mild. In general, a flare phenomenon is associated with good response rates of pain relief (6,33,47).

Bone marrow toxicity is the major side-effect in both [^{89}Sr]$SrCl_2$ and [^{153}Sm] Sm-EDMTP. Decreases in thrombocyte and leucocyte counts in the peripheral blood because of myelosuppression is frequently observed, but mainly low-grade and transient. In a study by

Zenda et al. (29) grade 3-4 leucopenia was only found in 1.8% of patients, while in a study by Kraeber-Bodere et al. (14) high grade leuco-thrombopenia was observed in 5% of patients.

When treating patients with [^{89}Sr]$SrCl_2$, the lowest blood cell count (nadir) occurs between 12–16 weeks, showing recovery within six weeks depending on the extent of bone metastases and bone marrow reserve (3,6,48,49). It generally consists of a transient mild thrombocytopenia of around 30%. In theory, because of a longer half-life and maximum beta-radiation energy, [^{89}Sr]$SrCl_2$ yields a longer period of myelosuppression. Therefore, longer follow-up is deemed necessary.

In patients treated with [^{153}Sm]Sm-EDMTP, nadir is usually measured between 3-5 weeks and recovery takes places 6-8 weeks after therapy. Likewise, after repeated doses of [^{153}Sm]Sm-EDMTP the bone marrow toxicity has been shown to be transient and mild (38,40,44).

Discussion

Both [^{89}Sr]$SrCl_2$ and [153Sm]Sm-EDMTP have been widely proven to be effective to reduce pain in patients with bone metastases. Various studies have compared the efficacy of different radiopharmaceuticals in treating metastatic bone pain relief. Most studies reported no significant difference between [^{89}Sr]$SrCl_2$ and [^{153}Sm]Sm-EDMTP regarding toxic effects and response rate (23,28,50–52). Therefore, factors such as availability, cost, and clinical experience are often used to decide which radiopharmaceutical to use for palliative pain relief from bone metastases.

Since effectiveness depends on the osteoblastic nature of the metastases, there are some differences in pain relief success among metastases from different cancer types. Ye et al. compared the efficacy of [^{89}Sr]$SrCl_2$ in treating bone metastases in lung versus breast and prostate cancer as a control group. They found that the efficacy was significantly lower in patients with lung cancer than in patients with breast or prostate cancer (75% vs. 90%). Moreover, toxicity was higher for patients with lung cancer, with 67% of patients showing mild-to-moderate reductions of leukocyte and platelet counts 4 weeks after [^{89}Sr]$SrCl_2$ treatment (compared to 47% in the control group) (31). In another study, it was also concluded that treatment non-responders are often patients with primary lung cancer (34 out of 51 non-responders) (36). Although [^{89}Sr]$SrCl_2$ and [^{153}Sm]Sm-EDMTP are indicated for all painful metastatic osteoblastic bone lesions (as confirmed by areas of intense uptake on radionuclide bone scans), this could be explained given the fact that lung cancer often develops osteolytic metastases to bone (53).

When it comes to survival benefits, studies with [^{223}Ra]$RaCl_2$, an alpha-emitter radionuclide, have shown to improve overall survival in patients with metastatic castrate resistant prostate cancer and bone metastases (without visceral metastases). Survival benefits after therapy with [^{89}Sr]$SrCl_2$ and [^{153}Sm]Sm-EDMTP have not been investigated, and thus there is no evidence that they improve overall survival. However, [^{89}Sr]$SrCl_2$ and [^{153}Sm]Sm-EDMTP have been shown to provide palliative pain relief for a wider patient population, as opposed to [^{223}Ra]$RaCl_2$ which is limited to castration resistant prostate cancer patients with bone pain and no visceral metastases.

The efficacy of other anti-cancer treatments combined with boneseeking radionuclide therapy has been investigated. Results are contradictory. Treatment with the combination of [^{89}Sr]$SrCl_2$ and external beam radiation therapy (EBRT) was shown to have similar response rates in some studies (26,54), while in another study pain relief was higher in patients receiving a combination of [^{89}Sr]$SrCl_2$ and EBRT compared to a single treatment of [^{89}Sr]$SrCl_2$ alone (55). However, a combination of a radionuclide and bisphosphonates seems to be promising. Concurrent therapy of [^{89}Sr]$SrCl_2$ and zoledronic acid (bisphosphonate) has been shown to have a higher rate of pain relief (94% of patients) and improvement of quality of life compared to [^{89}Sr]$SrCl_2$ or zoledronic acid use alone, without any increase of toxicity (56). Similar outcomes were found for combination therapy of [^{153}Sm]Sm-EDMTP with bisphosphonates, leading to significantly higher pain responses and better quality of life (57,58).

Conclusion

Both [^{89}Sr]$SrCl_2$ and [^{153}Sm]Sm-EDMTP are beta-emitting radiopharmaceuticals with decades of proven clinical safety and effectiveness to reduce pain in patients with bone metastases.

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References

1. Saad F, Clarke N, Colombel M. Natural history and treatment of bone complications in prostate cancer. Eur Urol. 2006;49:429-40
2. Levy MH. Pharmacologic Treatment of Cancer Pain. N Engl J Med. 1996;10;335:1124-32
3. Handkiewicz-Junak D, Poeppel TD, Bodei L, Aktolun C, Ezziddin S, Giammarile F, et al. EANM guidelines for radionuclide therapy of bone metastases with beta-emitting radionuclides. Eur J Nucl Med Mol Imaging. 2018;45:846-59
4. Janjan N. Bone metastases: Approaches to management. Semin Oncol. 2001;28:28-34

5. M.G.E.H. Lam, J.M.H. de Klerk, P.P. van Rijk, B.A. Zonnenberg. Bone Seeking Radiopharmaceuticals for Palliation of Pain in Cancer Patients with Osseous Metastases. Anti-Cancer Agents Med Chem. 2007;7:381-97
6. Finlay IG, Mason MD, Shelley M. Radioisotopes for the palliation of metastatic bone cancer: a systematic review. Lancet Oncol. 2005;6:392-400
7. FDA label 89-strontium-chloride
8. Dickinson CZ, Hendrix NS. Strontium-89 Therapy in Painful Bony Metastases. J Nucl Med Technol. 1993;21:133-7
9. FDA Label samarium-153-EDTMP [Internet]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020570s008lbl.pdf
10. Brenner W, Kampen WU, Kampen AM, Henze E. Skeletal uptake and soft-tissue retention of 186Re-HEDP and 153Sm-EDTMP in patients with metastatic bone disease. J Nucl Med Off Publ Soc Nucl Med. 2001;42:230-6
11. Goeckeler WF, Troutner DE, Volkert WA, Edwards B, Simon J, Wilson D. 153Sm radiotherapeutic bone agents. Int J Rad Appl Instrum B. 1986;13:479-82
12. DAngelo G, Sciuto R, Salvatori M, Sperduti I, Mantini G, Maini C, et al. Targeted "bone-seeking" radiopharmaceuticals for palliative treatment of bone metastases: a systematic review and meta-analysis. Q J Nucl Med Mol Imaging. 2012 Dec;56(6):538-43
13. Baczyk M, Milecki P, Baczyk E, Sowiński J. The effectivness of strontium 89 in palliative therapy of painful prostate cancer bone metastases. Ortop Traumatol Rehabil. 2003;5:364-8
14. Kraeber-Bodéré F, Campion L, Rousseau C, Bourdin S, Chatal JF, Resche I. Treatment of bone metastases of prostate cancer with strontium-89 chloride: efficacy in relation to the degree of bone involvement. Eur J Nucl Med. 2000;27:1487-93
15. Kurosaka S, Satoh T, Chow E, Asano Y, Tabata K ichi, Kimura M, et al. EORTC QLQ-BM22 and QLQ-C30 quality of life scores in patients with painful bone metastases of prostate cancer treated with strontium-89 radionuclide therapy. Ann Nucl Med. 2012;26:485-91
16. Turner SL, Gruenewald S, Spry N, Gebski V, Metastron Users Group. Less pain does equal better quality of life following strontium-89 therapy for metastatic prostate cancer. Br J Cancer. 2001;84:297-302
17. Terrisse S, Karamouza E, Parker CC, Sartor AO, James ND, Pirrie S, et al. Overall Survival in Men With Bone Metastases From Castration-Resistant Prostate Cancer Treated With Bone-Targeting Radioisotopes: A Meta-analysis of Individual Patient Data From Randomized Clinical Trials. JAMA Oncol. 2020;6:206-16
18. Dafermou A, Colamussi P, Giganti M, Cittanti C, Bestagno M, Piffanelli A. A multicentre observational study of radionuclide therapy in patients with painful bone metastases of prostate cancer. Eur J Nucl Med. 2001;28:788-98
19. Lewington VJ, McEwan AJ, Ackery DM, Bayly RJ, Keeling DH, Macleod PM, et al. A prospective, randomised double-blind crossover study to examine the efficacy of strontium-89 in pain palliation in patients with advanced prostate cancer metastatic to bone. Eur J Cancer. 1991;27:954-8
20. Pons F, Herranz R, Garcia A, Vidal-Sicart S, Conill C, Grau JJ, et al. Strontium-89 for palliation of pain from bone metastases in patients with prostate and breast cancer. Eur J Nucl Med. 1997;24:1210-4
21. Kasalický J, Krajská V. The effect of repeated strontium-89 chloride therapy on bone pain palliation in patients with skeletal cancer metastases. Eur J Nucl Med. 1998;25:1362-7
22. Fuster D, Herranz D, Vidal-Sicart S, Muñoz M, Conill C, Mateos JJ, et al. Usefulness of strontium-89 for bone pain palliation in metastatic breast cancer patients. Nucl Med Commun. 2000;21:623-6
23. Sciuto R, Festa A, Pasqualoni R, Semprebene A, Rea S, Bergomi S, et al. Metastatic bone pain palliation with 89Sr and 186Re HEDP in breast cancer patients. Breast Cancer Res Treat. 2001;66:101-9
24. Ashayeri E, Omogbehin A, Sridhar R, Shankar RA. Strontium 89 in the treatment of pain due to diffuse osseous metastases: a university hospital experience. J Natl Med Assoc. 2002;94:706-11
25. Zorga P, Birkenfeld B, Listewnik MH, Piwowarska-Bilska H. Effectiveness of strontium-89 palliative therapy in patients with painful bone metastases. Ann Acad Med Stetin. 2011;57:49-53; discussion 53.
26. Oosterhof GON, Roberts JT, de Reijke TM, Engelholm SA, Horenblas S, von der Maase H, et al. Strontium(89) chloride versus palliative local field radiotherapy in patients with hormonal escaped prostate cancer: a phase III study of the European Organisation for Research and Treatment of Cancer, Genitourinary Group. Eur Urol. 2003;44:519-26
27. Gunawardana DH, Lichtenstein M, Better N, Rosenthal M. Results of strontium-89 therapy in patients with prostate cancer resistant to chemotherapy. Clin Nucl Med. 2004;29:81-5
28. Liepe K, Kotzerke J. A comparative study of 188Re-HEDP, 186Re-HEDP, 153Sm-EDTMP and 89Sr in

the treatment of painful skeletal metastases. Nucl Med Commun. 2007;28:623-30
29. Zenda S, Nakagami Y, Toshima M, Arahira S, Kawashima M, Matsumoto Y, et al. Strontium-89 (Sr-89) chloride in the treatment of various cancer patients with multiple bone metastases. Int J Clin Oncol. 2014;19:739-43
30. Furubayashi N, Negishi T, Ura S, Hirai Y, Nakamura M. Palliative effects and adverse events of strontium-89 for prostate cancer patients with bone metastasis. Mol Clin Oncol. 2015;3:257-63
31. Ye X, Sun D, Lou C. Comparison of the efficacy of strontium-89 chloride in treating bone metastasis of lung, breast, and prostate cancers. J Cancer Res Ther. 2018;14(Supplement):S36-40
32. Serafini AN, Houston SJ, Resche I, Quick DP, Grund FM, Ell PJ, et al. Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. J Clin Oncol Off J Am Soc Clin Oncol. 1998;16:1574-81
33. Resche I, Chatal JF, Pecking A, Ell P, Duchesne G, Rubens R, et al. A dose-controlled study of 153Sm-ethylenediaminetetramethylen ephosphonate (EDTMP) in the treatment of patients with painful bone metastases. Eur J Cancer. 1997;33:1583-91
34. Menda Y, Bushnell DL, Williams RD, Miller S, Thomas MO. Efficacy and safety of repeated samarium-153 lexidronam treatment in a patient with prostate cancer and metastatic bone pain. Clin Nucl Med. 2000;25:698-700
35. Collins C, Eary JF, Donaldson G, Vernon C, Bush NE, Petersdorf S, et al. Samarium-153-EDTMP in bone metastases of hormone refractory prostate carcinoma: a phase I/II trial. J Nucl Med Off Publ Soc Nucl Med. 1993;34:1839-44
36. Tian JH, Zhang JM, Hou QT, Oyang QH, Wang JM, Luan ZS, et al. Multicentre trial on the efficacy and toxicity of single-dose samarium-153-ethylene diamine tetramethylene phosphonate as a palliative treatment for painful skeletal metastases in China. Eur J Nucl Med. 1999;26:2-7
37. Dolezal J. Systemic radionuclide therapy with Samarium-153-EDTMP for painful bone metastases. Nucl Med Rev Cent East Eur. 2000;3:161-3
38. Sapienza MT, Ono CR, Guimarães MIC, Watanabe T, Costa PA, Buchpiguel CA. Retrospective evaluation of bone pain palliation after samarium-153-EDTMP therapy. Rev Hosp Clin. 2004;59:321-8
39. Etchebehere ECS de C, Pereira Neto CAC, Lima MCL de, Santos A de O, Ramos CD, Silva CM, et al. Treatment of bone pain secondary to metastases using samarium-153-EDTMP. Sao Paulo Med J. 2004;122:208-12
40. Sartor O, Reid RH, Hoskin PJ, Quick DP, Ell PJ, Coleman RE, et al. Samarium-153-Lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. Urology. 2004;63:940-5
41. Tripathi M, Singhal T, Chandrasekhar N, Kumar P, Bal C, Jhulka PK, et al. Samarium-153 ethylenediamine tetramethylene phosphonate therapy for bone pain palliation in skeletal metastases. Indian J Cancer. 2006;43:86-92
42. Ripamonti C, Fagnoni E, Campa T, Seregni E, Maccauro M, Bombardieri E. Incident pain and analgesic consumption decrease after samarium infusion: a pilot study. Support Care Cancer Off J Multinatl Assoc Support Care Cancer. 2007;15:339-42
43. Gallicchio R, Giacomobono S, Nardelli A, Pellegrino T, Simeon V, Gattozzi D, et al. Palliative treatment of bone metastases with samarium-153 EDTMP at onset of pain. J Bone Miner Metab. 2014;32:434-40
44. Correa-González L, Arteaga de Murphy C, Pichardo-Romero P, Pedraza-López M, Moreno-García C, Correa-Hernández L. (153) Sm-EDTMP for pain relief of bone metastases from prostate and breast cancer and other malignancies. Arch Med Res. 2014;45:301-8
45. Thapa P, Nikam D, Das T, Sonawane G, Agarwal JP, Basu S. Clinical Efficacy and Safety Comparison of 177Lu-EDTMP with 153Sm-EDTMP on an Equidose Basis in Patients with Painful Skeletal Metastases. J Nucl Med. 2015;56:1513-9
46. Elzahry M, Diab W, Sinzinger H. Assessment of Bone Pain Response in Cancer Patients Receiving Single Dose of Sm-153 EDTMP Therapy. J Nucl Med Radiat Ther. 2017;8:4
47. Taylor AJ. Strontium-89 for the palliation of bone pain due to metastatic disease. J Nucl Med. 1994;35:2054
48. Lewington VJ. Bone-seeking radionuclides for therapy. J Nucl Med Off Publ Soc Nucl Med. 2005;46 Suppl 1:38S-47S
49. Ahmadzadehfar H, Essler M, Rahbar K, Afshar-Oromieh A. Radionuclide Therapy for Bone Metastases: Utility of Scintigraphy and PET Imaging for Treatment Planning. PET Clin. 2018;13:491-503
50. Dickie GJ, Macfarlane D. Strontium and samarium therapy for bone metastases from prostate carcinoma. Australas Radiol. 1999;43:476-9
51. Nair N. Relative efficacy of 32P and 89Sr in palliation in skeletal metastases. J Nucl Med.

1999;40:256-61
52. Jong JM van D de, Oprea-Lager DE, Hooft L, de Klerk JMH, Bloemendal HJ, Verheul HMW, et al. Radiopharmaceuticals for Palliation of Bone Pain in Patients with Castration-resistant Prostate Cancer Metastatic to Bone: A Systematic Review. Eur Urol. 2016;70:416-26
53. Otsuka S, Hanibuchi M, Ikuta K, Yano S, Goto H, Ogino H, et al. A bone metastasis model with osteolytic and osteoblastic properties of human lung cancer ACC-LC-319/bone2 in natural killer cell-depleted severe combined immunodeficient mice. Oncol Res. 2009;17:581-91
54. Smeland S, Erikstein B, Aas M, Skovlund E, Hess SL, Fosså SD. Role of strontium-89 as adjuvant to palliative external beam radiotherapy is questionable: results of a double-blind randomized study. Int J Radiat Oncol Biol Phys. 2003;56:1397-404
55. Heianna J, Toita T, Endo W, Kasuya G, Ariga T, Hashimoto S, et al. Concurrent use of strontium-89 with external beam radiotherapy for multiple bone metastases: early experience. Ann Nucl Med. 2015;29:848-53
56. Storto G, Klain M, Paone G, Liuzzi R, Molino L, Marinelli A, et al. Combined therapy of Sr-89 and zoledronic acid in patients with painful bone metastases. Bone. 2006;39:35-41
57. Rasulova N, Lyubshin V, Arybzhanov D, Sagdullaev Sh, Krylov V, Khodjibekov M. Optimal Timing of Bisphosphonate Administration in Combination with Samarium-153 Oxabifore in the Treatment of Painful Metastatic Bone Disease. World J Nucl Med. 2013;12:14-8
58. Baczyk M, Baczyk E, Sowiński J. Preliminary results of combined application of radioisotopes and biphosphonates in the management of pain associated with osteoblastic-osteolytic bone metastases of breast cancer. Ortop Traumatol Rehabil. 2003;5:234-7

[^{131}I]*m*IBG therapy in neuroblastoma – 35 Years of experience

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Abstract

Neuroblastoma is the most common extracranial solid malignancy of childhood. Approximately half of patients have high-risk neuroblastoma (HR-NBL), typically presenting with widespread metastatic disease at diagnosis. Despite aggressive multimodality treatment, patients with HR-NBL have a long-term survival of less than 50%, due to a high relapse/progression rate and therapy-resistant disease. To overcome therapy-resistance in neuroblastoma, researchers are exploring diverse treatment strategies including radionuclide therapy. For several decades now, radiolabelled meta-iodobenzylguanidine (*m*IBG) has been used as a theranostic (therapeutic and diagnostic) radiopharmaceutical in neuroblastoma. [^{123}I]*m*IBG imaging with scintigraphy/SPECT is the international standard to assess dissemination at diagnosis and to evaluate treatment response. In contrast, the role of [^{131}I]*m*IBG therapy is less clear. Over the past 35 years, [^{131}I]*m*IBG therapy has been studied in more than 1500 patients. In initial studies, [^{131}I]*m*IBG monotherapy was used as second-line treatment for patients with relapse/progression or refractory disease. In current applications, [^{131}I]*m*IBG therapy is combined with chemotherapy, radiosensitizers, and/or immunotherapy, also including front-line setting in patients with newly-diagnosed HR-NBL. This review provides an overview on contemporary literature regarding [^{131}I]*m*IBG therapy in HR-NBL.

Introduction

Neuroblastoma is the most common extracranial solid malignancy of childhood, with an incidence of 30 patients annually in the Netherlands (1). Patients are stratified into risk groups by age, stage, and tumour biology (figure 1) (2). Patients with low-risk neuroblastoma can show spontaneous regression, while patients with high-risk neuroblastoma (HR-NBL) frequently develop therapy-resistant tumour growth with fatal outcome. Approximately half of patients have HR-NBL at diagnosis, typically presenting as widespread metastatic disease affecting bone/bone marrow and lymph nodes (1). Standard HR-NBL treatment consists of three phases with both systemic and local therapies (2). "Induction" consists of several courses of chemotherapy, followed by primary tumour resection. During "consolidation", remaining tumour cells are eliminated by myeloablative high dose chemotherapy (HDCT), which is followed by reinfusion of hematopoietic stem cells that were harvested before (so called autologous stem cell transplantation, ASCT) and external beam radiotherapy. Lastly, any minimal residual disease is treated during "maintenance" with anti-GD2 immunotherapy (dinutuximab-beta) and isotretinoin.

Despite this aggressive multimodality treatment, long term survival of HR-NBL is only 40-50% (1,2). The most challenging problem of HR-NBL, is the high relapse/progression rate (40-50%) after initial (front-line) treatment. Relapsed/progressive disease has a dismal outcome with long term survival of less than 20% (3). Treatment options for those who fail front-line treatment are limited, mainly due to therapy-resistance. To overcome therapy-resistance in neuroblastoma, researchers are exploring new (combination) treatment strategies. Second-line treatments are based on a backbone of immunochemotherapy including irinotecan or topotecan, temozolomide, and dinutuximab-beta. In addition, individual tumours can be molecularly characterized for subsequent targeted treatment (4). Since neuroblastoma is a radiosensitive tumour, radionuclide therapy is one of the systemic treatment options.

For several decades, radiolabelled *meta*-iodobenzylguanidine (*m*IBG) has been used as theranostic (therapeutic

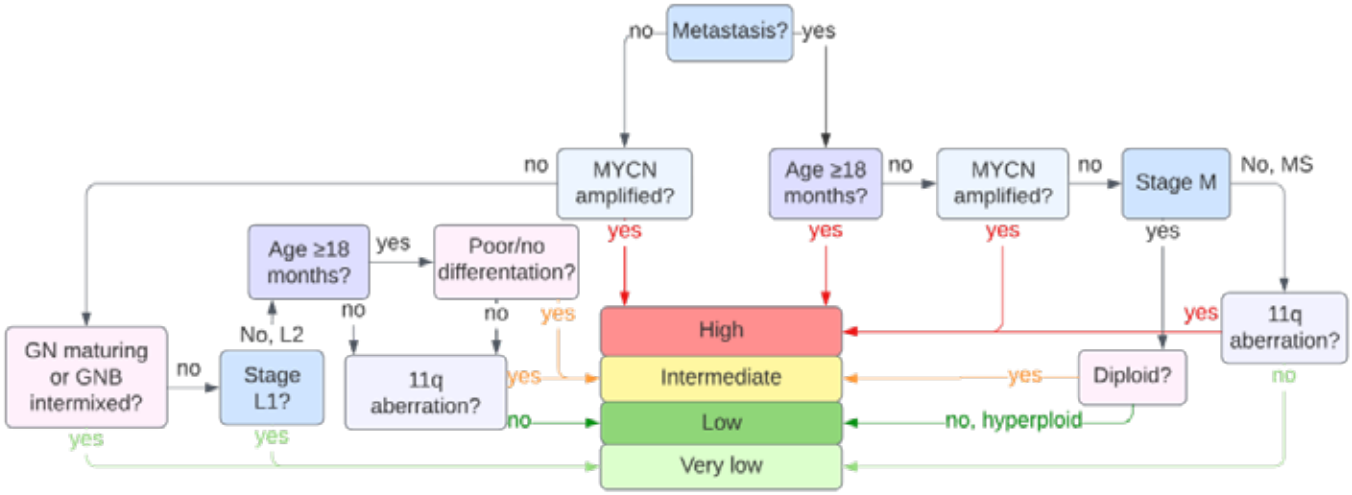

Figure 1. Neuroblastoma risk classification according to the International Neuroblastoma Risk Group.
Poor prognostic factors include age ≥18 months, more advanced disease stage, MYCN amplification, poorly differentiated or undifferentiated tumour histology, diploid DNA content, and the presence of segmental chromosome 11q aberrations.
Abbreviations: GN, ganglioneuroma; GNB, ganglioneuroblastoma.

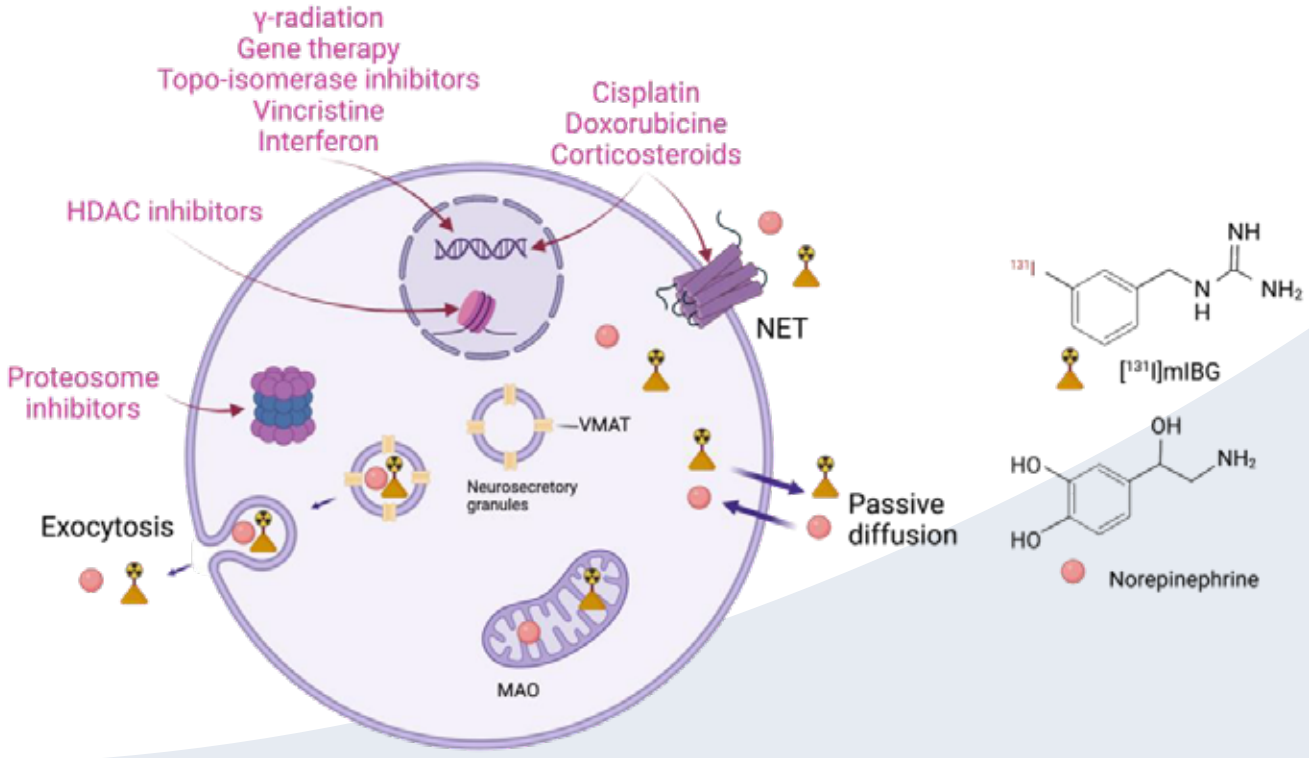

Figure 2. Mechanisms to enhance [^{131}I]*m*IBG efficacy in neuroblastoma cells. [^{131}I]*m*IBG uptake occurs mainly through (specific) active uptake via NET and to a lesser extent via (non-specific) passive diffusion. There are several strategies to increase [^{131}I]*m*IBG uptake, retention, and cytotoxicity of neuroblastoma cells. It is possible to increase the sensitivity of neuroblastomas to [^{131}I]*m*IBG therapy but also to directly increase NET mRNA expression or enhance NET function. Figure adapted from Schmidt *et al*. 2016 (4).
Abbreviations: *m*IBG, meta-iodobenzylguanidine; norepinephrine transporter, NET; HDAC, histone deacetylase; VMAT, vesicular monoamine transporter; MAO, monoamine oxidase inhibitors.

and diagnostic) radiopharmaceutical in neuroblastoma (figure 2: [^{123}I]/[^{131}I]*m*IBG scintigraphy). *m*IBG is a norepinephrine analogue that is taken up by cells via the norepinephrine transporter (NET). Neuroblastoma cells abundantly express NET and, therefore, radiolabelled *m*IBG offers excellent tumour cell targeting (5). [^{123}I]*m*IBG scintigraphy is currently the best-established and standard nuclear imaging technique to determine disease extent in patients with neuroblastoma; at initial staging and during therapeutic response monitoring. In contrast to [^{123}I]*m*IBG imaging, the role of [^{131}I]*m*IBG therapy in the management of neuroblastoma is less clear. In principle, [^{131}I]*m*IBG therapy can be an effective treatment to induce response of primary tumour and metastatic sites or to inhibit progression.

Over the past 35 years, [^{131}I]*m*IBG therapy has been studied in more than 1500 patients with HR-NBL (6). After the introduction of [^{131}I]*m*IBG therapy in neuroblastoma (1984), many trials were performed to establish the feasibility, toxicity, and maximum tolerated activity of [^{131}I]*m*IBG monotherapy (6). Matthay *et al*. (1998) showed that the maximum tolerated activity was 444 MBq/kg, however, a higher ("myeloablative") activity of [^{131}I]*m*IBG therapy can be administered if combined with ASCT (7). Later, combination treatments were investigated to increase the therapeutic effect of [^{131}I]*m*IBG with a variety of chemotherapeutic agents, radiosensitizers (figure 3), and immunotherapy (6).
In early studies, [^{131}I]*m*IBG therapy was mainly studied as second-line (salvage) treatment in HR-NBL patients who failed front-line treatment. In the past 10 years, studies have focused on integrating [^{131}I]*m*IBG therapy in front-line treatment of HR-NBL. It is hypothesized that early treatment with [^{131}I]*m*IBG therapy may prevent the development of therapy-resistant tumour cells.
The aim of this review was to provide an overview on [^{131}I]*m*IBG therapy in the treatment of HR-NBL over the past 35 years, by discussing several major studies and providing an update of contemporary literature and ongoing studies.

Front-line [^{131}I]*m*IBG therapy

Upfront

Upfront [^{131}I]*m*IBG therapy in the treatment of HR-NBL is an approach that was pioneered in the Netherlands. In a prospective (phase II) trial, de Kraker *et al*. (2008) included 44 patients with HR-NBL between 1989 and 1999 (8). Patients were treated with at least two cycles (median 3, maximum 5) of [^{131}I]*m*IBG therapy at four-week intervals (fixed activity of 7.4 GBq for first cycle, 3.7–5.6 GBq for further cycles). Cumulative activity per patient ranged from 13 to 35 GBq (median 18.5). Forty-one patients were evaluable after two courses of [^{131}I]*m*IBG therapy, 27 (66%) of whom had a partial or complete response. In 24 patients (group A), [^{131}I]*m*IBG cycles were continued as induction treatment, as replacement of induction chemotherapy. The other 17 patients (group B) continued with cycles of induction chemotherapy, the most frequent reason being stable disease. Use of these two induction regimens resulted in a (partial/complete) response rate of 73% in the 41 patients. Complete macroscopic resection of the primary tumour was possible in 67%, which is an important advantage of upfront [^{131}I]*m*IBG therapy. Only 11 patients from group A and 6 patients from group B continued with consolidation (HDCT and ASCT), and maintenance (isotretinoin). Five-year event-free survival (EFS) and overall survival (OS) in this cohort was remarkably poor: 12% and 15%, respectively.
Subsequently, Bleeker et al. (2013) retrospectively analysed acute toxicity in the same HR-NBL cohort, plus additional patients (of all stages) after two cycles of upfront [^{131}I]*m*IBG therapy (9). This cohort (n=66) was unique in investigating toxicity of [^{131}I]*m*IBG without prior treatment, in the first month following [^{131}I]*m*IBG therapy. The median first administered activity was 441 MBq/kg (range 157-804 MBq/kg) for the first cycle and 328 MBq/kg (range 113-727 MBq/kg) for the second cycle. Upfront [^{131}I]*m*IBG therapy had an acceptable safety profile if the condition of the patient was taken into consideration.

As a result of these studies, upfront [^{131}I]*m*IBG therapy was incorporated in the Dutch NBL2009 study for patients with HR-NBL. Within two weeks of diagnosis, two cycles of [^{131}I]*m*IBG therapy (7.4 and 5.5 GBq) were administered within a four-week interval. At a 21-day interval after the second cycle, patients started induction chemotherapy. Patients were excluded from [^{131}I]*m*IBG therapy if they were in poor clinical condition (uncontrollable hypertension, orbital masses, and/or pleural effusion) or in case of [^{131}I]*m*IBG negative disease. Kraal *et al*. (2017) conducted a retrospective multicentre study of this treatment regimen (2005-2011) in 32 HR-NBL patients (10). No stem cell rescue was needed after [^{131}I]*m*IBG therapy. The partial/complete response rates after [^{131}I]*m*IBG therapy was 38% and after consolidation 71% . However, upfront [^{131}I]*m*IBG therapy was removed from the Dutch treatment protocol in 2016, as it was frequently not feasible due to weak clinical condition of patients or logistical reasons.

Induction/consolidation

The Children's Oncology Group (COG) evaluated the safety and feasibility of [^{131}I]*m*IBG therapy at the end of induction in a (single-

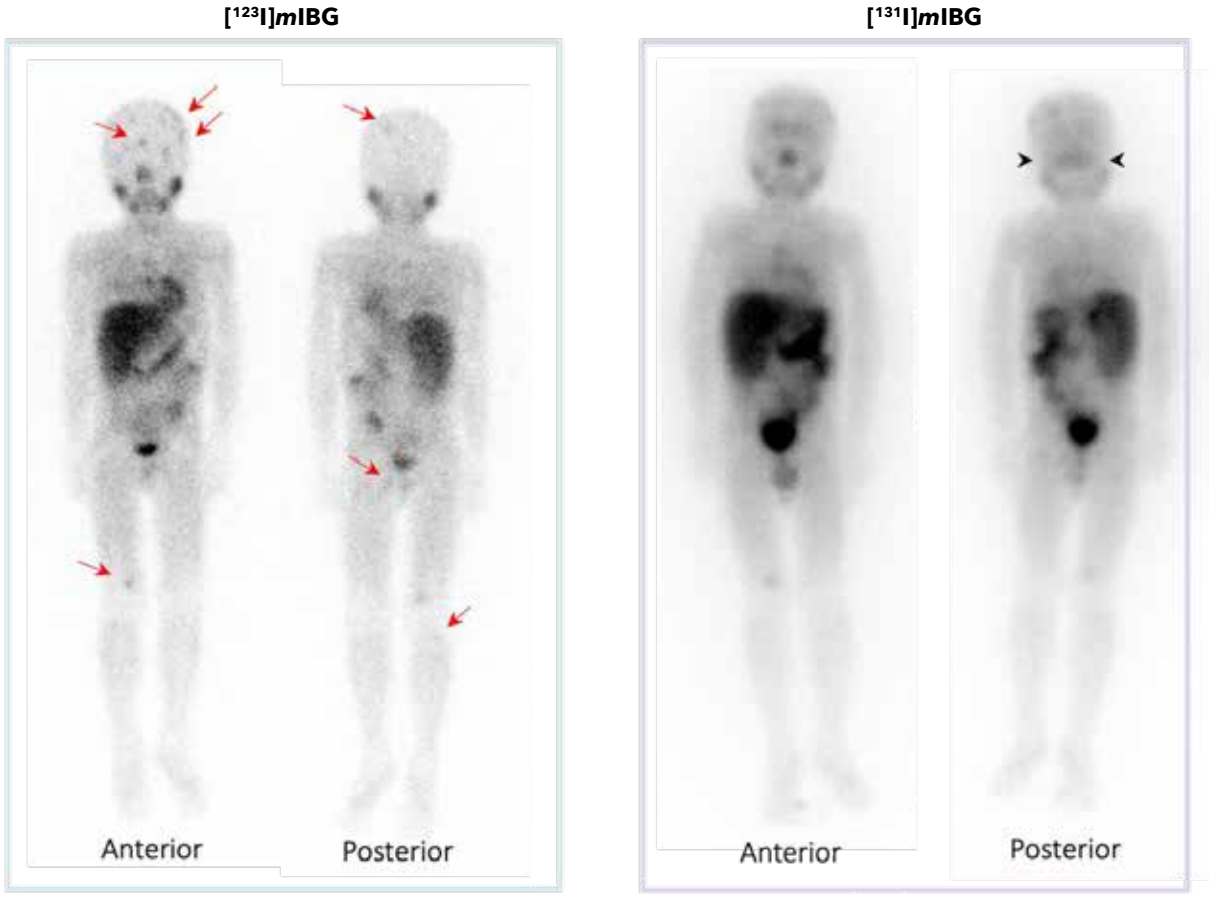

Figure 3. Distribution of meta-[^{123}I]/[^{131}I]iodobenzylguanidine on scintigraphy.
^{123}I is a principal γ emitter (T½ 13 hours), whereas ^{131}I emits both γ and β radiation (T½ 8 days). Because of the higher energy of ^{131}I γ radiation (364 keV, abundance 81%) compared to ^{123}I γ radiation (159 keV, abundance 83%), [^{131}I]*m*IBG scintigraphy is performed with high-energy-general-purpose collimators, which have a slightly lower resolution than the medium-energy-general-purpose collimators used for [^{123}I]*m*IBG scintigraphy. Physiological uptake of *m*IBG occurs in the salivary glands, heart, liver, thyroid (if not or inadequately blocked with thyroid prophylaxis), lacrimal glands, adrenal glands, nasal mucosa, myocardium; and in lesser extent in the spleen, lungs, skeletal muscles, and brown adipose tissue. As *m*IBG is excreted by the urinary tract and gastro-intestinal system, activity is seen in the bladder and intestines. Uptake in cerebellum and basal ganglia (black arrowheads) is only seen on post [^{131}I]*m*IBG therapy scintigraphy and not for diagnostic activities of [^{123}I]*m*IBG. Red arrows indicate pathological skeletal uptake on [^{123}I]*m*IBG scintigraphy. As a higher activity is used for [^{131}I]*m*IBG therapy compared to diagnostic [^{123}I]*m*IBG imaging, often more lesions are visible on post-[^{131}I]*m*IBG scintigraphy.

arm) pilot study (ANBL-09P1) (11). Patients who completed five cycles of induction chemotherapy were eligible to undergo [^{131}I]*m*IBG therapy instead of the sixth cycle of chemotherapy. The trial was designed to an "activity" escalation (444, 555, and 666 MBq/kg), with a required 10-week gap before continuing with HDCT of consolidation. Of the 68 eligible patients at the end of induction chemotherapy, 59 (86.8%) received [^{131}I]*m*IBG therapy. Of the 45 patients evaluable for [^{131}I]*m*IBG and HDCT, 37 (82.2%) received this combination. At a 555 MBq/kg activity level, the feasibility rate of [^{131}I]*m*IBG was 97% (95% CI: 83-99%) and the rate of [^{131}I]*m*IBG followed by HDCT after 10 weeks was 81% (95% CI: 60–92%). Three-year EFS of [^{131}I]*m*IBG and HDCT was 60% ± 8.3. This pilot study demonstrated the feasibility and tolerability of [^{131}I]*m*IBG therapy followed by consolidation in newly-diagnosed patients with HR-NBL. The study also laid the groundwork for the ongoing COG ANBL1531 trial (table 1). This large multicentre trial will study the role of [^{131}I]*m*IBG

Table 1. Ongoing multicentre trials on [^{131}I]*m*IBG therapy in patients with high-risk neuroblastoma.

Clinical trial name*	Centres (countries)	Clinical setting	Trial description	Treatment arms	Primary endpoint
OPTIMUM NCT03561259	21 (United States)	Relapse Progression	Phase II n=60	1) *m*IBG monotherapy 2) *m*IBG, vorinostat	Overall response
NANT2017-01 NCT03332667	12 (United States)	Relapse Progression Refractory disease	Phase I n=45	1) *m*IBG, dinutuximab 2) *m*IBG, dinutuximab, vorinostat	Safety/tolerability
MiNivAN NCT02914405	3 (United Kingdom and United States)	Relapse Progression Refractory disease	Phase I n=36	1) *m*IBG, nivolumab 2) *m*IBG, nivolumab, low dose dinutuximab 3) *m*IBG, nivolumab, full dose dinutuximab	Safety/tolerability
VERITAS NCT03165292	9 (France, Austria, Italy, Netherlands, Spain)	Refractory disease	Phase II RCT n=150	1) TEMIRI, *m*IBG, topotecan, ASCT 2) TEMIRI, HD thiotepa, ASCT	3-year EFS
ANBL1531 NCT03126916	160 (United States, Canada, Puerto Rico)	Front-line	Phase III RCT n=658	1) TC + CEM, tandem ASCT 2) *m*IBG, TC + CEM, tandem ASCT 3) *m*IBG, HD BuMel, single ASCT	3-year EFS

* ClinicalTrials.gov Identifier
Abbreviations: TEMIRI, Temozolomide-Irinotecan; *m*IBG, *meta*-[^{131}I]iodobenzylguanidine; RCT, randomized controlled trial; TC, thiotepa cyclophosphamide; BuMel, busulfan melphalan; CEM, carboplatin etoposide melphalan; ASCT, autologous stem cell transplantation, EFS, event-free survival.

therapy, double ASCT, and ALK-inhibitor crizotinib in 658 newly-diagnosed patients with HR-NBL. Patient with tumours harbouring ALK mutations are treated in the two non-randomized treatment arms. Patients without ALK mutations and [^{123}I]*m*IBG-positive disease are randomized among three other treatment arms. In two of the three arms patients are treated with [^{131}I]*m*IBG therapy after three cycles of induction chemotherapy. The aim of the randomization is to determine whether the addition of [^{131}I]*m*IBG during induction improves 3-year EFS with acceptable long-term toxicity. It should be mentioned that this study is the first randomized controlled trail (RCT) that will compare [^{131}I]*m*IBG therapy to no [^{131}I]*m*IBG therapy. Lee *et al*. (2017) performed a single arm, phase I/II trial (SMC NB-2009), in which [^{131}I]*m*IBG therapy (444 or 666 MBq/kg) was incorporated into consolidation (tandem HDCT, ASCT, and local radiotherapy) (12). Between 2009–2013, 54 patients with newly-diagnosed HR-NBL were included after 9 cycles of induction chemotherapy. Of these 54 patients, 47 received tandem HDCT (43 with [^{131}I]*m*IBG therapy), ASCT, and radiotherapy; and continued with maintenance (isotretinoin, immunotherapy, interleukin-2). The 5-year EFS rate and OS rate were 58 and 72%, respectively. Results were compared to the previous protocol (SMC NB-2004), in which HR-NBL patients were treated with total body irradiation instead of [^{131}I]*m*IBG therapy, with significant toxicity. [^{131}I]*m*IBG could achieve an equivalent survival rate (67.5 vs. 58%) with lower toxicity.

Second line [^{131}I]*m*IBG therapy

[^{131}I]*m*IBG therapy has also been studied in patients who failed front-line treatment. Three types of treatment failure in neuroblastoma can be recognized.
Recurrent disease after a complete response to therapy, often referred to as "relapse"; Progressive disease after an incomplete response to therapy; often referred to as "progression"; Residual (non-progressive)

disease after completing induction chemotherapy, requiring alternative therapy to improve remission status before proceeding to consolidation treatment; often referred to as "refractory".
Nevertheless, definitions of "relapse", "progression" and "refractory" often differ between studies; and different types of treatment failure are often pooled and studied together.

Meta-analysis

In a meta-analysis, Wilson *et al*. (2014) analysed 27 studies including 1121 patients who failed front-line treatment and underwent [^{131}I]*m*IBG therapy as second-line treatment between 1984-2005 (13). In all studies, patients with [^{123}I]*m*IBG-negative disease were not eligible for [^{131}I]*m*IBG therapy. There were 20 studies on [^{131}I]*m*IBG monotherapy and seven studies where [^{131}I]*m*IBG was combined with chemotherapy. Only four studies were comparative studies, all non-randomized. Study populations ranged from 10 to 164 patients. Mean (complete or partial) response rates, reported in 25 studies (782 patients), varied between 4-75%, with an overall mean response rate of 32% (95% CI 29-36%). In patients who received [^{131}I]*m*IBG monotherapy, response rate was 32% (199/629) compared to 39% in patients who received concomitant chemotherapy (48/124). However, there was no evidence that these responses lead to a better EFS or OS.

In the largest comparative study, 111 patients from the German NB97 Trial with stage 4 refractory HR-NBL after induction chemotherapy, were retrospectively identified (14). Patients in the intervention arm (n=40) received [^{131}I]*m*IBG therapy (444 MBq/kg). The control arm (n=71) consisted of patients whose treating physicians decided against [^{131}I]*m*IBG therapy. In the univariate analysis, there was a statistically significant difference in 3-year EFS and OS between the two arms. However, this difference was confounded as the intervention arm more often received consolidation treatment afterwards. In the subgroup analysis of patients who underwent consolidation therapy (n=66), outcomes for the [^{131}I]*m*IBG arms vs. control arm were more similar: 3-year EFS 49% vs. 33%, respectively (p=0.171) and OS 59% vs. 59%, respectively (p=0.285). By multivariate analysis, [^{131}I]*m*IBG therapy had no statistically significant impact on 3-year EFS (p=0.494) and OS (p=0.891). In conclusion, an independent advantage of [^{131}I]*m*IBG therapy could not be proven, which emphasises the importance of confounding factors (and other forms of bias) in non-randomized comparative studies. Results on [^{131}I]*m*IBG therapy of the latest German NB2004 Trial have not been reported yet (4).

In the largest single-arm (phase II) trial of Matthay et al. (2007), 164 HR-NBL patients with any type of treatment failure were prospectively included (15). Most patients (90%) received an administered activity of 666 MBq/kg and 33% of patients were supported by ASCT. Overall (complete or partial) response rate was 36% (95% CI 29-44%) and 34% of patients had stable disease. One-year EFS was 18% and the 2-year OS was 29%.
Another single-arm prospective trial (Johnson *et al*. 2011) studied the safety and efficacy of tandem [^{131}I]*m*IBG therapy (16). In total, 76 patients who failed to respond to standard induction therapy were included. After a first cycle of [^{131}I]*m*IBG therapy (666 MBq/kg), patients who had available hematopoietic stem-cells and showed either response or stable disease, followed with a second cycle (6–14 weeks after the initial cycle). After the first cycle, 30% of 76 patients showed a partial/complete response and 49% stable disease. After the second cycle (n=41), partial/complete response was seen in 29% and stable disease in 37%. Authors concluded that a second cycle of [^{131}I]*m*IBG therapy safely reduces disease burden in patients with HR-NBL that failed front-line treatment. Interestingly, in five patients [^{123}I]*m*IBG scintigraphy showed complete response but post-[^{131}I]*m*IBG scintigraphy showed substantial disease burden. This supports the potential use of [^{131}I]*m*IBG therapy in cases of apparent complete remission on [^{123}I]*m*IBG scintigraphy.

UCSF and NANT trials

Results of a large retrospective cohort study in patients with relapsed/progressive and refractory HR-NBL who were treated with [^{131}I]*m*IBG therapy at UCSF Benioff Children's Hospital (NCT01370330); or New Approaches to Neuroblastoma Therapy (NANT) clinical trials, between 1996 and 2014, was reported by Zhou et al. in 2015 (17). In total, 218 patients were analysed, 102 (47%) of whom were also included by the meta-analysis of Wilson et al. (2014). Half of patients received an activity of 666 MBq/kg [^{131}I]*m*IBG or higher. Complete or partial response rate after [^{131}I]*m*IBG therapy was 27%; without significant difference between relapse/progression vs. refractory disease. However, patients with relapse had a lower 2-year OS after [^{131}I]*m*IBG therapy compared to patients with refractory disease (38.7% vs. 65.3%, respectively, p<0.001).

In one of the included phase II trials (NANT2001-02), [^{131}I]*m*IBG therapy was incorporated before consolidation in patients who failed induction therapy (18). In the total study population (n=50), two cohorts could be identified: 1) efficacious cohort (n=8) with a partial response at the end of induction chemotherapy; 2) inefficacious cohort with no response to induction therapy (n=27) or progressive disease (n=15). Patients were treated with [^{131}I]*m*IBG therapy (444 MBq/kg), followed

by consolidation treatment after 14-17 days. Response assessment was performed two months after the end of consolidation. Complete or partial responses were seen in 10% of the evaluable 41 patients in the inefficacious cohort. For the inefficacious cohort, 3-year EFS and OS were 20% and 62%, respectively. The addition of [^{131}I]*m*IBG before consolidation had comparable toxicities to consolidation treatment alone in these already highly pre-treated patients and did not affect hematologic recovery after ASCT. These results led to further studies on this combination.

NCT02258815 trial

Recently, results of a phase I/II trial (NCT02258815) were published in which 68 patients that presented with relapse (n=54) or refractory (n=3) HR-NBL after consolidation between 2010 and 2017 were included (19). Patients received second-line treatment with haploidentical stem cell transplant (haplo-SCT) followed by six cycles of dinutuximab-beta plus three cycles of interleukin-2. At the discretion of the treating centres, [^{131}I]*m*IBG therapy (8-15.2 GBq) was given to 43 (63.2%) patients before haplo-SCT. [^{131}I]*m*IBG therapy was associated with a significant higher OS and EFS. From time of relapse, 5-year OS for [^{131}I]*m*IBG therapy yes vs. no was 67 (95% CI 51-79%) vs. 31% (95% CI 14-50); and 5-year EFS was 55% (95% CI 39-69) vs. 23% (95% CI 8–41), respectively. In the multivariate analysis, the hazard ratio of [^{131}I]*m*IBG therapy (compared to no [^{131}I]*m*IBG therapy) was 0.3 (95% CI 0.1-0.8) for OS and 0.3 (0.1-0.7) for EFS.

Radiosensitizer studies

Researchers are investigating the combination of [^{131}I]*m*IBG therapy with radiosensitizers that enhance the sensitivity of neuroblastoma cells to radiation therapy (figure 3) (6). Phase I studies (NANT2004-06, NCT01313936, NANT2007-03) in HR-NBL patients with any type of treatment failure, studied the combined use of vincristine and irinotecan together with [^{131}I]*m*IBG (666 MBq/kg) (20); or vorinostat, a histone deacetylase inhibitor, with [^{131}I]*m*IBG (666 MBq/kg) (21).
These studies were followed by a larger phase II randomized trial (NANT2011-01) in which these two regimens were compared to [^{131}I]*m*IBG monotherapy in 114 HR-NBL patients with all types of treatment failure with more than one [^{123}I]*m*IBG-positive site between 2014 and 2019 (22). Administered activity for [^{131}I]*m*IBG was 666 MBq/kg combined with ASCT. Included patients (n=105) were randomly allocated to one of three treatment arms: A. [^{131}I]*m*IBG and vorinostat (n=34); B. [^{131}I]*m*IBG, vincristine, and irinotecan (n=35); C. [^{131}I]*m*IBG monotherapy (n=36). Across the three study arms, 20% (21/105) had an objective response to the treatment. An improved response rate was observed in patients treated with arm A compared with arms B or C. Partial or complete response rates for arms A, B, and C, after [^{131}I]*m*IBG therapy were 32% (95% CI 18-51), 14% (5-31%) and 17% (5-30), respectively. Rates of any grade ≥3 non-hematologic toxicity after the [^{131}I]*m*IBG therapy were 19%, 49%, and 35%, respectively. [^{131}I]*m*IBG and vorinostat (arm A) is likely the arm with the highest true response rate with manageable toxicity. The combination of vincristine and irinotecan (arm B) does not appear to improve the response and was associated with increased toxicity.

Ongoing trials

There are several ongoing trials on [^{131}I]*m*IBG therapy in the second-line treatment, focusing on the combination of [^{131}I]*m*IBG with radiosensitizers and immunotherapy (table 1). OPTIMUM (NCT03561259) is a two-arm, phase II trial, in which [^{131}I]*m*IBG is combined with the radiosensitiser vorinostat and compared to [^{131}I]*m*IBG monotherapy in patients with relapse/progression. Primary outcome is overall response. Secondary outcomes are durability of effect (after 12 weeks, 2 years), relative Curie score (after 6 weeks, 12 weeks, and 2 years), and safety (including correlation with whole body radiation dose).
NANT2017-01 (NCT03332667) is a two-arm, phase I trial, in patients with relapse/progression, comparing [^{131}I]*m*IBG therapy with dinutuximab-beta to [^{131}I]*m*IBG therapy with dinutuximab-beta and vorinostat. The primary outcome is safety/tolerability and secondary outcome is overall response. Preliminary results on the combination of [^{131}I]*m*IBG therapy with standard doses of dinutuximab-beta and GM-CSF were presented in a conference abstract (23). This radioimmunotherapy regimen was well-tolerated without additive toxicity. A recommended activity of 666 MBq/kg [^{131}I]*m*IBG therapy was suggested. Preliminary efficacy data are encouraging in this heavily pre-treated patient population and a phase II trial is underway.
MiNivAN (NCT02914405) is a three-arm trial, in which [^{131}I]*m*IBG therapy is studied in combination with immune check-point inhibitor nivolumab and two different doses of dinutuximab-beta. The design is a treatment escalation study. Primary outcome is safety/tolerability. Secondary outcomes are EFS, overall response, and associations between KIR/KIR-Ligand or FcγR genotype and response.
The only randomized trial in refractory patients is VERITAS (NCT03165292), a European study. Patients with refractory disease after induction chemotherapy (SIOPEN score >3) are included and randomized into two treatment intensification strategies. All patients receive three courses of temozolomide and irinotecan. Then

randomization arm A receives two cycles of [^{131}I]*m*IBG therapy combined with topotecan and followed by ASCT; randomization arm B receives high dose thiotepa followed by ASCT. Afterwards, patients continue with standard consolidation and maintenance. Primary outcome is EFS. Secondary outcomes are OS, safety, overall response, and feasibility of [^{131}I]*m*IBG/topotecan in a multicentre setting. Unfortunately, this trial was recently discontinued, due to less than expected recruitment and limited availability of [^{131}I]*m*IBG in some centres.

Toxicity of [^{131}I]*m*IBG therapy

Toxicities associated with [^{131}I]*m*IBG therapy can be divided in three categories: acute events, early side effects, and late effects. As most patients are treated with several other therapies before/after [^{131}I]*m*IBG therapy, toxicity caused by [^{131}I]*m*IBG alone is difficult to determine.

Acute events occur within hours or days of [^{131}I]*m*IBG administration and are mostly activity-dependent. The cohort of Bleeker et al. (2013) studying upfront [^{131}I]*m*IBG therapy is unique in investigating toxicity of [^{131}I]*m*IBG alone. During intravenous infusion of [^{131}I]*m*IBG over 60-120 min, less than 10% of patients experience transient tachycardia or hypertension, due to increased sympathetic activity (6). Within hours/days, patients may experience nausea and vomiting (20%, max. grade II radiation gastritis (9)); and/or radiation sialadenitis (50%), all typically managed by supportive care (6).

Early side effects occur within weeks, with the primary toxicity being hematotoxicity. Hematotoxicity is more common in patients who receive higher activities of [^{131}I]*m*IBG therapy, those with bone marrow metastases, and those who are heavily pre-treated. Hematotoxicity is activity-dependent, often occurring in an administered activity > 444 MBq/kg (7). Activities > 555 MBq/kg are considered myeloablative and require stem cell rescue (6). Patients with hematotoxicity typically present with myelosuppression (anemia, thrombocytopenia, neutropenia, and/or lymphopenia), 2-4 weeks after [^{131}I]*m*IBG infusion, which may persist for several months (6). With upfront [^{131}I]*m*IBG therapy, thrombocytopenia, anemia or leukocytopenia occurred in up to 5% of patients after the first [^{131}I]*m*IBG therapy and in 3% of patients after the second; and did not result in episodes of major bleeding (9). No stem cell rescue was needed. Non-hematologic grade 3-4 toxicities are rare when [^{131}I]*m*IBG is administered as a single agent. Organ toxicities increase when [^{131}I]*m*IBG is used in combination with myeloablative doses of chemotherapy, with hepatic toxicities approaching 15% in this situation (6).

Late effects can occur months or years after [^{131}I]*m*IBG therapy, the most frequent being thyroid damage. Despite the use of thyroid blocking agents, free ^{131}I may accumulate in the thyroid gland. In a study by van Santen *et al*. (2002), 22 of 42 patients with neuroblastoma presented with (subclinical) hypothyroidism after a mean of 1.4 years after [^{131}I]*m*IBG therapy, eight of whom required thyroxine replacement therapy (24). In a follow-up study, eight (50%) of sixteen survivors developed hypothyroidism and required thyroxine after a median of 15.5 years post-[^{131}I]*m*IBG therapy (25). Thyroid nodules were found in nine survivors, two of whom were diagnosed with papillary thyroid carcinoma. In retrospect, these patients had received adequate thyroid protection, and no thyroidal [^{131}I]*m*IBG uptake was observed on post-[^{131}I]*m*IBG imaging. In addition, primary ovarian insufficiency has been documented in two patients who were treated with only [^{131}I]*m*IBG therapy suggesting that [^{131}I]*m*IBG therapy alone may damage the female gonads (26). Secondary malignancies, such as acute myelogenous leukaemia and myelodysplastic syndrome, have been reported in <5% of patients after [^{131}I]*m*IBG therapy (6). Nevertheless, the causal relation between [^{131}I]*m*IBG therapy and the occurrence of late effects is confounded by multimodality treatment.

Discussion

Despite the challenges of performing [^{131}I]*m*IBG studies in neuroblastoma, this form of therapy has been studied in more than 1500 children with HR-NBL. Thirty-five years of experience show that [^{131}I]*m*IBG therapy can be an effective treatment to reduce tumour burden in approximately one third of children. The independent effect of [^{131}I]*m*IBG therapy on long-term survival and side effects remain unclear. Up till recent years, no survival benefit for [^{131}I]*m*IBG therapy could be proven. However, the introduction of [^{131}I]*m*IBG combination therapies shows promise for improving EFS and OS, with tolerable (hemato) toxicity. Nevertheless, caution is warranted because of potential long-term toxicity, such as thyroidal/gonadal dysfunction, and secondary malignancies.

The lack of comparative studies, many confounding factors, and other forms of bias make it difficult to assess the true effect of [^{131}I]*m*IBG therapy. Despite more than 50 published studies, there are no RCTs that compare [^{131}I]*m*IBG therapy to no [^{131}I]*m*IBG therapy. RCTs are crucial to study the efficacy and (long-term) safety of [^{131}I]*m*IBG monotherapy and different combination therapies. Furthermore, comparison between trials is difficult because of large heterogeneity in patient population, treatment activity/schedule, and reporting of outcomes.

With an objective tumour response rate of approximately 30%, apparently not all patients respond well to

[^{131}I]*m*IBG therapy. It is important to identify which patients most likely benefit from [^{131}I]*m*IBG therapy. Therefore, efficacy of [^{131}I]*m*IBG therapy should be studied in different patient populations, for example for different types of treatment failure. Currently, the activity of [^{131}I]*m*IBG (MBq) to be administered is based on the patient's weight; and administered activity is often used as a measure to correlate with response rates and other outcomes. More preferable would be to determine the optimal activity with more standardized techniques such as [^{124}I]*m*IBG PET, which enables accurate quantification of *m*IBG uptake and anticipated whole-body/tumour absorbed doses, and to correlate personalized dosimetry with response.

Often, tumour lesions are missed on [^{123}I]*m*IBG scintigraphy/SPECT because of its suboptimal resolution (16). There is a need for better diagnostic imaging that can detect the full disease extent, aid in the selection of patients for [^{131}I]*m*IBG therapy, and assessment of post-[^{131}I]*m*IBG response. Currently, PET radiopharmaceuticals are under investigation, such as [^{124}I]*m*IBG and [^{18}F]mFBG (27).
In conclusion, [^{131}I]*m*IBG combination treatments hold great promise for improving outcomes for patients with HR-NBL. However, [^{131}I]*m*IBG therapy does not hold a standard position in treatment of HR-NBL and continues to be studied in trials and off-protocol. Future studies, preferably in the form of RCTs, will hopefully define the optimal use of [^{131}I]*m*IBG therapy in the front- or second-line treatment of HR-NBL.

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References

1. Tas ML, Reedijk AMJ, Karim-Kos HE, Kremer LCM, van de Ven CP, Dierselhuis MP, et al. Neuroblastoma between 1990 and 2014 in the Netherlands: Increased incidence and improved survival of high-risk neuroblastoma. Eur J Cancer [Internet]. 2020;124:47-55. Available from: https://doi.org/10.1016/j.ejca.2019.09.025
2. Pinto NR, Applebaum MA, Volchenboum SL, Matthay KK, London WB, Ambros PF, et al. Advances in Risk Classification and Treatment Strategies for Neuroblastoma. J Clin Oncol [Internet]. 2015;33(27):3008-17. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26304901
3. Moreno L, Rubie H, Varo A, Le Deley MC, Amoroso L, Chevance A, et al. Outcome of children with relapsed or refractory neuroblastoma: A meta-analysis of ITCC/SIOPEN European phase II clinical trials. Pediatr Blood Cancer [Internet]. 2017;64:25-31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27555472
4. Schmidt M, Hero B, Simon T. I-131-mIBG therapy in neuroblastoma: established role and prospective applications. Clin Transl Imaging [Internet]. 2016;4:87-101. Available from: https://doi.org/10.1007/s40336-016-0173-z
5. Vik TA, Pfluger T, Kadota R, Castel V, Tulchinsky M, Farto JCA, et al. (123)I-mIBG scintigraphy in patients with known or suspected neuroblastoma: Results from a prospective multicenter trial. Pediatr Blood Cancer [Internet]. 2009;52:784-90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19185008
6. Parisi MT, Eslamy H, Park JR, Shulkin BL, Yanik GA. 131I-Metaiodobenzylguanidine Theranostics in Neuroblastoma: Historical Perspectives; Practical Applications. Semin Nucl Med. 2016;46:184-202
7. Matthay KK, DeSantes K, Hasegawa B, Huberty J, Hattner RS, Ablin A, et al. Phase I dose escalation of 131I-metaiodobenzylguanidine with autologous bone marrow support in refractory neuroblastoma. J Clin Oncol Off J Am Soc Clin Oncol. 1998;16:229-36
8. de Kraker J, Hoefnagel KA, Verschuur AC, van Eck B, van Santen HM, Caron HN. Iodine-131-metaiodobenzylguanidine as initial induction therapy in stage 4 neuroblastoma patients over 1 year of age. Eur J Cancer. 2008;44:551-6
9. Bleeker G, Schoot RA, Caron HN, de Kraker J, Hoefnagel CA, van Eck BL, et al. Toxicity of upfront 131I-metaiodobenzylguanidine (131I-MIBG) therapy in newly diagnosed neuroblastoma patients: a retrospective analysis. Eur J Nucl Med Mol Imaging. 2013;40:1711-7
10. Kraal KCJM, Bleeker GM, van Eck-Smit BLF, van Eijkelenburg NKA, Berthold F, van Noesel MM, et al. Feasibility, toxicity and response of upfront metaiodobenzylguanidine therapy therapy followed by German Pediatric Oncology Group Neuroblastoma 2004 protocol in newly diagnosed stage 4 neuroblastoma patients. Eur J Cancer. 2017;76:188-96
11. Weiss BD, Yanik G, Naranjo A, Zhang FF, Fitzgerald W, Shulkin BL, et al. A safety and feasibility trial of (131) I-MIBG in newly diagnosed high-risk neuroblastoma: A Children's Oncology Group study. Pediatr Blood Cancer. 2021;68:e29117
12. Lee JW, Lee S, Cho HW, Ma Y, Yoo KH, Sung KW, et al. Incorporation of high-dose (131) I-metaiodobenzylguanidine treatment into tandem high-dose chemotherapy and autologous stem cell transplantation for high-risk neuroblastoma: results of the

SMC NB-2009 study. J Hematol Oncol. 2017;10:108
13. Wilson JS, Gains JE, Moroz V, Wheatley K, Gaze MN. A systematic review of 131I-meta iodobenzylguanidine molecular radiotherapy for neuroblastoma. Eur J Cancer. 2014;50:801-15
14. Schmidt M, Simon T, Hero B, Eschner W, Dietlein M, Sudbrock F, et al. Is there a benefit of 131 I-MIBG therapy in the treatment of children with stage 4 neuroblastoma? A retrospective evaluation of The German Neuroblastoma Trial NB97 and implications for The German Neuroblastoma Trial NB2004. Nuklearmedizin. 2006;45:140-5
15. Matthay KK, Yanik G, Messina J, Quach A, Huberty J, Cheng S-C, et al. Phase II study on the effect of disease sites, age, and prior therapy on response to iodine-131-metaiodobenzylguanidine therapy in refractory neuroblastoma. J Clin Oncol Off J Am Soc Clin Oncol. 2007;25:1054-60
16. ohnson K, McGlynn B, Saggio J, Baniewicz D, Zhuang H, Maris JM, et al. Safety and efficacy of tandem 131 I-metaiodobenzylguanidine infusions in relapsed/refractory neuroblastoma. Pediatr Blood Cancer [Internet]. 2011;57:1124-9. Available from: http://doi.wiley.com/10.1002/pbc.23062
17. Zhou MJ, Doral MY, DuBois SG, Villablanca JG, Yanik GA, Matthay KK. Different outcomes for relapsed versus refractory neuroblastoma after therapy with (131)I-metaiodobenzylguanidine ((131)I-MIBG). Eur J Cancer. 2015;51:2465-72
18. Yanik GA, Villablanca JG, Maris JM, Weiss B, Groshen S, Marachelian A, et al. 131I-metaiodobenzylguanidine with intensive chemotherapy and autologous stem cell transplantation for high-risk neuroblastoma. A new approaches to neuroblastoma therapy (NANT) phase II study. Biol blood marrow Transplant J Am Soc Blood Marrow Transplant. 2015;21:673-81
19. Flaadt T, Ladenstein RL, Ebinger M, Lode HN, Arnardóttir HB, Poetschger U, et al. Anti-GD2 Antibody Dinutuximab Beta and Low-Dose Interleukin 2 After Haploidentical Stem-Cell Transplantation in Patients With Relapsed Neuroblastoma: A Multicenter, Phase I/II Trial. J Clin Oncol Off J Am Soc Clin Oncol. 2023 Feb;JCO2201630
20. DuBois SG, Allen S, Bent M, Hilton JF, Hollinger F, Hawkins R, et al. Phase I/II study of (131) I-MIBG with vincristine and 5 days of irinotecan for advanced neuroblastoma. Br J Cancer. 2015;112:644-9
21. DuBois SG, Groshen S, Park JR, Haas-Kogan DA, Yang X, Geier E, et al. Phase I Study of Vorinostat as a Radiation Sensitizer with 131I-Metaiodobenzylguanidine (131I-MIBG) for Patients with Relapsed or Refractory Neuroblastoma. Clin cancer Res an Off J Am Assoc Cancer Res. 2015;21:2715-21
22. DuBois SG, Granger MM, Groshen S, Tsao-Wei D, Ji L, Shamirian A, et al. Randomized Phase II Trial of MIBG Versus MIBG, Vincristine, and Irinotecan Versus MIBG and Vorinostat for Patients With Relapsed or Refractory Neuroblastoma: A Report From NANT Consortium. J Clin Oncol Off J Am Soc Clin Oncol. 2021;39:3506-14
23. Cash T, Marachelian A, DuBois SG, Chi Y-Y, Groshen SG, Shamirian A, et al. Phase I study of 131I-MIBG with dinutuximab for patients with relapsed or refractory neuroblastoma: A report from the new approaches to neuroblastoma therapy (NANT) consortium. J Clin Oncol [Internet]. 2022;40(16_suppl):10038. Available from: https://doi.org/10.1200/JCO.2022.40.16_suppl.10038
24. van Santen HM, de Kraker J, van Eck BLF, de Vijlder JJM, Vulsma T. High incidence of thyroid dysfunction despite prophylaxis with potassium iodide during (131)I-meta-iodobenzylguanidine treatment in children with neuroblastoma. Cancer. 2002;94:2081-9
25. Clement SC, van Eck-Smit BLF, van Trotsenburg ASP, Kremer LCM, Tytgat GAM, van Santen HM. Long-term follow-up of the thyroid gland after treatment with 131I-Metaiodobenzylguanidine in children with neuroblastoma: Importance of continuous surveillance. Pediatr Blood Cancer [Internet]. 2013;60:1833-8. Available from: https://doi.org/10.1002/pbc.24681
26. Clement SC, Kraal KCJM, van Eck-Smit BLF, van den Bos C, Kremer LCM, Tytgat GAM, et al. Primary ovarian insufficiency in children after treatment with 131I-metaiodobenzylguanidine for neuroblastoma: report of the first two cases. J Clin Endocrinol Metab. 2014;99:E112-6
27. Samim A, Blom T, Poot AJ, Windhorst AD, Fiocco M, Tolboom N, et al. [(18)F]mFBG PET-CT for detection and localisation of neuroblastoma: a prospective pilot study. Eur J Nucl Med Mol Imaging. 2023;50:1146-57

Current status of clinical dosimetry and personalized radionuclide therapy

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Abstract

The number of patients treated with radionuclide therapy (RNT) has made a giant leap with the approval of targeted Lutetium-labelled radiopharmaceuticals by the European Medicines Agency (EMA). Though treatments with radioiodine still make up for over 85% of the RNTs in Europe, the scientific breakthroughs are nowadays achieved with new radiolabelled small-molecules and microspheres in various oncological settings. With these advances, the discussions are again raised regarding the need for standard post-therapy imaging followed by absorbed dose verification. On the one hand, clinical dosimetry has always been considered too complicated, providing results with high uncertainties, and requiring an increased burden on the patient and the department, without scientific evidence to establish a clear clinical benefit yet. On the other hand, important steps are made to standardize various aspects of the dosimetry workflow to improve patient's safety, treatment effectiveness and accuracy. Furthermore, there are numerous small clinical studies that do show distinct dose-effect relationships for both normal organ toxicity and tumor control in RNT, thus suggesting there is room to optimize treatment outcome by performing either personalized dose prescription or better patient selection (1,2).
This overview will define current clinical status of dosimetry to guide Lutetium-labelled targeted therapy and radioembolization treatment in the oncological setting. The fundamental elements for any clinical dosimetry calculation will be discussed, as well as the uncertainties and limitations of such a workflow. To conclude, key research areas in active development are mentioned, and we will glance at the future of personalized radionuclide treatment planning.

Implementation of the EU-directive

The general debate surrounding clinical dosimetry in radionuclide therapy (RNT) has been given additional momentum by the European Union (EU) Council Directive 2013/59/Euratom stating in article 56 that *'For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned, and their delivery appropriately verified…'*, suggesting treatment modification based on dosimetry outcomes for radiotherapy, including nuclear medicine for therapeutic purposes. However, in the same EU-Directive the concept of standardized versus non-standardized RNT was introduced. Where standardized refers to prescription of EMA-approved pharmaceuticals, non-standardized therapies are those still in developmental phases or used in an off-label setting. This conflict of EMA-approved dosing versus EU-imposed exposure optimization has led to a confusing situation, which was described in a recent EANM position paper (3). Three compliance levels to the EU-Directive were proposed for the nuclear community:
Level 1. Activity-based prescription and cohort-averaged dosimetry for standardized RNT,
Level 2. Activity-based prescription and patient-specific absorbed dose verification for non-standardized therapies,
Level 3. Dosimetry-guided patient-specific prescription and dose verification.
The majority of RNTs applied in the current clinical setting can be classified as Level 1, except for the transarterial radioembolization (TARE) of liver malignancies currently classified as Level 2-3 depending on the method of activity prescription used. At present, TARE is the only nuclear therapy for which dosimetry-driven treatment planning is advised in recent guidelines (more details in the next paragraph), though technically the radiolabeled microspheres are classified as medical device rather than a radiopharmaceutical. When for radiopharmaceuticals deviations are made from an EMA-approved therapeutic dose or indication, even in a standard clinical setting, it is considered off-label use and Level 2-3 dosimetry is advised. With this proposed EANM-classification, minimal compliance to the imposed EU-Directive can be implemented for

Lutetium-therapies and TARE in many hospitals without much effort. But what will be needed to take RNT one step further, and is personalized dosimetry-based planning the way to improve patient outcome?

Tumor control: a radiobiological perspective

From a radiobiological perspective it makes sense to prescribe high activity dosages of nuclides with high dose rates and long half-lives to achieve maximal tumor control. However, for personalized treatment planning to be clinically relevant and safe, it should include dose thresholds for specific organs-at-risk to reduce the chance of radiation-induced (early) toxicities, and secondly, it should offer data on the tumor-control probability.
Although the relationship between absorbed dose and the induction of a biological effect in tissue is generally acknowledged, there are still fundamental knowledge gaps in this interaction especially for RNT (4). In external beam radiation therapy (EBRT), the abundance of scientific data has led to the development of statistical models to describe the tumor control probability (TCP) and normal tissue complication probability (NTCP) at certain absorbed doses in various tissues. The most complex model can take factors like planned dose, radiosensitivity, repopulation, repair, dose rate, linear energy transfer (LET) and dose heterogeneity into consideration. Nevertheless, the survival chance of a single cell after irradiation, described with the well-established Linear-Quadratic (LQ) model, often forms the basis of these probability models. The cell survival equation consists of a linear component determined by a cell's radiosensitivity ('single hit' response) and a quadratic part which describes a cell's ability to repair sub-lethal damage before a second irradiation event ('multiple hit' response). In EBRT, these models are used to compare different radiotherapeutic fractionation schemes and predict biological effects to optimize treatments (5,6).
Our current understanding of dose-effects relationships in RNT is heavily based on the acquired knowledge from EBRT, but it is also recognized that this cannot reliably be extrapolated as aspects such as dose rate, exposure time, fractionation schemes and type of radiation all differ. For example, an absorbed dose of 40 Gy delivered over three weeks

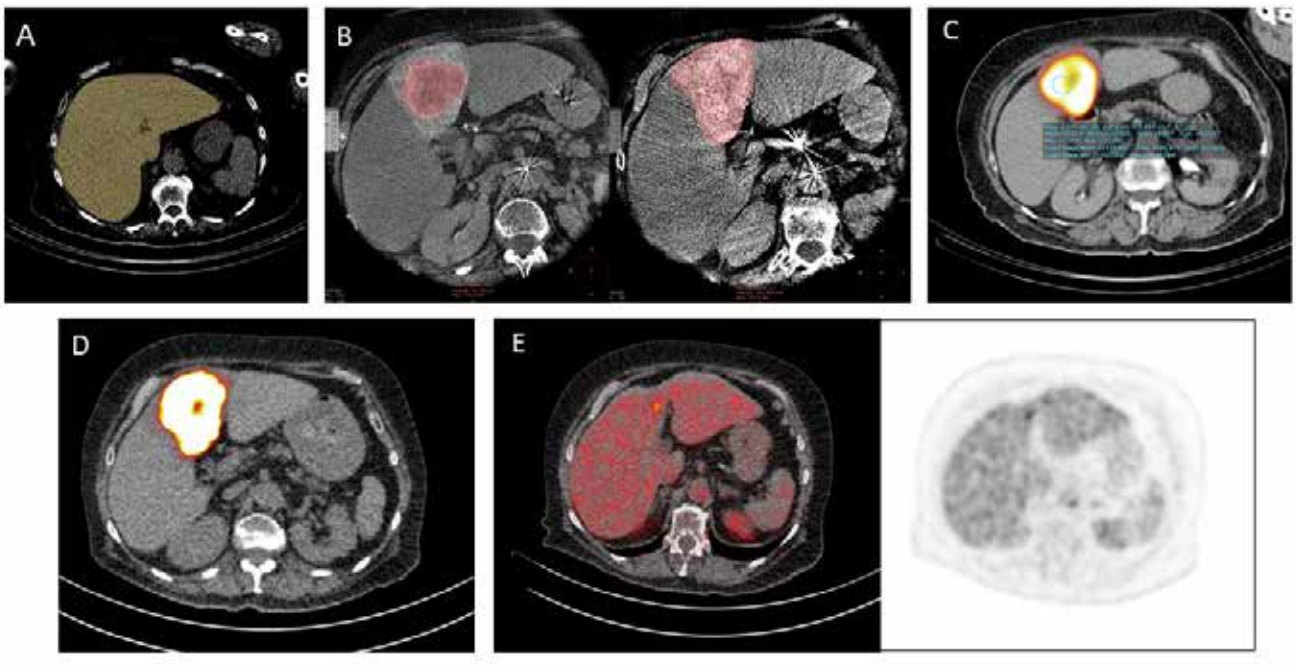

Figure 1. Segmentectomy in a patient with oligometastatic colorectal cancer. Total liver volume determined on CE-CT is 2300ml (A), with one FDG-avid hypervascular tumor lesion located in segment 4. During angiographic work-up a Conebeam-CT is made at the injection position, and treatment volume is segmented (350ml) (B). Tumor-to-normal ratio is estimated at 2.4 on [^{99m}Tc]Tc-MAA SPECT/CT (C). The planned dose on the tumor was 200Gy, resulting in a prescribed activity of 850MBq to the treatment volume. The distribution of ^{90}Y-microspheres (D) nicely matches the [^{99m}Tc]Tc-MAA accumulation. Follow-up FDG-PET one year after radiation segmentectomy shows a marked response and no new lesions (E).

at a dose rate that is exponentially reducing has a quite different biological effect on tissues compared to the same dose of 40 Gy delivered at high dose rates in fractions of 2 Gy (e.g., radiotherapy). The different biological effect of RNT compared to EBRT is further complicated due to its heterogeneous localization of the deposited energy, both at a tissue, cellular and subcellular level, which is directly related to the biodistribution of a specific radiopharmaceutical.
To complicate matters even more, therapeutic efficacy and cell survival are also influenced by complex processes within cells that are not directly targeted, so-called 'bystander effect', and activation of the immune system (7).
More preclinical studies should be undertaken that combine (sub)cellular absorbed dose measurements with biological data on for instance DNA damage-repair, cell-survival pathways, immune-activation, radiosensitizers, and so on, to better understand these complicated interactions. While these types of experiments will eventually lead to more suitable dose limits and tumor target doses of RNT, they are often hampered by incomplete physics and dosimetry reporting. Through recognizing these common shortcomings, efforts are now made to 1) standardize dosimetric measures and reporting, 2) define preclinical models for radiobiology, and 3) identify suitable biomarkers of response (8-10). As this research operates on the crossroad between physics, biochemistry, radiobiology, pharmacology, and medicine, collaboration and integration will also be needed to optimize these experiments and clinical trials.

Dosimetry: calculations and uncertainties

A prerequisite for clinical implementation of personalized treatment verification, and eventually treatment planning, are accurate absorbed dose measurements.
As computational and camera technologies progress, internal dosimetry is becoming more widely implemented in clinical studies that assess safety and effectiveness of RNT, thus providing us with the necessary basic data to evaluate dose-response relations. In this respect, it must be recognized that standardization and harmonization of both imaging input data and applied dosimetry models are highly relevant. Proper dosimetry reporting and evaluating the degree of uncertainties in absorbed dose estimates for specific protocols, both in clinical and preclinical setting, will increase the validity of dosimetry and will help to separate true from false dose-effect findings. Recent efforts of the EANM community have resulted in several recommendations that cover the entire dosimetry workflow for specific indications (11-16).

Traditionally, absorbed dose estimates are performed to determine risk profiles of (new) radiopharmaceuticals at a population level, so this MIRD-methodology focusses on absorbed doses (*D* in Gray) in entire organs.
The dose is calculated using the time-integrated activity (A_T in MBq) and an S-factor, which describes the absorbed energy in a specific organ per radionuclide disintegration. The type of decay (alpha, beta, auger electrons, gamma) will determine whether the activity in a certain tissue volume will also contribute to the deposition of energy in nearby tissues (so-called crossfire effect). A spatial S-value distribution is generally referred to as a 'Dose Point Kernel'. To calculate the dose deposited in solid tissues of 2-300 grams by certain alpha, beta, and auger electron emitters, it can be assumed that all energy is deposited in a small area referred to as 'Local Energy Deposition (LED)'. When three-dimensional imaging data is used as input for dose biodistributions either a Dose Point Kernel or Local Energy Deposition model can be used to convert counts into radiation doses. The time-integrated activity is estimated for each treatment by fitting a curve through the uptake data from quantitative imaging acquired at multiple time points after administration.
Quantification of activity in tissue is influenced by multiple factors, for instance type of acquisition (SPECT vs. conjugated view vs. planar), image corrections (scatter, attenuation, partial volume effect, smoothing), camera cross-calibration, count rate, segmentation, and volume of the target. In SPECT-based dosimetry, uncertainties in absorbed dose estimates are dominated by the ability to define its volume and accurately quantify uptake for small lesions or tissues (e.g., salivary glands), while in larger lesions or organs (e.g., kidney, spleen liver), accurate curve fitting of the time-integrated activity has the largest impact.

Dose limits and target doses in TARE

TARE is a special form of RNT as it is performed by arterial administration of radiolabeled microspheres.
They lodge in tumor-associated microvasculature and irradiate the lesions. Currently, this treatment is approved in the third line setting for liver-dominant non-resectable metastatic colorectal cancer or hepatocellular carcinoma. There are three different commercial products available, labelled with either Holmium-166 (^{166}Ho) or Yttrium-90 (^{90}Y); SIR-Spheres (Sirtex), TheraSpheres (Boston Scientific) and QuiremSpheres (Terumo), each product has its characteristics with respect to material, activity per sphere and specific gravity. To simulate the hepatic distribution of microspheres, either [^{99m}Tc]Tc-MAA or ^{166}Ho-Scout is infused at selected tumor-supplying hepatic arteries followed by abdominal SPECT/CT imaging.

Together with a recent diagnostic contrast-enhanced CT or MRI, these images form the basic input for dose planning. The presence of a dose-response relationship for TARE was demonstrated in various clinical trials, and consequently, a shift was made for all types of microspheres from single compartment or body surface area activity prescription towards personalized dose planning (17,18). The dosimetry for TARE is relatively simple, as the therapeutic microspheres do not degrade after administration, the time-integrated activity is only determined by the known physical half-life of the isotope and the distribution remains constant over time. There are three relevant compartments over which the microspheres can distribute: lungs, liver parenchyma and tumor. The standard MIRD formalism states that the activity to be administered (A) could be calculated given a planned tumor-absorbed dose (D_T) by

$$A[GBq] = \frac{D_T\,[Gy] \times (M_N\,[kg] + M_T \times r)}{CF \times r \times (1 - L)}$$

with *M* being the mass of the tumor or parenchyma, r is the ratio of accumulated counts between tumor and parenchyma, *CF* is an isotope dose conversion factor (^{90}Y = 49.67 J/GBq; ^{166}Ho = 15.85 J/GBq) and *L* is the lung shunt fraction. For treatment planning, the volumes and average accumulation should be determined for the lesions and normal parenchyma in each administration positions.
To aid definition of perfusion areas within the liver, it is advised to perform a Cone Beam CT at each planned infusion position. More methodological

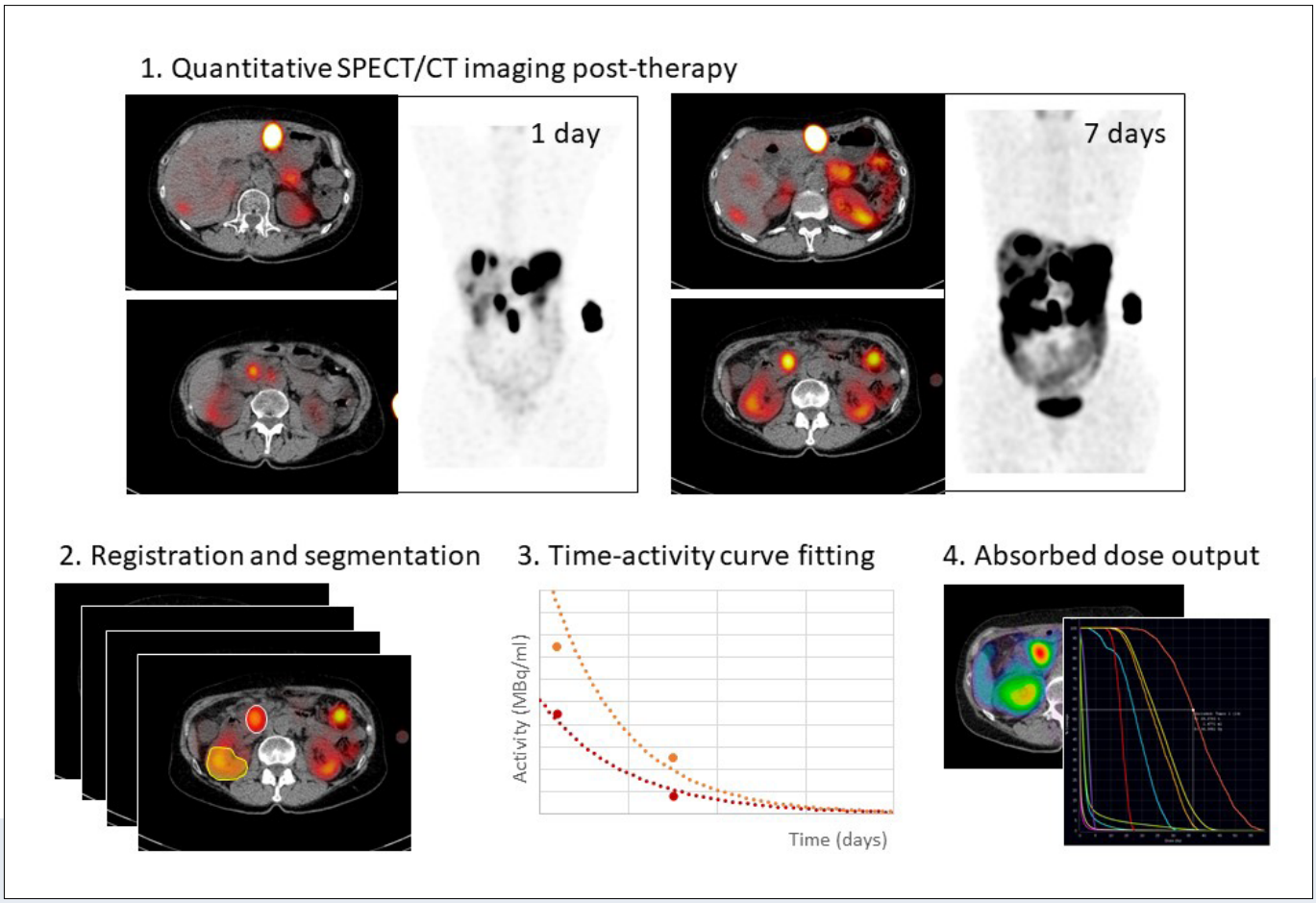

Figure 2. Dosimetric verification of ^{177}Lu-therapies involves nuclear imaging of the biodistribution at 1 and 5-7 days after administration. Post-treatment images are registrated to eachother, and if needed also to diagnostics scans, to delineate organs-at-risk and target lesions. Accumulated activity in each delineated volume is estimated by determining the area under the time-activity curves. Imaging data is converted into an absorbed dose output using predefined Dose Point Kernels.

details regarding the various technical aspects of the dosimetry workflow were recently described by scientific committees (12,19,20). Personalized dose planning can also be performed through voxel-based dosimetry, in which the pre-therapeutic [^{99m}Tc]Tc-MAA or ^{166}Ho-Scout are used to generate 3D-dosemaps like in modern EBRT-planning. Voxel-based dosimetry for TARE is clinically available in various commercial software systems, but its usefulness is still under debate. Both compartment- and voxel-based dosimetry relay on the assumption that the microsphere distribution is accurately simulated with pre-therapeutic SPECT/CT. In specific cases when the distribution is not representative or could not be quantified, for instance in small or infiltrative lesions, one-compartment dosimetry could still be applied.
In personalized treatment planning for TARE a holistic view of the patient is essential, so factors like disease stage, tumor morphology, previous treatments, liver function and arterial liver anatomy need to be considered when defining treatment intent (what do we want to achieve) and therapeutic strategy (how do we want to achieve this). There are roughly three types of treatments defined: bi-lobar (whole liver), lobar, and ablative selective TARE. Though patient work-up for these treatments is quite similar, the dose planning has some specific considerations. In patients with bi-lobar manifestations care must be taken to limit the absorbed dose to the parenchyma. Table 1 provides an overview of the recommended dose limits per commercial product. In patients with limited tumor load in 1-3 liver segments who are not suitable for surgery, a more aggressive and localized form of TARE can be considered, which is also referred to as radiation segmentectomy. Though this approach is relatively new, and most data is acquired for ^{90}Y-microspheres, these high tumor-absorbed doses of over 200 Gy lead to high response rates and long tumor control in both HCC and mCRC. However, radiation segmentectomies can only be performed if arterial liver anatomy is suitable and the remaining liver function is sufficient (18,21,22).

Evidence for organ dose limits in ^{177}Lu-therapies

Over the past years, two important radiopharmaceuticals have been introduced in clinical practice.
The first one is the EMA approved [^{177}Lu]Lu-DOTATATE (Lutathera®, Novartis Europharm Limited).
It is indicated for the treatment of unresectable or metastatic, progressive, well-differentiated, grade I/II somatostatin receptor positive-gastroenteropancreatic neuroendocrine tumours (GEP-NETs) using a regime of 7.4 GBq every eight weeks for four cycles (23). The second one is [^{177}Lu]Lu-vipivotide-tetraxetan (Pluvicto®, Novartis Europharm Limited) for treatment of progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC). This radiopharmaceutical is approved by the EMA at a dosing of 7.4 GBq every six weeks for up to a total of six doses (24). In both registrations, dose modifications are allowed to manage severe (≥ Grade 3) or intolerable toxicities, with the most common being hematological toxicity, renal toxicity, and in the case of [^{177}Lu]Lu-vipivotide-tetraxetan, xerostomia. In the EMA registration dossier, there is no mentioning of dose modification to optimize the therapeutic efficacy, but data on absorbed doses in critical organs and tumors from various small prospective studies is available.
Red bone marrow is one of the critical organs in most RNTs, though data covering its dose-effect relation is limited and contradicting. Radiation induced acute **hematological toxicities** is recognized as the most common adverse event in ^{177}Lu-RNT (~10-15% of patients develop grade 3-4 toxicity within weeks), and yet it might not solely be induced by exposure to marrow, but also to some extent to accumulation in the spleen and lymphocytes. Results from the VISION dosimetry sub-study indicate

Table 1. Approximate proposed dose limits and tumor-absorbed doses for TARE.

		SIR-Spheres	TheraSpheres	QuiremSpheres
Dose limit	Liver parenchyma	≤40 Gy	≤120 Gy	≤60 Gy
	Pre-treated liver or compromised function	≤30 Gy	Not mentioned	Not mentioned
	Lung	Single ≤30 Gy	Single ≤30 Gy	Single ≤30 Gy
Target dose	Tumour (HCC/mCRC)	100-120 Gy	200-250 Gy	>100-150 Gy
	Ablative TARE	>150 Gy	>400 Gy	Not mentioned

that the calculated absorbed dose to red marrow was 0.25 ± 0.15 Gy for one cycle and 1.5 ± 0.9 Gy for six cycles of 7.4 GBq (n = 29 patients); for [^{177}Lu]Lu-DOTATATE this was 0.22 Gy for one cycle (n = 20 patients). Previous small-scale studies showed quite similar absorbed dose values for [^{177}Lu]Lu-DOTATATE ranging from 0.02-0.08 Gy/GBq (25,26,27). Late-onset myelodysplastic syndrome (MDS) and acute leukemia have been observed after treatment with [^{177}Lu]Lu-DOTATATE, but disease etiology and its relation to dose parameters are lacking. In hematological non-compromised patients, a dose threshold of 2 Gy has been associated with an increased risk of acute toxicity (based on data from Iodine-131 therapy), but it is being debated whether a dose limit of 2 Gy is safe in patients with impaired hematological function or those who received prior chemotherapy or EBRT.
The physiological excretion of small-molecules and peptides is mainly through the kidneys, so these organs are generally relevant in defining the patient's tolerability to RNT (28). Due to an unspecific reabsorption of [^{177}Lu]Lu-DOTATATE in the proximal tubular cells, the kidneys are the dose-limiting organs for this specific therapy. Sub-acute radiation induced **kidney toxicity** can progressively develop over months to years after treatment, however severe adverse events are rare (< 1.5% for Grade 3-4) in Lutetium-based RNT when proper renal-protection protocols including aminoacid-infusions are applied. Still, early onset kidney impairment is frequently observed (5-25% for Grade 1-2) and may result in a persistent reduction of kidney function that requires dose reduction or permanent discontinuation of therapy. Extrapolations of absorbed doses from EBRT have led to advised renal dose thresholds of 23-28 Gy for patients with compromised kidney function, and up to 40 Gy for non-compromised patients. Data from the VISION and NETTER-1 studies demonstrated average calculated absorbed doses to the kidneys of 0.43 ± 0.16 Gy/GBq (19 ± 7.3 Gy for six cycles) and 0.65 ± 0.29 Gy/GBq (4.8 Gy for one cycle), respectively. In literature, both [^{177}Lu]Lu-DOTATATE (with renal protection) and [^{177}Lu]Lu-PSMA (various ligands) absorbed doses vary per study and per patient, but ranges roughly between 0.6-1.0 Gy/GBq. Patients with mild or moderate preexisting renal impairment may be at greater risk of developing radiation induced toxicities as the residence times (biological half-life) may be prolonged.

A critical organ for RNT with [^{177}Lu]Lu-PSMA-ligands are the salivary glands, due to both specific and a-specific binding that may lead to **salivary gland toxicity.** Mechanisms underlying this radiation-induced salivary gland hypofunction and xerostomia (e.g., feeling of dry mouth) are largely unknown, but various studies do document acute reversible (mild) xerostomia in many patients treated with [^{177}Lu]Lu-PSMA (> 30% of the patients, Grade 1-2) (29). During EBRT in head and neck cancer, reported absorbed doses vary around 20-30 Gy, which results in a dose-dependent loss of secretory cells, so absorbed dose limits of ± 20 Gy have been proposed to reduce the probability of developing salivary gland toxicity (30). For [^{177}Lu]Lu-vipivotide-tetraxetan, data from the VISION trial showed an average calculated absorbed doses to the salivary glands of 0.63 ± 0.36 Gy/GBq (28 ± 16 for six cycles), other studies report mean absorbed doses between 0.5-2.5 Gy/GBq.
As can be concluded from the above, there is basic data on dose thresholds for organs-at-risk that can be used as starting point for dosimetry-based personalized RNT. Treatment planning can also be achieved by optimizing the dose to the tumor, as is the case for TARE. However, dosimetry-based activity prescription of systemic RNT is more complicated as tumor accumulation of targeted radiopharmaceuticals shows large inter- and intra-patient variability, and different tumor phenotypes will react differently to radiation. Furthermore, consolidation of retrospective data to deduce dose-effect relations will be difficult as the approved ^{177}Lu-based therapies are currently applied in a second- or third-line setting resulting in large variabilities regarding patient data. Identification of radiobiological mechanisms that might indicate why certain patients do, and others do not, benefit from RNT is likely to be overshadowed by inherent variations in therapeutic schemes and absorbed dose calculations. So currently, no specific recommendations can be provided to guide treatment using tumor target doses for RNT.

First steps to personalize ^{177}Lu-therapies

Personalization and optimization of RNT can come in many forms as differences in number of given cycles, activity dosing per cycle, time between fractions, peptide and specific activity of the radiopharmaceutical are all factors that will influence the induced biological effects within the body, both for normal tissue and tumor lesions. Recently published data of prospective studies mainly focused on individualized treatment with [^{177}Lu]Lu-DOTATATE based on renal dosimetry.
The PP-PRRT trial (NCT02754297) is a prospective, single-center study, in which the injected activity per cycle was adjusted to reach a prescribed cumulative absorbed kidney dose of 23 Gy over four cycles [^{177}Lu]Lu-octreotate (31). The prescribed activity was determined according

to GFR, body surface area and prior absorbed renal doses, aiming at 5-6 Gy per cycle. Dosimetry was done per cycle, so at approximately 4, 24 and 72 hours after administration quantitative SPECT/CTs were performed covering liver, kidneys, vertebral bodies, and target tumor lesions. This therapeutic regime led to a wide-ranging per-cycle activities (0.7-32.4 GBq; median 8.8 GBq). Not only was the cumulative administered activity 1.24 times higher compared to empiric dosing at four-times 7.4 GBq, also the median absorbed dose in tumor lesions increased 1.26-fold. It must be noted that the incidence of severe toxicities was quite similar to those reported for the empiric dosing. Data to determine the progression-free and overall survival is not yet complete, but first preliminary results are encouraging.

The ILUMINET trial (NCT01456078), a prospective phase-II study, also evaluated the safety and efficacy of individualized [^{177}Lu]Lu-octreotate therapy in 97 patients (32). In this study, cycles of 7.4 GBq [^{177}Lu]Lu-octreotate were given until the kidney dose threshold of 27 Gy was achieved, and patients without risk factors for renal or hematological toxicity could receive up to 40 Gy (both defined as cumulative Biological Effective Dose). For dosimetry, planar scintigraphy at 1, 24, 48, 96 and 168 hour post injection were combined with one SPECT/CT at 24 hours. This prescription methodology resulted in a considerable variation in number of treatment cycles, as absorbed kidney doses show quite some patient variability. The overall toxicity was mild, and the median kidney absorbed dose per cycle was 4.5 Gy (range 2.2-14.3). After a follow-up of 42-months, the PFS and OS were 29 months and 47 months, respectively, and the best overall response rate was 34% (complete plus partial response). Though direct comparison of this study with the results from the NETTER-1 trial is difficult (28 and 48 months, 18%, respectively), dosimetry-based RNT seems to be more effective.

Future of dosimetry in RNT

In the Netherlands, efforts are ongoing to harmonize post-therapy imaging for ^{166}Ho and ^{177}Lu SPECT/CT, with respect to imaging time-points and acquisition protocols. These efforts started to limit variations in data acquired in prospective clinical trials, including the CAIRO-7 (NCT05092880, ^{166}Ho-TARE in elderly and frail) and the Bullseye (NCT04443062, [^{177}Lu]Lu-PSMA in oligometastatic PCa), but they are gaining increasing support from other centers. It is hopeful that in a well-equipped country such as the Netherlands the ambition exists to at least harmonize post-treatment imaging and dosimetry data collection. Additionally, there are a few recent developments that, when combined, can take RNT one step further towards personalized dosimetry-based planning.

Image processing and voxel-based dosimetry

The conversion of imaging data into dose maps is often seen as a complex undertaking that needs extensive support from skilled personnel, however proper implementation of a dosimetry workflow is becoming less complicated with the advances in quantitative camera technologies and image processing software. The main camera suppliers have nowadays implemented quantitative SPECT/CT workflows with protocolized quality assurance suitable for the clinical practice. The biggest progress is made in the post-processing software. Vendors such as Hermes, MiM, Dosisoft and ABX-CRO are introducing CE-marked solutions for TARE and ^{177}Lu-therapies that can be used for clinical decision making, thus making in-house developed software redundant. To generalize, these applications convert count-data using predefined calibration factors into voxel-based dose maps that can be displayed as 3D dose-isocontours or dose volume histograms to visualize the spatial distribution of the administered dose or predict absorbed doses based on previous treatments. These vendors are now pointing their arrows on the approval of AI-based algorithms for segmentation of both normal organs and tumor lesions.

Single-timepoint curve fitting

As the goodness-of-fit for the time-activity curve determines the accuracy of absorbed dose estimates, so ideally SPECT/CT would be made at multiple time-points after administration of systemic RNT. This sequential imaging and (manual) segmentations are a highly time- and resource-intensive process that hamper broader clinical implementation of dosimetry. So, studies have focused on methods to limit the number of scans, while balancing accuracy and uncertainty of absorbed dose estimates (33,34,35). To estimate individual organ absorbed doses in [^{177}Lu]Lu-PSMA therapy, a single-timepoint SPECT/CT at 24-48 hours after administration could be used in combination with predefined population-based organ-specific kinetics. Evaluation of tumor lesions is more complex as it shows a larger inter- and intra-patient variability, so in addition to one early time-point a second 'late' time-point (168 hours) might be needed. A similar approach may be adopted for other receptor-targeted Lutetium-based RNTs.

Pharmacometric modelling

Understanding and interpreting the dose-concentration-effect relationship is an eminent part of

drug-development. Pharmacokinetic (dose-concentration) and pharmacodynamic (concentration-effect) models are widely applied for instance to translate preclinical results to humans, select a safe dose for first-in-man studies, or start phase I/II studies. In later phases of research, models can be used to assess for instance population variability or predict an individual's biodistribution in a certain physiological status. The physiologically based pharmacokinetic (PBPK) models help to understand and predict kinetics, by combining predefined drug-specific information with physiological or biological data in a complex multi-compartment model to predict tissue accumulation profiles. The population PK models, on the other hand, are based on lumbed compartments to describe concentration-time profiles and its variability within a population of interest. Combination of these pharmacokinetic models with pharmacodynamic and tumor-growth data for therapeutic radiopharmaceuticals is very new but could provide important insights into the various factors that impact biodistribution (36). Recent studies have used pharmacometrics modeling to for example estimate time-integrated activities with limited imaging time-points, predict treatment response for [^{177}Lu]Lu-PSMA and related pretreatment Gallium-68 imaging with [^{177}Lu]Lu-PSMA accumulation (37,38,39).

Conclusion

With the proposed EANM-classification for RNT prescription and dosimetry, minimal compliance to the EU-Directive 2013/59/Euratom can be implemented for the EMA-approved [^{177}Lu]Lu-therapies and TARE in most Dutch hospitals. Still the field is moving on, and despite important knowledge gaps with respect to radiobiology, evidence for more individualized RNT prescription is mounting. For TARE personalized treatment planning is now recommended for all types of microspheres and indications. The clinical implementation of dosimetry for treatment planning and verification in systemic ^{177}Lu-based RNT is not widely applied and adopted in guidelines. Still, important leaps are made to reduce imaging time-points, userfriendly CE-marked dosimetry software, harmonization of quantitative imaging and clinical RNT protocols.

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References

1. Sgouros G, Bodei L, McDevitt MR, Nedrow JR. Radiopharmaceutical therapy in cancer: clinical advances and challenges. Nat Rev Drug Discov. 2020;19:589-608
2. Strigari L, Konijnenberg M, Chiesa C, Bardies M, Du Y, Gleisner KS, et al. The evidence base for the use of internal dosimetry in the clinical practice of molecular radiotherapy. Eur J Nucl Med Mol Imaging. 2014;41:1976-88
3. Konijnenberg M, Herrmann K, Kobe C, Verburg F, Hindorf C, Hustinx R, et al. EANM position paper on article 56 of the Council Directive 2013/59/Euratom (basic safety standards) for nuclear medicine therapy. Eur J Nucl Med Mol Imaging. 2021;48:67-72
4. Aerts A, Eberlein U, Holm S, Hustinx R, Konijnenberg M, Strigari L, et al. EANM position paper on the role of radiobiology in nuclear medicine. Eur J Nucl Med Mol Imaging. 2021;48:3365-77.
5. McMahon SJ. The linear quadratic model: usage, interpretation and challenges. Phys Med Biol. 2018;64:01TR01
6. Spoormans K, Crabbe M, Struelens L, De Saint-Hubert M, Koole M. A Review on Tumor Control Probability (TCP) and Preclinical Dosimetry in Targeted Radionuclide Therapy (TRT). Pharmaceutics. 2022;14:2007
7. Pouget JP, Santoro L, Piron B, Paillas S, Ladjohounlou R, Pichard A, et al. From the target cell theory to a more integrated view of radiobiology in Targeted radionuclide therapy: The Montpellier group's experience. Nucl Med Biol. 2022;104-105:53-64
8. Draeger E, Sawant A, Johnstone C, Koger B, Becker S, Vujaskovic Z, et al. A Dose of Reality: How 20 Years of Incomplete Physics and Dosimetry Reporting in Radiobiology Studies May Have Contributed to the Reproducibility Crisis. Int J Radiat Oncol Biol Phys. 2020;106:243-52
9. Group ERW, Pouget JP, Konijnenberg M, Eberlein U, Glatting G, Gabina PM, et al. An EANM position paper on advancing radiobiology for shaping the future of nuclear medicine. Eur J Nucl Med Mol Imaging. 2023;50:242-6
10. Verburg FA, Nonnekens J, Konijnenberg MW, de Jong M. To go where no one has gone before: the necessity of radiobiology studies for exploration beyond the limits of the "Holy Gray" in radionuclide therapy. Eur J Nucl Med Mol Imaging. 2021;48:2680-2
11. Gear JI, Cox MG, Gustafsson J, Gleisner KS, Murray I, Glatting G, et al. EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations. Eur J Nucl Med Mol Imaging. 2018;45:2456-74
12. Chiesa C, Sjogreen-Gleisner K, Walrand S, Strigari L, Flux G, Gear J, et al. EANM dosimetry committee series on standard operational procedures: a

unified methodology for (99m) Tc-MAA pre- and (90)Y peri-therapy dosimetry in liver radioembolization with (90) Y microspheres. EJNMMI Phys. 2021;8:77
13. Sjogreen Gleisner K, Chouin N, Gabina PM, Cicone F, Gnesin S, Stokke C, et al. EANM dosimetry committee recommendations for dosimetry of 177Lu-labelled somatostatin-receptor- and PSMA-targeting ligands. Eur J Nucl Med Mol Imaging. 2022;49:1778-809
14. Dickson JC, Armstrong IS, Gabina PM, Denis-Bacelar AM, Krizsan AK, Gear JM, et al. EANM practice guideline for quantitative SPECT-CT. Eur J Nucl Med Mol Imaging. 2022
15. Ljungberg M, Celler A, Konijnenberg MW, Eckerman KF, Dewaraja YK, Sjogreen-Gleisner K, et al. MIRD Pamphlet No. 26: Joint EANM/MIRD Guidelines for Quantitative 177Lu SPECT Applied for Dosimetry of Radiopharmaceutical Therapy. J Nucl Med. 2016;57:151-62
16. Herrmann K, Giovanella L, Santos A, Gear J, Kiratli PO, Kurth J, et al. Joint EANM, SNMMI and IAEA enabling guide: how to set up a theranostics centre. Eur J Nucl Med Mol Imaging. 2022;49:2300-9
17. Cremonesi M, Chiesa C, Strigari L, Ferrari M, Botta F, Guerriero F, et al. Radioembolization of hepatic lesions from a radiobiology and dosimetric perspective. Front Oncol. 2014;4:210
18. Roosen J, Klaassen NJM, Westlund Gotby LEL, Overduin CG, Verheij M, Konijnenberg MW, et al. To 1000 Gy and back again: a systematic review on dose-response evaluation in selective internal radiation therapy for primary and secondary liver cancer. Eur J Nucl Med Mol Imaging. 2021;48:3776-90
19. Levillain H, Bagni O, Deroose CM, Dieudonne A, Gnesin S, Grosser OS, et al. International recommendations for personalised selective internal radiation therapy of primary and metastatic liver diseases with yttrium-90 resin microspheres. Eur J Nucl Med Mol Imaging. 2021;48:1570-84
20. Weber M, Lam M, Chiesa C, Konijnenberg M, Cremonesi M, Flamen P, et al. EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds. Eur J Nucl Med Mol Imaging. 2022;49:1682-99
21. Entezari P, Gabr A, Salem R, Lewandowski RJ. Yttrium-90 for colorectal liver metastasis - the promising role of radiation segmentectomy as an alternative local cure. Int J Hyperthermia. 2022;39:620-6
22. Montazeri SA, De la Garza-Ramos C, Lewis AR, Lewis JT, LeGout JD, Sella DM, et al. Hepatocellular carcinoma radiation segmentectomy treatment intensification prior to liver transplantation increases rates of complete pathologic necrosis: an explant analysis of 75 tumors. Eur J Nucl Med Mol Imaging. 2022;49:3892-7
23. https://www.ema.europa.eu/en/documents/product-information/lutathera-epar-product-information_en.pdf
24. https://www.ema.europa.eu/en/documents/product-information/pluvicto-epar-product-information_en.pdf
25. Cremonesi M, Ferrari ME, Bodei L, Chiesa C, Sarnelli A, Garibaldi C, et al. Correlation of dose with toxicity and tumour response to (90)Y- and (177)Lu-PRRT provides the basis for optimization through individualized treatment planning. Eur J Nucl Med Mol Imaging. 2018;45:2426-41
26. Bodei L, Cremonesi M, Grana CM, Fazio N, Iodice S, Baio SM, et al. Peptide receptor radionuclide therapy with (1)(7)(7)Lu-DOTATATE: the IEO phase I-II study. Eur J Nucl Med Mol Imaging. 2011;38:2125-35
27. Kudo A, Tateishi U, Yoshimura R, Tsuchiya J, Yokoyama K, Takano S, et al. Safety and response after peptide receptor radionuclide therapy with (177) Lu-DOTATATE for neuroendocrine tumors in phase 1/2 prospective Japanese trial. J Hepatobiliary Pancreat Sci. 2022;29:487-99
28. Geenen L, Nonnekens J, Konijnenberg M, Baatout S, De Jong M, Aerts A. Overcoming nephrotoxicity in peptide receptor radionuclide therapy using [(177)Lu]Lu-DOTA-TATE for the treatment of neuroendocrine tumours. Nucl Med Biol. 2021;102-103:1-11
29. Heynickx N, Herrmann K, Vermeulen K, Baatout S, Aerts A. The salivary glands as a dose limiting organ of PSMA- targeted radionuclide therapy: A review of the lessons learnt so far. Nucl Med Biol. 2021;98-99:30-9
30. Mohan V, Bruin NM, Steenbakkers R, Noordzij W, Terhaard CHJ, de Keizer B, et al. Dose response modelling of secretory cell loss in salivary glands using PSMA PET. Radiother Oncol. 2022;177:164-71
31. Del Prete M, Buteau FA, Arsenault F, Saighi N, Bouchard LO, Beaulieu A, et al. Personalized (177)Lu-octreotate peptide receptor radionuclide therapy of neuroendocrine tumours: initial results from the P-PRRT trial. Eur J Nucl Med Mol Imaging. 2019;46:728-42
32. Sundlov A, Gleisner KS, Tennvall J, Ljungberg M, Warfvinge CF, Holgersson K, et al. Phase II trial demonstrates the efficacy

and safety of individualized, dosimetry-based (177)Lu-DOTATATE treatment of NET patients. Eur J Nucl Med Mol Imaging. 2022;49:3830-40
33. Peters SMB, Mink MCT, Prive BM, de Bakker M, de Lange F, Muselaers CHJ, et al. Optimization of the radiation dosimetry protocol in Lutetium-177-PSMA therapy: toward clinical implementation. EJNMMI Res. 2023;13:6
34. Jackson PA, Hofman MS, Hicks RJ, Scalzo M, Violet J. Radiation Dosimetry in (177) Lu-PSMA-617 Therapy Using a Single Posttreatment SPECT/CT Scan: A Novel Methodology to Generate Time- and Tissue-Specific Dose Factors. J Nucl Med. 2020;61:1030-6
35. 35. Rinscheid A, Kletting P, Eiber M, Beer AJ, Glatting G. Influence of sampling schedules on [(177) Lu]Lu-PSMA dosimetry. EJNMMI Phys. 2020;7:41
36. Siebinga H, de Wit-van der Veen BJ, Stokkel MDM, Huitema ADR, Hendrikx J. Current use and future potential of (physiologically based) pharmacokinetic modelling of radiopharmaceuticals: a review. Theranostics. 2022;12:7804-20
37. Siebinga H, Prive BM, Peters SMB, Nagarajah J, Dorlo TPC, Huitema ADR, et al. Population pharmacokinetic dosimetry model using imaging data to assess variability in pharmacokinetics of (177) Lu-PSMA-617 in prostate cancer patients. CPT Pharmacometrics Syst Pharmacol. 2023. Online ahead of print
38. Hardiansyah D, Kletting P, Begum NJ, Eiber M, Beer AJ, Pawiro SA, et al. Important pharmacokinetic parameters for individualization of (177) Lu-PSMA therapy: A global sensitivity analysis for a physiologically-based pharmacokinetic model. Med Phys. 2021;48:556-68
39. Hardiansyah D, Riana A, Eiber M, Beer AJ, Glatting G. Population-based model selection for an accurate estimation of time-integrated activity using non-linear mixed-effects modelling. Z Med Phys. 2023;S0939-3889(23)00007-7

Peptide receptor radionuclide therapy (PRRT) for neuroendocrine tumours

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Abstract
Neuroendocrine neoplasms are a rare type of tumour that typically have a slow growing pattern. Most neuroendocrine tumours express high levels of somatostatin receptors type 2 (SSTR-2) on their cell surface. These receptors are a potential target for radiolabelled somatostatin analogues. Since 2017, peptide receptor radionuclide therapy (PRRT) with [^{177}Lu]Lu-DOTATATE is EMA and FDA approved for treatment of metastatic and/or advanced gastroenteropancreatic neuroendocrine tumours (GEPNETs). Along with a reported good objective response, both increased survival and improved quality-of-life are the most important outcomes. Subacute toxicity to the kidneys and bone marrow is usually mild and self-limiting. Reported long-term adverse events include myelodysplastic syndrome and acute leukaemia in up to 2-3%. Renal failure is rare. Hence, PRRT is now a generally accepted effective and safe therapeutic option for patients with inoperable neuroendocrine tumours and/or metastases. Provided that SSTR-2 receptor expression is sufficient, PRRT is now well established in the treatment algorithm from the neo-adjuvant to salvage setting.

Introduction
Neuroendocrine neoplasms (NENs) are a rare type of tumours that can arise almost anywhere in the body, but most often originate in the digestive tract and lungs. The typical relatively slow-growing nature of NENs and relatively good prognosis make it the second most prevalent gastrointestinal tumour (1). In 2018 in The Netherlands, approximately 1000 patients were diagnosed with a neuroendocrine tumour (NET) and 400 patients with a more aggressive neuroendocrine carcinoma (NEC) (2). In the majority of patients, the primary tumour was found in the gastrointestinal tract.
NETs can be hormonally active. This excessive hormonal secretion can cause a variety of symptoms, based on the type of hormone produced (e.g. serotonin, gastrin, insulin). The typical symptoms of the carcinoid syndrome (i.e. flushing, diarrhoea and bronchospasm) are, however, not specific for a NEN of the small intestine and may also be attributed to e.g. menopause, irritable bowel disease, asthma. Consequently, the possibility of a NEN as a differential diagnosis is oftentimes not recognized by primary care physicians and non-specialized internal medicine physicians, resulting in a significant diagnostic delay. The median time between symptoms until the initial diagnosis is 36 months for a small intestinal NEN and 24 months for a pancreatic NEN (3). In 31% of patients the diagnosis is made in an emergency care setting. If not hormonally active, NETs can present with symptoms due to local growth and development of metastases. At diagnosis, 21-30% of NETs present with distant metastases, as do 50% of the NECs, however this may be an underestimation due to inadequate diagnostic testing (1). Metastases are most often found in regional lymph nodes and the liver (4). Metastatic spread limits therapeutic options, with surgery being the only potentially curative treatment (5).
For most metastatic NETs, treatment with somatostatin analogues (SSAs) (e.g. octreotide) is prescribed as first line treatment (4). In addition to a minor cytostatic effect, SSAs can also significantly decrease hormonally induced symptoms (6,7). Also, targeted therapies such as protein kinase inhibitors (e.g. everolimus and sunitinib) are being approved for NETs from various origins (8).
One of the major breakthroughs in the therapeutic management of metastatic and/or inoperable NETs in the past decades has been the development of peptide receptor radionuclide therapy (PRRT). PRRT with [^{177}Lu]Lu-[DOTA0,Tyr3]octreotate ([^{177}Lu]Lu-DOTATATE) is now a well-established second- or third line treatment for patients with progressive, advanced gastroenteropancreactic neuroendocrine tumours (GEPNETs). It is also the first "theranostic" with an FDA and EMA registration in the field of NENs.
This review will give an overview of the clinical use and the current evidence for the efficacy and safety of PRRT.

Background of PRRT
The vast majority of NENs overexpress a high number of the somatostatin

receptors (SSTRs) on their cell surface. SSTRs are G-protein coupled receptors and at this moment there are five main subtypes of the receptor known (SSTR1-5). Subtype 2 is found most frequently on NENs. Radiolabelled SSAs, such as the beta-particle emitting ([^{177}Lu]Lu-DOTATATE, can bind to the receptor and become internalised within the tumour cell. This results in an internal irradiation in highly specific target locations.

The technique of tumour targeting with radionuclide-labelled SSAs was first applied in the late 1980's using ^{123}I-Tyr3- octreotide for scintigraphic localisation of NETs (9). Soon thereafter a switch was made to ^{111}In-diethylenetriamine pentaacetic acid0-octreotide ([^{111}In]In-DTPA-octreotide) for use in imaging and since 1992 in therapy at Erasmus MC Rotterdam, using the Auger and conversion electron emission of the radionuclide (9,10). With the development of the chelator 1,4,7,10-tetraazacyclotetradecane-1,4,7,10-tetraacetic acid (DOTA), SSAs could be linked to beta emitters resulting in a higher radiation dose on the tumours. With modification of the SSA octreotide into octreotate (threonine substitutes C-terminal threoninol), a nine-fold higher affinity for SSTR2 was achieved (11,12).

At the start of PRRT both Yttrium-90 and Lutetium-177 were used as beta emitting radionuclides. Yttrium-90 is a pure beta emitter with a half-life of 2.7 days, decay energy of 2.28 MeV and a maximum tissue penetration of 12 mm; but is not well suited for imaging as it produces only a few positron- and Bremsstrahlung emissions in its radioactive decay. Contrary, Lutetium-177 emits both beta-particles (half-life 6.7 days, decay energy 0.5 MeV, maximum tissue penetration 2 mm) and sufficient gamma rays of 113 and 208 keV useful for scintigraphic imaging. Lutetium-177 has less side-effects than Yttrium-90, and better post-therapy imaging possibilities for treatment evaluation and dosimetry. For these reasons Lutetium-177 is now the radionuclide of choice for PRRT. In 2017, therapy with [^{177}Lu]Lu-DOTATATE was approved by the FDA and EMA for treatment of NETs based on the data of the NETTER-1 trial and the phase-2 Erasmus MC data (13,14).

Selection for PRRT

One of the major selection criteria for PRRT is the imaging evaluation of the SSTR expression in the tumour. Formerly, this was based on uptake on [^{111}In]In-DTPA-octreotide scintigraphy using the "Krenning score". This semiquantitative score relates the visual uptake in the tumour to that in normal organ tissue, particularly the liver and spleen. However, the emergence of ^{68}Ga-SSA positron emitting tomography (PET) imaging, with a better diagnostic performance and a higher patient comfort, has made the use of [^{111}In]In-DTPA-octreotide and the traditional Krenning score obsolete. In the Netherlands both [^{68}Ga]Ga-DOTATATE and [^{68}Ga]Ga-DOTATOC are used for imaging of NENs. To be eligible for PRRT, the uptake in the tumour should be higher than in normal liver parenchyma (considered by some to be equivalent to the traditional Krenning 3 score). During treatment patients should be self-supporting and therefore a Karnofsky performance status (KPS) of at least 60 is required. To prevent severe toxicity, the following pre-treatment laboratory values are required: creatinine clearance >40 mL/min, haemoglobin levels ≥6 mmol/L, leucocytes >2 x 10^9/L, platelet count >75 x 10^9/L, bilirubin, alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) <3 times the upper limit of normal and albumin >30 g/L. Contra-indications are severe cardiac impairment (NYHA III or IV), pregnancy or breastfeeding and a life expectancy of less than 3 months (14).

Efficacy of PRRT

Tumour response

The effect of PRRT on tumour growth and survival was proven in several phase-2 studies and the phase-3 NETTER-1 study (15). In the latter study, the effect of four cycles of 7.4 GBq [^{177}Lu]Lu-DOTATATE plus long-acting octreotide 30 mg was compared to a control group that was treated with high dose of 60 mg long-acting octreotide. Patients had a grade 1 or 2 midgut NET and were all progressive on long-acting octreotide. Results of PRRT were impressive. The rate of progression free survival (PFS) after 20 months as well as the over-all response rate were about six times higher for patients treated with [^{177}Lu]Lu-DOTATATE (20 months PFS 65%, ORR 18%) than in the control group (20 months PFS 11% and ORR 3%). Moreover, the risk of progressive disease (PD) or death was 79% lower in the [^{177}Lu]Lu-DOTATATE group than in the control group. Recently, an update of the overall survival (OS) data was published (16). After a follow-up of 76 months in the intention-to-treat population, the median OS was 48 months in the [^{177}Lu]Lu-DOTATATE group, which did not significantly differ from the median OS of 36 months in the control group. However, 36% of the patients in the control group switched to the PRRT treatment during follow-up, which probably had a major effect on the results. Data for the different types of GEPNETs and bronchial NETs were provided by the large prospective phase-2 study from the Erasmus MC (14). This study included patients with GEPNET, bronchial NET and NET of unknown primary origin, and all patients were treated with [^{177}Lu]Lu-DOTATATE. A median PFS of 29 months and a median OS of 63 months were observed in 443 patients with bronchial- and GEPNET who received

a cumulative activity of 22.2-29.6 GBq (600-800 mCi) [^{177}Lu]Lu-DOTATATE. An ORR of 39% after PRRT was found, whereas stable disease (SD) was observed in 43% of the patients. Results of PRRT in the largest phase 2/3 studies are presented in table 1.

Quality of life

In addition to tumour response and survival, PRRT can influence quality-of-life. In a group of 265 patients with metastatic or inoperable NETs, receiving 22.2-29.6 GBq [^{177}Lu]Lu-DOTATATE (completed by 241/265), European Organisation for Research and Treatment of Cancer quality of life questionnaire scores were prospectively registered, to measure global health status quality of life (GHS/QoL), as well as several clinical symptoms and several domains of functioning (20). Independent of tumour response, there was an increase in GHS/QoL, emotional and social functioning and a decrease of insomnia, appetite loss and diarrhoea. In patients who reported decreased GHS/QoL at baseline, clinically relevant improvements were seen in 36%, in patients who reported fatigue, in 49%; for nausea/vomiting, in 70%; for pain, in 53%; for dyspnoea, in 44%; for insomnia, in 59%; for appetite loss, in 63%; for constipation in 60%; and for diarrhoea in 67% (21). The effect on QOL was confirmed in the phase-3 NETTER-1 study, which demonstrated a longer time to deterioration (TTD) in the domains of global health, physical functioning, diarrhoea, pain, body image, disease-related worries and fatigue (22).

By reducing disease activity and hormone hypersecretion, PRRT can have an effect on levels of circulation hormones and correlating symptoms. In patients with a carcinoid syndrome the effect of PRRT was especially significant regarding both flushing and bowel movements. Two-thirds of the patients who had at least two episodes of flushing per day had a minimal decrease of 50% of these episodes. The bowel movement frequency of patients with diarrhoea at least four times a day, 47% experienced more than 30% decrease in frequency of diarrhoea, and 29% experienced even more than 50% decrease (21). Also, positive effects of PRRT on hormonal levels and symptoms have been observed in patients with functioning pancreatic NET syndromes, such as insulinoma, gastrinoma, glucagonoma and VIPoma (23).

Toxicity

(Sub)acute toxicity

Acute and subacute side effects of PRRT are generally mild. Nausea and vomiting are mostly related to the co-infusion of amino acids, administered for renal protection by preventing tubular uptake of [^{177}Lu]Lu-DOTATATE and consequent radiation of the renal parenchyma. Other side effects include fatigue, mild hair loss and mild abdominal pain in a minority of patients. Bone marrow toxicity mainly affects red blood cells, platelets and white blood cells, with the nadir to be expected 4-6 weeks after each therapy. However, the bone marrow toxicity is usually self-limiting. Large series report grade 3/4 hematotoxicity in 3.1-11.3% for [^{177}Lu]Lu-DOTATATE. In general, blood counts restore within 3-6 months after treatment (24-26). The most commonly found predictors for subacute hematotoxicity are poor renal function, low blood cell counts at baseline and previous chemotherapy (25-29). Long-term adverse events relate mainly to the kidneys and the bone marrow.

Long-term nephrotoxicity

PRRT can lead to a yearly decline of renal function due to radiation damage. An important part of the dose to the kidneys is due to reabsorption of the radiolabelled peptide in the proximal renal tubular cells. This can partially be prevented

Table 1. Results of the largest phase 2 and phase 3 studies including different types of neuroendocrine tumour patients.

	No patients	ORR (%)	SD (%)	PD (%)	Median PFS (months)	Median OS (months)
Strosberg et al (15,16)	117	18	60	23	28	48
Brabander et al (14)	443	39	43	12	29	63
Hamiditabar et al (17)	132	9	50	41	NR	NR
Roman et al (18)	200	24	38	4	27	43
Demirci et al (19)	160	50	22	28	36	55

by co-infusion of positively charged amino acids (30-33). A combination of lysine and arginine has shown to be safe and effective, resulting in a dose reduction of up to 40%, allowing for escalation of administered activity. Currently, the use of amino acids is standard of care and implemented in all guidelines. The most commonly found risk factors for nephrotoxicity are old age, hypertension, diabetes mellitus, high renal dose, impaired renal function at baseline and previous chemotherapy (25,26,34-37). In the NETTER-1 study and in the data from the Erasmus MC (13,38), there was no therapy related long term kidney failure established. PRRT in combination with co-infusion of amino acids is therefore considered a safe treatment for the kidneys.

Long-term hematological toxicity

A known risk of PRRT is the induction of secondary myelodysplastic syndrome (MDS) and acute leukemia (AL). These events are considered stochastic and are observed in the years after PRRT (39). In the studies where patients were only treated with [^{177}Lu]Lu-DOTATATE, the combined incidence of MDS/AL was approximately 2-3%, with AL being the least common (about 0.7%) and generally occurring after several years (at least 12 months) (38,40). An unusual high incidence was reported by Brieau et al., however (41). In 20 patients, heavily pre-treated with alkalizing chemotherapeutic agents and receiving [^{177}Lu]Lu- DOTATATE (intended dose 22.2–29.6 GBq), 3 (15%) patients developed MDS and one (5%) patient developed AL. These patients were pre-treated with 6–20 cycles chemotherapy with alkalizing agents; the high incidence of this alarming effect most likely reflects the natural course after treatment with myelotoxic chemotherapies. Therefore, PRRT should preferably be given prior to these therapies or at the point no alternative therapeutic option is left.

PRRT in the international guidelines

Several major randomised controlled trials have led to the registration of systemic, targeted approaches for the treatment of advanced and inoperable grade 1 and 2 NETs. For intestinal and pancreatic NETs with a Ki-67 index of <10%, treatment with non-radionuclide labelled ('cold') SSAs is now the standard first line treatment. For NETs of the small intestine PRRT with [^{177}Lu]Lu-DOTATATE is the preferable second line treatment in both the ENETS and ESMO guidelines (4,42), as the NETTER-1 study was performed in patients with midgut NETs. At this moment, there is no phase-3 evidence for the treatment of pancreatic NETs. However, there is abundant data from phase-2 studies and meta-analyses demonstrating the excellent effect of PRRT in panNETs. The results of several phase-3 studies in panNETs are to be expected in the coming years. Until then, the recommended second-line treatments for panNETS are targeted drugs such as everolimus (an inhibitor of mammalian target of rapamycin) and sunitinib (a tyrosine kinase inhibitor). The RADIANT trials support the use of everolimus in advanced NETs associated with carcinoid syndrome (RADIANT-2) (43), advanced P-NETs (RADIANT-3) (44) and advanced non-functioning NETs from the lung and gastrointestinal tract (RADIANT-4) (45). The effect of sunitinib was shown in a randomised trial in 2011, with a median PFS of 11.4 months in the sunitinib group versus 5.5 months in the placebo group (46).

Salvage therapy

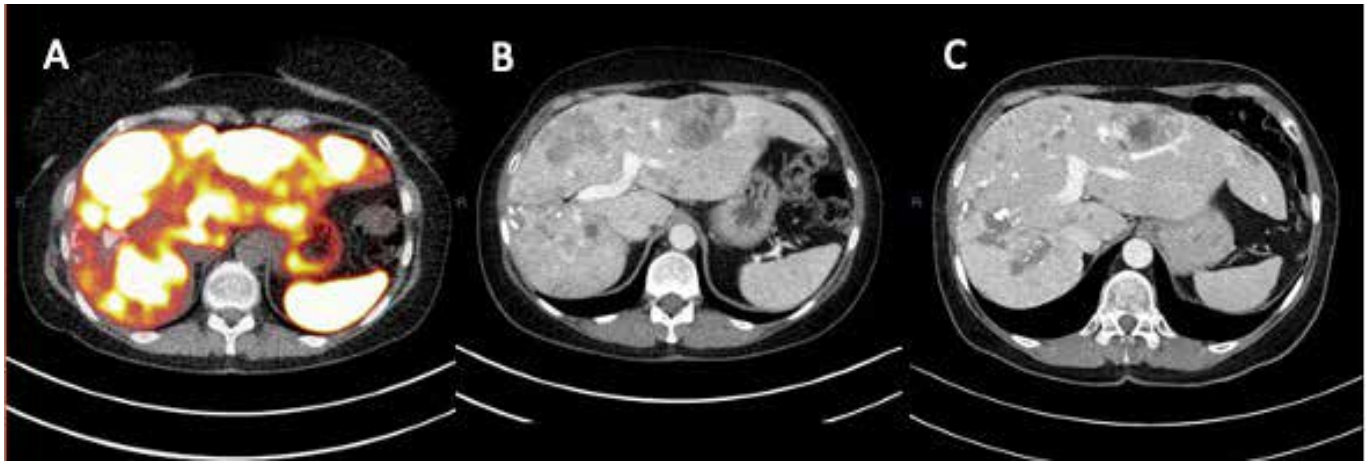
For patients who initially had benefit from PRRT (i.e. a tumour response of at least 18 months after the first cycle of PRRT), salvage treatment can be considered in case of disease progression. In a meta-analysis on the effect of re-PRRT (R-PRRT), the pooled median PFS was 14 months with a pooled median OS of 27 months. Similarly, the pooled ORR was 17% with a disease control rate of 77% (47). These results are not as good as initial treatment, however only two cycles of 7.4 GBq are administered to these patients (instead of four cycles of 7.4 GBq). Also, the increase in tumour burden might be an explanation for the results. Toxicity rates are in line with primary treatment and no additional cases of MDS/AL were reported (48). Moreover, no additional kidney toxicity was reported in the largest study in retreatment. It is therefore considered safe to treat patients with two, four, or occasionally, providing blood counts and kidney parameters are in good order, even six additional cycles of [^{177}Lu]Lu -DOTATATE.

Neo-adjuvant treatment

With surgery being the only treatment with curative intent, PRRT can be applied in a neo-adjuvant setting. Due to involvement of adjacent vascular structures and organs of advanced panNETs, surgery may be complex or accompanied with an increased risk of recurrence and surgery-related morbidity. The ORR in panNETs is 13-57% (17,38,49,50) and could be therefore an option for downstaging of neo-adjuvant treatment. The largest study in 49 patients who were treated with a neo-adjuvant intent, eventually 26 patients underwent surgery (51). Downstaging of the tumour-vessel interface was observed in 38% of patients. The median OS was 14.7 years in the group patients who underwent surgery and 5.5 years in the group who received only PRRT. These results demonstrate that the neo-adjuvant use of PRRT is a valuable option for patients with locally advanced panNETs and can be considered for selected patients.

PRRT for other SSTR positive tumours

Several malignancies other than NETs can overexpress SSTRs, including meningiomas, paragangliomas, small cell lung carcinomas, melanomas and



Images of a partial response after re-re-re-PRRT (cycle 9 and 10) in a patient with a NET of unknown origin with extensive metastases in the liver. A: Axial slice of [^{68}Ga]Ga-DOTATATE PET-CT before PRRT demonstrating multiple SSTR positive metastases in the liver. B and C: Axial slice of contrast enhanced CT before (B) and after (C) PRRT demonstrating a partial response.

thyroid cancer. However, even high expression of SSTRs (and thus a high effective dose) may not be enough to be effective, since the tumour cell type must be radiosensitive as well. Moreover, tumours with a high growth rate, such as small cell lung carcinomas, may not be sufficiently treated in an 8 weeks interval schedule (52). A recent retrospective study including 15 patients with progressive, treatment-refractory meningiomas was published (53). Currently, no established systemic therapy is available for this subgroup of patients. Although the median PFS after PRRT was limited, it seemed to be longer than the current standard of care. Also, treatment with [^{177}Lu]Lu-DOTATATE reduced the tumour growth rate in the majority of patients and resulted in disease stabilization in approximately half of the study population. A review on PRRT used in thyroid cancer identified 88 patients (in 15 publications) treated with four different radiopharmaceuticals (54). Best outcome was PR in 4.5% and SD in 43%. Though in the latter study the fraction of disease progression at baseline is unknown and unsuccessful cases may be unreported, it shows that treatment with radiolabelled SSAs can be a viable option for patients with non-NET SSTR positive tumours, especially when alternative therapeutic options are lacking.

PRRT with alpha emitting radionuclides

The use of alpha emitting radionuclides in radioligand therapy for both prostate cancer and NETs has emerged in the last decade. Alpha emitters offers advantages over beta emission due to the high linear energy transfer (LET) and limited range in tissue. This results in the selective radiation of tumours cells through double strand DNA breaks while sparing healthy tissue. In NETs the use of Actinium-225, Lead-212 and Bismuth-213 are being studied (55-57). For [^{225}Ac]Ac-DOTATATE most publications come from India (56). The largest study including 32 patients that were treated with 100 kBq/kg demonstrated a PR in 15/24 patients (63%) and a SD in 9/24 patients (38%). The optimal amount of activity is not yet known and a phase-1 dose-escalation study with [^{225}Ac]Ac-DOTATATE will start in 2023 in the Erasmus MC. For Lead-212 a recent dose-escalation study was published (57). This study included 20 patients that received four cycles of [^{212}Pb]Pb-DOTAMTATE. A radiological response was found in 80% of patients and no severe side effects were reported. The use of alpha emitting radionuclides will probably increase in the upcoming years; however, much research is needed to establish the optimal amount of activity and the best place in the treatment sequence.

Conclusion

PRRT with [^{177}Lu]Lu-DOTATATE is a safe and effective treatment option for patients with metastatic or inoperable NETs. In terms of radiographical response, patients' quality-of-life and progression free survival, the results of PRRT are outstanding. With appropriate patient selection, side effects from PRRT are typically mild and self-limiting. After the EMA and FDA approval of this radiopharmaceutical, the use in clinical practice has emerged and implementation in the international guidelines is accomplished. Ongoing research will determine the role in other SSTR positive tumours and new strategies to improve this treatment even further.

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References

1. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One Hundred Years After "Carcinoid": Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States. J Clin Oncol. 2008;26:3063-72
2. IKNL GEP NET report 2020
3. Basuroy R, Bouvier C, Ramage JK, Sissons M, Kent A, Srirajaskanthan R. Presenting Symptoms and Delay in Diagnosis of Gastrointestinal and Pancreatic Neuroendocrine Tumours. Neuroendocrinology. 2018;107:42-9
4. Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Neuroendocrinology. 2016;103:172-85
5. Knigge U, Hansen CP. Surgery for GEP-NETs. Best Pract Res Clin Gastroenterol. 2012;26:819-31
6. Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group. J Clin Oncol. 2009;27:4656-63
7. Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al. Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. N Engl J Med. 2014;371:224-33
8. Lee A, Chan DL, Wong MH, Li BT, Lumba S, Clarke SJ, et al. Systematic Review of the Role of Targeted Therapy in Metastatic Neuroendocrine Tumors. Neuroendocrinology. 2017;104:209-22
9. Krenning EP, Bakker WH, Breeman WA, Koper JW, Kooij PP, Ausema L, et al. Localisation of endocrine-related tumours with radioiodinated analogue of somatostatin. Lancet. 1989;1(8632):242-4
10. Krenning EP, Kooij PP, Bakker WH, Breeman WA, Postema PT, Kwekkeboom DJ, et al. Radiotherapy with a radiolabeled somatostatin analogue, [111In-DTPA-D-Phe1]-octreotide. A case history. Ann N Y Acad Sci. 1994;733:496-506
11. Kwekkeboom DJ, Bakker WH, Kooij PP, Konijnenberg MW, Srinivasan A, Erion JL, et al. [177Lu-DOTAOTyr3]octreotate: comparison with [111In-DTPAo] octreotide in patients. Eur J Nucl Med. 2001;28:1319-25
12. Reubi JC, Schär JC, Waser B, Wenger S, Heppeler A, Schmitt JS, et al. Affinity profiles for human somatostatin receptor subtypes SST1–SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. Eur J Nucl Med. 2000;27:273-82
13. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 Trial of 177 Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med. 2017;376:125-35
14. Brabander T, van der Zwan WA, Teunissen JJM, Kam BLR, Feelders RA, de Herder WW, et al. Long-Term Efficacy, Survival, and Safety of [177Lu-DOTA0 ,Tyr3]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors. Clin Cancer Res. 2017;23:4617-24
15. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med. 2017;376:125-35
16. Strosberg JR, Caplin ME, Kunz PL, Ruszniewski PB, Bodei L, Hendifar A, et al. 177Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. Lancet Oncol. 2021;22:1752-63
17. Hamiditabar M, Ali M, Roys J, Wolin EM, O'Dorisio TM, Ranganathan D, et al. Peptide Receptor Radionuclide Therapy With 177Lu-Octreotate in Patients With Somatostatin Receptor Expressing Neuroendocrine Tumors: Six Years' Assessment. Clin Nucl Med. 2017;42:436-43
18. Garske-Román U, Sandström M, Fröss Baron K, Lundin L, Hellman P, Welin S, et al. Prospective observational study of 177Lu-DOTA-octreotate therapy in 200 patients with advanced metastasized neuroendocrine tumours (NETs): feasibility and impact of a dosimetry-guided study protocol on outcome and toxicity. Eur J Nucl Med Mol Imaging. 2018;45:970-88
19. Demirci E, Kabasakal L, Toklu T, Ocak M, Şahin OE, Alan-Selcuk N, et al. 177Lu-DOTATATE therapy in patients with neuroendocrine tumours including high-grade (WHO G3) neuroendocrine tumours: response to treatment and long-term survival update. Nucl Med Commun. 2018;39:789-96
20. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials

in oncology. J Natl Cancer Inst. 1993;85:365-76
21. Khan S, Krenning EP, van Essen M, Kam BL, Teunissen JJ, Kwekkeboom DJ. Quality of Life in 265 Patients with Gastroenteropancreatic or Bronchial Neuroendocrine Tumors Treated with [177Lu-DOTA0,Tyr3]Octreotate. J Nucl Med. 2011;52:1361-8
22. Strosberg J, Wolin E, Chasen B, Kulke M, Bushnell D, Caplin M, et al. Health-Related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumors Treated With 177Lu-Dotatate in the Phase III NETTER-1 Trial. J Clin Oncol Off J Am Soc Clin Oncol. 2018;36:2578-84
23. Zandee WT, Brabander T, Blažević A, Kam BLR, Teunissen JJM, Feelders RA, et al. Symptomatic and Radiological Response to 177Lu-DOTATATE for the Treatment of Functioning Pancreatic Neuroendocrine Tumors. J Clin Endocrinol Metab. 2019;104:1336-44
24. Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, et al. Treatment With the Radiolabeled Somatostatin Analog [177Lu-DOTA0,Tyr3] Octreotate: Toxicity, Efficacy, and Survival. J Clin Oncol. 2008;26:2124-30
25. Imhof A, Brunner P, Marincek N, Briel M, Schindler C, Rasch H, et al. Response, Survival, and Long-Term Toxicity After Therapy With the Radiolabeled Somatostatin Analogue [90Y-DOTA]-TOC in Metastasized Neuroendocrine Cancers. J Clin Oncol. 2011;29:2416-23
26. Bodei L, Kidd M, Paganelli G, Grana CM, Drozdov I, Cremonesi M, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. Eur J Nucl Med Mol Imaging. 2015;42:5-19
27. Bergsma H, Konijnenberg MW, Kam BLR, Teunissen JJM, Kooij PP, de Herder WW, et al. Subacute haematotoxicity after PRRT with 177Lu-DOTA-octreotate: prognostic factors, incidence and course. Eur J Nucl Med Mol Imaging. 2016;43:453-63
28. Svensson J, Berg G, Wängberg B, Larsson M, Forssell-Aronsson E, Bernhardt P. Renal function affects absorbed dose to the kidneys and haematological toxicity during 177Lu-DOTATATE treatment. Eur J Nucl Med Mol Imaging [Internet]. 2015 Feb 6 [cited 2015 Mar 25]; Available from: http://link.springer.com/10.1007/s00259-015-3001-1
29. Kesavan M, Claringbold PG, Turner JH. Hematological Toxicity of Combined 177 Lu-Octreotate Radiopeptide Chemotherapy of Gastroenteropancreatic Neuroendocrine Tumors in Long-Term Follow-Up. Neuroendocrinology. 2014;99108-17
30. Rolleman EJ, Valkema R, de Jong M, Kooij PPM, Krenning EP. Safe and effective inhibition of renal uptake of radiolabelled octreotide by a combination of lysine and arginine. Eur J Nucl Med Mol Imaging. 2003;30:9-15
31. Rolleman EJ, Melis M, Valkema R, Boerman OC, Krenning EP, de Jong M. Kidney protection during peptide receptor radionuclide therapy with somatostatin analogues. Eur J Nucl Med Mol Imaging. 2010;37:1018-31
32. Bodei L, Cremonesi M, Zoboli S, Grana C, Bartolomei M, Rocca P, et al. Receptor-mediated radionuclide therapy with 90Y-DOTATOC in association with amino acid infusion: a phase I study. Eur J Nucl Med Mol Imaging. 2003;30:207-16
33. Jamar F, Barone R, Mathieu I, Walrand S, Labar D, Carlier P, et al. 86Y-DOTA0)-D-Phe1-Tyr3-octreotide (SMT487)--a phase 1 clinical study: pharmacokinetics, biodistribution and renal protective effect of different regimens of amino acid co-infusion. Eur J Nucl Med Mol Imaging. 2003;30:510-8
34. Mariniello A, Bodei L, Tinelli C, Baio SM, Gilardi L, Colandrea M, et al. Long-term results of PRRT in advanced bronchopulmonary carcinoid. Eur J Nucl Med Mol Imaging. 2016;43:441-52
35. Bodei L, Cremonesi M, Ferrari M, Pacifici M, Grana CM, Bartolomei M, et al. Long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with 90Y-DOTATOC and 177Lu-DOTATATE: the role of associated risk factors. Eur J Nucl Med Mol Imaging. 2008;35:1847-56
36. Valkema R, Pauwels SA, Kvols LK, Kwekkeboom DJ, Jamar F, de Jong M, et al. Long-term follow-up of renal function after peptide receptor radiation therapy with (90)Y-DOTA(0),Tyr(3)-octreotide and (177)Lu-DOTA(0), Tyr(3)-octreotate. J Nucl Med Off Publ Soc Nucl Med. 2005;46 Suppl 1:83S-91S
37. Erbas B, Tuncel M. Renal Function Assessment During Peptide Receptor Radionuclide Therapy. Semin Nucl Med. 2016;46:462-78
38. Brabander T, van der Zwan WA, Teunissen JJM, Kam BLR, Feelders RA, de Herder WW, et al. Long-Term Efficacy, Survival, and Safety of [177Lu-DOTA0 ,Tyr3]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors. Clin Cancer Res. 2017;23:4617-24
39. Kesavan M, Turner JH. Myelotoxicity of Peptide Receptor Radionuclide Therapy of Neuroendocrine Tumors: A Decade of Experience. Cancer Biother Radiopharm.

2016;31:189-98
40. Sabet A, Ezziddin K, Pape UF, Ahmadzadehfar H, Mayer K, Poppel T, et al. Long-Term Hematotoxicity After Peptide Receptor Radionuclide Therapy with 177Lu-Octreotate. J Nucl Med. 2013;54:1857-61
41. Brieau B, Hentic O, Lebtahi R, Palazzo M, Ben Reguiga M, Rebours V, et al. High risk of myelodysplastic syndrome and acute myeloid leukemia after 177 Lu-octreotate PRRT in NET patients heavily pretreated with alkylating chemotherapy. Endocr Relat Cancer. 2016;23:L17-23
42. Pavel M, Öberg K, Falconi M, Krenning EP, Sundin A, Perren A, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31:844-60
43. Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet. 2011;378:2005-12
44. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011;364:514-23
45. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2015;387:968-77
46. Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011;36:501-13
47. Kim YI. Salvage peptide receptor radionuclide therapy in patients with progressive neuroendocrine tumors: a systematic review and meta-analysis. Nucl Med Commun. 2021;42:451-8
48. van der Zwan WA, Brabander T, Kam BLR, Teunissen JJM, Feelders RA, Hofland J, et al. Salvage peptide receptor radionuclide therapy with [177Lu-DOTA,Tyr3]octreotate in patients with bronchial and gastroenteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2019;46:704-17
49. Ezziddin S, Khalaf F, Vanezi M, Haslerud T, Mayer K, Al Zreiqat A, et al. Outcome of peptide receptor radionuclide therapy with 177Lu-octreotate in advanced grade 1/2 pancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2014;41:925-33
50. Bodei L, Cremonesi M, Grana CM, Fazio N, Iodice S, Baio SM, et al. Peptide receptor radionuclide therapy with 177Lu-DOTATATE: the IEO phase I-II study. Eur J Nucl Med Mol Imaging. 2011;38:2125-35
51. Minczeles NS, van Eijck CHJ, van Gils MJ, van Velthuysen MLF, Nieveen van Dijkum EJM, Feelders RA, et al. Induction therapy with 177Lu-DOTATATE procures long-term survival in locally advanced or oligometastatic pancreatic neuroendocrine neoplasm patients. Eur J Nucl Med Mol Imaging. 2022;49:3203-14
52. van Essen M, Krenning EP, Kooij PP, Bakker WH, Feelders RA, de Herder WW, et al. Effects of therapy with [177Lu-DOTA0, Tyr3] octreotate in patients with paraganglioma, meningioma, small cell lung carcinoma, and melanoma. J Nucl Med. 2006;47:1599-606
53. Minczeles NS, Bos EM, de Leeuw RC, Kros JM, Konijnenberg MW, Bromberg JEC, et al. Efficacy and safety of peptide receptor radionuclide therapy with [177Lu] Lu-DOTA-TATE in 15 patients with progressive treatment-refractory meningioma. Eur J Nucl Med Mol Imaging. 2023;50:1195-204
54. Salavati A, Puranik A, Kulkarni HR, Budiawan H, Baum RP. Peptide Receptor Radionuclide Therapy (PRRT) of Medullary and Nonmedullary Thyroid Cancer Using Radiolabeled Somatostatin Analogues. Semin Nucl Med. 2016;46:215-24
55. Kratochwil C, Giesel FL, Bruchertseifer F, Mier W, Apostolidis C, Boll R, et al. 213Bi-DOTATOC receptor-targeted alpha-radionuclide therapy induces remission in neuroendocrine tumours refractory to beta radiation: a first-in-human experience. Eur J Nucl Med Mol Imaging. 2014;41:2106-19
56. Ballal S, Yadav MP, Bal C, Sahoo RK, Tripathi M. Broadening horizons with 225Ac-DOTATATE targeted alpha therapy for gastroenteropancreatic neuroendocrine tumour patients stable or refractory to 177Lu-DOTATATE PRRT: first clinical experience on the efficacy and safety. Eur J Nucl Med Mol Imaging. 2020;47:934-46
57. Delpassand ES, Tworowska I, Esfandiari R, Torgue J, Hurt J, Shafie A, et al. Targeted α -Emitter Therapy with 212 Pb-DOTAMTATE for the Treatment of Metastatic SSTR-Expressing Neuroendocrine Tumors: First-in-Humans Dose-Escalation Clinical Trial. J Nucl Med. 2022;63:1326-33

Radiosynoviorthese in persisterende synovitis, relatief onbekend en ondergebruikt in Nederland

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Introductie

Het concept radiosynoviorthese of radiatie synovectomie (RSO), oftewel het intra-articulair toedienen van een radio-isotoop ter behandeling van artritis of synovitis, werd ongeveer een eeuw geleden voor het eerst beschreven in de medische literatuur. Een van de vroegste publicaties over toediening van radio-isotopen in gewrichten stamt uit 1924 (1) en de eerste klinische resultaten van RSO werden in 1952 gepubliceerd door Fellinger en Schmid (2). Op dit moment wordt deze nucleair geneeskundige therapie in sterk wisselende mate uitgevoerd op verschillende plekken in de wereld. In Duitstalige landen wordt het frequent toegepast, vooral in Duitsland zelf, waar het de tweede meest toegepaste nucleair geneeskundige therapie is met circa 70.000 behandelingen per jaar (3). In Spaanstalige landen zoals Spanje en Argentinië, maar ook in Turkije, de Filipijnen en in de Verenigde Staten wordt RSO ook relatief vaak uitgevoerd, echter niet alleen ter behandeling van therapieresistente synovitis, maar ook bij hemofilie artropathie (4).
Hoewel precieze getallen in de literatuur ontbreken, kan worden gesteld dat RSO in Nederland relatief onbekend en zeker ondergebruikt is. In Nederland biedt een handvol instituten RSO van de knie met [^{90}Y]Yttrium aan. Slechts in enkele ziekenhuizen wordt naast RSO van de knie met [^{90}Y]Yttrium RSO van kleinere gewrichten met [^{186}Re]Re-sulfide en [^{169}Er]Er-citraat gepraktiseerd.
Artritis en of synovitis is een veelvoorkomend probleem en is regelmatig een chronische conditie. Reumatoïde artritis (RA) is de meest voorkomende oorzaak van inflammatoire artritis. De prevalentie van RA ligt tussen de 0,24% en 1% en is hoger in de Verenigde Staten en Noordwest-Europa in vergelijking tot de rest van de wereld. De jaarlijkse incidentie van RA is in westerse landen ongeveer 40 per 100.000 (5-8). Artritis wordt ook geregeld gezien als onderdeel van psoriasis. De incidentie van psoriasis gerelateerde artritis is 6 per 100.000 per jaar met een prevalentie van 1 per 1000 (9,10). Vaker voorkomend is osteoartritis, een gewrichtsaandoening die veel bij ouderen wordt gezien. Een van de belangrijkste vormen van osteoartritis is knie osteoartritis, en heeft een incidentie van circa 240 gevallen per 100.000 persoon jaren (11).
In eerste instantie wordt artritis en synovitis behandeld met lokale en/of systemische medicatie zoals nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), glucocorticosteroïden (GC) en "biologicals". Bij onvoldoende resultaat kunnen glucocorticosteroïden intra-articulair worden toegediend. Wanneer de artritis/synovitis alsnog persisteert zijn chemische, chirurgische en radiatie synovectomie een optie. Chemische synovectomie kan worden uitgevoerd met osmiumzuur, maar is niet meer in zwang door de toxiciteit van deze stof, welke als bijwerking van de behandeling onder andere longfibrose en oogirritatie kan veroorzaken. Chirurgische synovectomie al dan niet in combinatie met RSO behoort wel tot het standaardrepertoire bij persisterende synovitis en is vaak eerste keuze bij synovitis pigmentosa villonodularis (pigmented villonodular synovitis (PVNS)), tegenwoordig beter bekend als tenosynovial giant cell tumours (TGCT).
In dit overzichtsartikel zal dieper worden ingegaan op radiosynoviorthese of radiatie synovectomie. Onder andere zal worden ingegaan op het werkingsmechanisme van RSO, de gebruikte radiofarmaca, klinische resultaten en de verwachting omtrent de toekomst van deze vorm van nucleair geneeskundige therapie.

Werkingsmechanisme van RSO

Bij RSO worden aan colloïd deeltjes gebonden β-emitterende isotopen in het gewricht ingespoten. Deze worden opgenomen door fagocyterende ontstekingscellen en macrofaag-achtige synoviocyten welke zich bevinden in de intima van de synoviale membraan die aan de synoviale vloeistof grenst. Op deze manier wordt het ontstoken gewrichtskapsel dus van binnenuit bestraald (12) en deze bestraling induceert vervolgens cel necrose en remming van cel proliferatie. Zodoende kan de synovitis tijdelijk worden gestopt en progressie van

gewrichtsschade kan worden geremd (13).
Wereldwijd zijn in de loop der jaren veel radionucliden toegepast bij RSO o.a. [^{198}Au]Aurum, [^{153}Sm]Samarium, [^{188}Re]Rhenium, [^{32}P]Fosfor, [^{177}Lu]Lutetium, [^{166}Ho]Holmium en [^{165}Dy]Dysprosium (14-20). Er zijn op dit moment echter drie radiofarmaca commercieel verkrijgbaar in Nederland: [^{90}Y]Y-citraat, [^{186}Re]Re-sulfide, en [^{169}Er]Er-citraat, waarvan alleen [^{90}Y]Y-citraat in Nederland is geregistreerd (21). [^{186}Re]Re-sulfide en [^{169}Er]Er-citraat zijn voor RSO ook geregistreerd in zes andere Europese landen, o.a. Duitsland, Spanje en Tsjechië (21). Voor de fysische eigenschappen van deze drie commercieel verkrijgbare radiofarmaca wordt verwezen naar tabel 1. In het algemeen worden glucocorticosteroiden (GCs) toegevoegd aan de radiofarmaca om drie verschillende redenen. In de eerste plaats helpt de toevoeging van GCs om radiatie geïnduceerde synovitis te voorkomen. Een andere reden is om, via het direct optredend therapeutisch effect van de GCs, de tijd tussen de toediening van de radiofarmaca en het begin van het meer langdurige effect van de bestraling te overbruggen. De derde reden voor het toedienen van GCs is om de omvang van inflammatie en hypervasculariteit te verminderen en daarmee in theorie de kans op en de mate van eventuele lekkage van nucliden uit het gewricht te verminderen. In tabel 2 staan de gebruikelijk toegepaste doses van de radiofarmaca en GCs. [^{90}Y]Yttrium wordt doorgaans alleen gebruikt voor RSO van de knie. [^{186}Re]Rhenium wordt gebruikt voor RSO van de middelgrote gewrichten van de onderste en bovenste extremiteiten, zoals pols, elleboog, schouder, heup en enkel. [^{169}Er]Erbium wordt gebruikt voor RSO van kleinere gewrichten zoals de vingergewrichten, teengewrichten, acromioclaviculair gewricht en temporomandibulair gewricht.

Indicaties

Gebruikelijke indicaties voor RSO zijn chronische inflammatoire atritiden, zoals RA en artritis psoriatica. Indicaties voor niet-inflammatoire aandoeningen zijn onder meer osteoartritis, chondromatosis, PVNS en recidiverende hemartrose bij hemofilie. In Nederland wordt de therapie het meest uitgevoerd in het kader van RA, vooral wanneer andere therapie onvoldoende effect sorteert en de klachten beperkt zijn tot één of enkele gewrichten.

Contra-indicaties

In tabel 3 staan contra-indicaties beschreven. De absolute contra-indicaties voorkomen in de eerste plaats onbedoelde stralingsbelasting van ongeboren kinderen en zuigelingen van vrouwen die RSO ondergaan. Hoewel borstvoeding als contra-indicatie in de bijsluiter van [^{90}Y]Y-colloidsuspensie staat (injecteerbare [^{90}Y]Y-colloïdensuspensie (geneesmiddeleninformatiebank.nl), wordt door Pigrée en collegae geadviseerd om borstvoeding tenminste 1 maand te stoppen (22). Daarnaast voorkomen de absolute contra-indicaties onbedoelde bestraling van de patiënt zelf op plaatsen buiten het behandelde gewricht, door het excluderen van patiënten met aandoeningen van het gewricht met verhoogde kans op extra-articulaire lekkage, of verhoogde afvloed van isotopen door hyperemie. De relatieve contra-indicaties zijn bedoeld om behandelingen te voorkomen bij gewrichtsaandoeningen waarbij de kans op succes van RSO beperkt is.

Bijwerkingen

RSO wordt over het algemeen beschouwd als een veilige procedure en bijwerkingen worden zelden gezien. Fisher en collegae rapporteerden een frequentie van 3,3 'adverse events' per 100.000 (23). De mate van optreden van bijwerkingen hangt af van co-morbiditeit, leeftijd en het behandelde gewricht. Bij grotere gewrichten is door de grotere hoeveelheid gebruikte radioactiviteit de kans op sommige bijwerkingen groter. Tot bijwerkingen behoren pijn, roodheid en irritatie ter plaatse van de injectieplaats die doorgaans weer binnen enkele dagen verdwijnen. Daarnaast kan er een

Tabel 1. Fysische karakteristieken van [^{90}Y]Y-citraat, [^{186}Re]Re-sulfide en [^{169}Er]Er-citraat.

Nucliden	T1/2 (uren)	Energy (MeV) γ	Energy (MeV) β	Penetratie van β in synovium (mm) Gemiddeld	Penetratie van β in synovium (mm) Max	Penetratie van β in kraakbeen (mm) Max
[^{90}Y]Y-citraat	64	-	2.27	3.6	11.0	2.8
[^{186}Re]Re-sulfide	89	0.137	1.07	1.2	3.7	0.9
[^{169}Er]Er-citraat	226	-	0.34	0.3	1.0	0.2

Tabel 2. Doses van de radionucliden en doses van triamcinolonacetonide (TA) voor onderstaande gewrichten.

Gewrichten	[^{90}Y]Y-citraat (MBq) en TA (mg)	[^{186}Re]Re-sulfide (MBq) en TA (mg)	[^{169}Er]Er-citraat (MBq) en TA (mg)
Knie	185 - 222 / 40		
Schouder		74 - 148 / 40	
Elleboog		74 - 111 / 40	
Pols		37 - 74 / 20	
Heup		74 - 148 / 40	
Enkel		74 / 40	
Subtalar		74 / 20	
MCP			20 - 80 / 8
PIP / SCJ			10 - 20 / 4
DIP			10 - 15 / 4
MTP			30 - 40 / 8
TMT			20 - 40 / 8

Afkortingen: MCP = metacarpophalangeaal gewricht, PIP = proximaal interphalangeaal gewricht, SCJ = sternoclaviculair gewricht, DIP = distaal interphalangeaal gewricht, MTP = metatarsophalangeaal gewricht, TMT = tarsometatarsaal gewricht, ACJ = acromioclaviculair gewricht, TMJ = temporomandibulair gewricht

Tabel 3. Contra-indicaties voor radiosynoviorthese

Contra-indicaties
Absoluut: Zwangerschap Borstvoeding Lokale huidinfectie of septische artritis Geruptureerde Bakerse cyste Recente (<6 weken) operatie van het gewricht Ongecontroleerde gewrichtsbloeding
Relatief: Gewrichtsinstabiliteit met botdestructie Hooggradige botdestructie

korter durende 'flush' optreden ten gevolge van de mede toegediende GCs. Meer serieuze bijwerkingen zijn osteonecrose en intra-articulaire infectie, maar deze zijn zeldzaam. Daarnaast kan een "needle tract burn" optreden wanneer het radiofarmacon terug lekt door het injectiekanaal. De EANM guideline voor RSO vermeldt dat er geen verhoogd risico op maligniteiten na RSO is gerapporteerd (21).

Klinisch effect van RSO

RSO staat bekend als een effectieve behandeling voor de genoemde indicaties in patiënten met onvoldoende respons op eerdere medicamenteuze therapie. Vaak leidt de therapie tot een vermindering van ontsteking van het behandelde gewricht met verbetering van de gewrichtsfunctie. Het klinisch effect van RSO wordt al decennialang bestudeerd. In veel onderzoeken zijn echter subjectieve en semi-kwantitatieve parameters zoals pijn, 'globale patiënt score' en gewrichtszwelling gebruikt om de uitkomst te meten. Dit maakt de vergelijkbaarheid van de studies in de vorm van een meta-analyse soms moeilijk. Naast deze subjectieve parameters zijn ook objectieve, kwantitatieve parameters onderzocht zoals veranderingen in haalbare gewrichtshoek als maat voor gewrichtsfunctie of metingen op 3-fasen skeletscintigrafie. Andere voorbeelden zijn het meten van synoviale dikte of hoeveelheid synoviaal vocht middels MRI of echo en bepalingen van ontstekingsgerelateerde laboratoriumwaarden zoals BSE. Naast multipele case-serie studies zijn er vele prospectieve en dubbelblinde studies uitgevoerd (24-49). De gepubliceerde effectiviteit varieert van 40-90%. Uit reviews, gedeeltelijk met systematische meta-analyse, kan geconcludeerd worden dat RSO effectief is in persisterende synovitis

bij RA, psoriasis, spondylarthropathie en andere oorzaken van synovitis (50-56). De effectiviteit van RSO in hemofilie is voornamelijk gebaseerd op case series (56). Wetenschappelijk bewijs voor de effectiviteit van RSO als adjuvante therapie bij PVNS is mager (56).
Studies over lange termijneffecten van RSO zijn minder frequent (39,57-59). De gemiddelde effectduur wisselt van 22 maanden tot 5,7 jaar (39,57,58). De groep van Szentezi beschreef excellente en goede resultaten van RSO na 5 jaar in 71% (95% CI 67-74%) van de patiënten. Na 10 jaar daalde de effectiviteit tot 65% (95% CI 59-71%) (58). Goede effectiviteit na 5 jaar werd gevonden in 79% van de RA patiënten en 59% en 62% bij ankolyserende spondylitis en osteoarthritis patiënten, respectievelijk.

Toekomstvisie

Voor zover bekend zijn er geen studies naar het aantal uitgevoerde RSOs in de loop der jaren in Nederland. Het aantal RSOs in Duitsland lijkt niet te dalen. Liepe beschreef in 2015 40.000-60.000 RSOs per jaar en Freudenberg publiceerde in 2022 70.000 RSOs per jaar (1,2). In onze eigen ervaring is het aantal RSOs vergeleken met 20 jaar terug
tenminste gehalveerd. Gedeeltelijk kan dit verklaard worden door verbeterde DMARDs en "biologicals", waardoor de synovitis beter onder controle wordt gehouden en behandeling met RSO niet meer nodig is. Wellicht speelt onbekendheid met RSO hierbij echter ook een rol. Er zijn voorbeelden van kennislacunes op dit vlak bij behandelend specialisten, waarbij patiënten onterecht behandeling met RSO werd onthouden, en waarbij patiënten zelf moesten aandringen op behandeling of voor therapie moesten uitwijken naar een ander ziekenhuis.

In Nederland zijn er geen gegevens over aantal en leeftijd van RSO-experts, maar in Duitsland is 75% van de RSO-experts ouder dan 50 jaar (1). De in ons land beperkte blootstelling aan nucleaire geneeskunde en in het bijzonder nucleaire therapie, waaronder RSO, in curricula van de verwijzend specialisten en onvoldoende aandacht voor nucleaire therapie in de opleiding van nucleair deskundigen kan aanleiding zijn voor de relatieve onbekendheid. Ook is er zorg vanuit Europa over de beperkte exposure aan radionuclidentherapieën in de Nederlandse curricula. Wellicht kan een netwerk van RSO-experts de bekendheid met RSO vergroten.
In de laatste honderd jaar zijn de mogelijke radio-isotopen, waaronder α, β of Auger elektronen emitters voor therapieën aanzienlijk toegenomen (60). Er zijn verschillende α stralende isotopen geschikt voor therapie (61). Het meest welsprekende voorbeeld van α stralers is [^{225}Ac]Ac-PSMA-617 voor prostaatcarcinoom (62). Voor zover bekend zijn er nog geen α emitterende radiofarmaca voor RSO. Wellicht zouden α stralers voordelen kunnen hebben t.o.v. van de huidige gebruikte radiofarmaca ([^{90}Y]Y-citraat, [^{186}Re]Re-sulfide, en [^{169}Er]Er-citraat). Met de huidige wet- en regelgeving zal het een hele uitdaging zijn om een α emitterend radiofarmacon voor RSO te produceren en toe te passen. Mede gezien de beperkte schaal ligt niet in de lijn der verwachting dat commerciële farmaceuten op korte termijn met alfa-emitterende radiofarmaca voor RSO gaan experimenteren, laat staan geschikt maken voor registratie.

Conclusie

RSO is effectief in persisterende artritis en synovitis bij RA, psoriasis, spondylarthropathie en andere oorzaken van synovitis. De effectiviteit van RSO in hemofilie is voornamelijk gebaseerd op case series. Wetenschappelijk bewijs voor de effectiviteit van RSO als adjuvante therapie bij PVNS is mager. RSO lijkt relatief onbekend in Nederland en wordt, in vergelijking met andere Europese landen waaronder Duitsland, in ons land ondergebruikt. Nieuwe ontwikkelingen, zoals het ontwikkelen van α emitterende radiofarmaca voor RSO zouden een extra impuls kunnen geven aan RSO.

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Referenties

1. Ishido C. Über die Wirkung des Radiothoriums auf die Gelenke. Strahlentherapie. 1924;15:537-44
2. Fellinger K, Schmid J. Die lokale Behandlung der rheumatischen Erkrankungen [Local therapy of rheumatic diseases]. Wien Z Inn Med. 1952;33:351-63
3. Freudenberg LS, Sewerin P, Ohlerth SM, Pomykala KL, Freudenberg S, Rischpler C, Lützen U. The future of radiosynoviorthesis: bright or bleak? Q J Nucl Med Mol Imaging. 2022;66:345-51. doi: 10.23736/S1824-4785.22.03475-6. Epub 2022 Jun 16
4. Liepe K. Radiosynovectomy in the therapeutic management of arthritis. World J Nucl Med. 2015;14:10-15
5. Hunter TM, Boytsov NN, Zhang X, Schroeder K, Michaud K, Araujo AB. Prevalence of rheumatoid arthritis in the United States adult population in healthcare claims databases, 2004-2014. Rheumatol Int. 2017;37:1551-7
6. Myasoedova E, Crowson CS, Kremers HM. Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955-2007. Arthritis Rheum. 2010;62:1576
7. Eriksson JK, Boytsov NN, Zhang X. Prevalence of rheumatoid arthritis in the United States

adult population in healthcare claims databases, 2004-2014. Rheumatol Int. 2017;37:1551-7
8. Crowson CS, Matteson EL, Myasoedova E, Michet CJ, Ernste FC, Warrington KJ, et al. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. Arthritis Rheum. 2011;63:633-9
9. Kaipaininen-Seppanen O. Incidence of psoriatic arthritis in Finland. Br J Rhematol. 1996:35:1289-91
10. Shbeeb M, Uramoto KM, Gibson LE, et al. The epidemiology of psoriatic arthritis in Olmsted County, Minnesota, USA, 1982-1991. J Rheumatol. 2000;27:1247-50
11. Oliveria SA, Felson DT, Reed JI, et al. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis Rheum. 1995;38:1134-41
12. Ingrand J. Characteristics of radio-isotopes for intra-articular therapy. Ann rheum Dis (Suppl). 1973;33:3-9
13. Meier-Ruge W, Muller W, Pavelka K. Effect of Yttrium-90 on experimental allergic arthritis in rabbits. Ann Rheum Dis. 1976;35:60-6
14. Ansell BM, Crook A, Mallard JR, E.G. B. Evaluation of intra-articular colloidal gold Au-198 in the treatment of persistent knee effusions. Ann Rheum Dis. 1963;22:435-9
15. Chinol M, Vallabhajosula S, Goldsmith SJ, Klein MJ, Deutsch KF, Chinen LK, et al. Chemistry and biological behavior of samarium-153 and rhenium-186-labeled hydroxyapatite particles: potential radiopharmaceuticals for radiation synovectomy. J Nucl Med. 1993;34:1536-42
16. Wang SJ, Lin WY, Chen MN, Chen JT, Ho WL, Hsieh BT, et al. Histologic study of effects of radiation synovectomy with Rhenium-188 microsphere. Nucl Med Biol. 2001;28:727-32
17. Ubios AM, Cabrini RL, Silberman FS, Miranda FF. Radiation effects produced by the intra-articular injection of 32P. Clin Orthop Relat Res. 1978;136:299-303
18. Abbasi I, Ishfaq M, Sohaib M. Preparation and pre-clinical study of 177Lu-labelled hydroxyapatite for application in radiation synovectomy of small joints. Q J Nucl Med Mol Imaging. 2011;55:458-68
19. Mumper RJ, Mills BJ, Ryo UY, Jay M. Polymeric microspheres for radionuclide synovectomy containing neutron-activated holmium-166. J Nucl Med. 1992;33:398-402
20. Hnatowich DJ, Kramer RI, Sledge CB, Noble J, Shortkroff S. Dysprosium-165 ferric hydroxide macroaggregates for radiation synovectomy. J Nucl Med. 1978;19:303-8
21. Kampen WU, Boddenberg-Pätzold B, Fischer M, Gabriel M, Klett R, Konijnenberg M, et al.; EANM Bone & Joint Committee, the Dosimetry Committee, the Oncology & Theranostics Committee. The EANM guideline for radiosynoviorthesis. Eur J Nucl Med Mol Imaging. 2022;49:681-708
22. Pigrée, G., Césini, J., Cruet-Hennequart, S. et al. Transfer of yttrium-90 to breast milk during radiosynoviorthesis of the knee joint. Eur J Nucl Med Mol Imaging. 2019;46:1591-93. https://doi.org/10.1007/s00259-019-04335-2.
23. Fischer M, Brinker A, Sickmüller B. Safety of Medicines: Detection and Reporting Adverse Reactions. In: Kampen W.U. FM, editor. Local Treatment of Inflammatory Joint Diseases: Springer International Publishing; 2015. p. 1-27
24. Bridgman JF, Bruckner F, Bleehen NM. Radioactive Yttrium in the treatment of rheumatoid knee effusions. Ann Rheum Dis. 1971;30:180-2
25. Gumpel JM, Roles NC. A controlled trial of intra-articular radiocolloids versus surgical synovectomy in persistent synovitis. Lancet. 1975;1:488-9
26. Menkes CJ, Le Go A, Verrier P, Aignan M, delbarre F. Double-blind study of Erbium 169 injection (synoviorthesis) in rheumatoid digitals joints. Ann Rheum Dis. 1977;36:254-6
27. Szanto E. Long-term follow-up of 90Yttrium-treated knee-joint arthritis. Scand J Rheumatol. 1977;6:209-12
28. Nissilä M, Antilla P, Hämäläinen M, Jalava S. Comparison of chemical, radiation and surgical synovectomy for kee joint synovitis. Scand J Rheumatol. 1978;7:225-8
29. Ruotsi A, Hypen M, Rekonen A, Oka M. Erbium-169 versus triamcinolone hexacetonide in the treatment of rheumatoid finger joints. Ann Rheum dis. 1979;38:45-7
30. Boussina I, Toussaint M, Ott H, Hermans P, Fallet GH. A double-blindstudy of Erbium 169 synoviorthesis in rheumatoid digital joints. Results after one year. Scand J Rheumatol. 1979;8:71-4
31. Gumpel JM, Metthews SA, Fisher M. Synoviorthesis with Erbium-169: a double -blind controlled comparison of Erbium-169 with corticosteroid. Ann Rheum Dis. 1979;38:71-4
32. Doherty M, Dieppe PA. Effect of intra-articular Yttrium-90 on chronic pyrophosphate artheopathy of the knee. Lancet. 1981;2:1243-6
33. Sheppeard H, Aldin A, Ward DJ.

Osmic acid versus Yttrium-90 in rheumatoid synovitis of the knee. Scand J Rheumatol. 1981;10:234-6
34. Stojanovic I, Stojanovic R, Gorkic D. A controlled study of the effect of radiation synovectomy of the knee joint in rheumatoid arthritis. Reumatologia. 1982;20:183-7
35. Grant AN, Bellamy N, Fryday-Field K, Disney T, Driedger A, Hobby K. Double-blind randomized controlled trial and six-year open follow-up of yttrium-90 radiosynovectomy versus triamcinolone hexacetonide in persistent rheumatoid knee synovitis. Inflammopharm. 1992;1:231-8
36. Edmonds J, Smart R, Laurent R et al. A comparative study of the safety and efficacy of dysprosium-165 hydroxide macro-aggregate and yttrium-90 silicate colloid in radiation synovectomy-a multicentre double blind clinical study. Br J Rheumatol. 1994;33:947-53
37. Tebib JG, Manil LM, Mödder G, et al. Better results with rhenium-186 radiosynoviorthesis than with cortivazol in rheumatoid arthritis (RA): a two-year follow-up randomized controlled multicentre study. Clin Exp Rheumatol. 2004;22: 609-16
38. Kahan A, Mödder G, Menkes CJ, et al. 169Erbium-citrate synoviorthesis after failure of local corticosteroid injections to treat rheumatoid arthritis-affected finger joints. Clin Exp Rheumatol. 2004;22:722-6
39. Jahangier ZN, Jacobs JWG, Lafeber FPJG, et al. Is radiation synovectomy for arthritis of the knee more effective than intra-articular treatment with gluccocorticoids? Arthritis Rheum. 2005;52:3391-402
40. Van der Zant FM, Jahangier ZN, Moolenburgh JD, Swen WAA, Boer RO, Jacobs JWG. Clinical effect of radiation synovectomy of the upper extremity joints: a randomised, double-blind, placebo-controlled study. Eur J Nucl Med Mol Imaging. 2007;34:212-8
41. Shin K, Lee JC, Choi HJ, Jeong JM, Son M, Lee YJ, Lee EB, Hong SH, Song YW. Radiation synovectomy using 188Re-tin colloid improves knee synovitis as shown by MRI in refractory rheumatoid arthritis. Nucl Med Commun. 2007;28:239-44
42. Chatzopoulos D, Moralidis E, Markou P, Makris V. Yttrium-90 radiation synovectomy in knee osteoarthritis: a prospective assessment at 6 and 12 months. Nucl Med Commun. 2009;30:472-9
43. Shamim SA, Kumar R, Halanaik D, Kumar A, Shandal V, Shukla J, Kumar A, Trikha V, Chandra P, Bandopadhayaya G, Malhotra A. Role of rhenium-188 tin colloid radiosynovectomy in patients with inflammatory knee joint conditions refractory to conventional therapy. Nucl Med Commun. 2010;31:814-20
44. Dos Santos MF, Furtado RN, Konai MS, Castiglioni ML, Marchetti RR, Silva CP, Natour J. Effectiveness of radiation synovectomy with Yttrium-90 and Samarium-153 particulate hydroxyapatite in rheumatoid arthritis patients with knee synovitis: a controlled, randomized, double-blinded trial. Clin Rheumatol. 2011;30:77-85
45. Liepe K, Zaknun JJ, Padhy A, Barrenechea E, Soroa V, Shrikant S, Asavatanabodee P, Jeong MJ, Dondi M. Radiosynovectomy using yttrium-90, phosphorus-32 or rhenium-188 radiocolloids versus corticoid instillation for rheumatoid arthritis of the knee. Ann Nucl Med. 2011;25:317-23
46. Kraft O, Kašparek R. Effectiveness of radiosynoviorthesis in the treatment of chronic synovitis of small and middle-sized joints affected by rheumatoid arthritis. Hell J Nucl Med. 2011;14:251-4
47. Vereb M, Liepe K, Fischer M, Kaliska L, Noskovicova L, Balogova S. Radiosynoviorthesis of acromioclavicular joint using 169Er-citrate: prospective evaluation of efficacy. Nucl Med Rev Cent East Eur. 2018;21:26-31
48. Szentesi M, Nagy Z, Géher P, Papp I, Kampen WU. A prospective observational study on the long-term results of 90Yttrium citrate radiosynoviorthesis of synovitis in osteoarthritis of the knee joint. Eur J Nucl Med Mol Imaging. 2019;46:1633-41
49. Zeiadin N, Rampakakis E, Turcotte E, Senta H, Sampalis JS, Thorne C. Safety and therapeutic value of radiosynoviorthesis with yttrium-90: a Canadian single-centre experience. Rheumatology (Oxford). 2021;60:2434-39
50. Deutsch E, Brodack JW, Deutsch KF. Radiation synovectomy revisited. Eur J Nucl Med. 1993;20:1113-27
51. Dos Santos MF, Furtado RN, Konai MS, Castiglioni ML, Marchetti RR, Silva CP, et al. Effectiveness of radiation synovectomy with Yttrium-90 and Samarium-153 particulate hydroxyapatite in rheumatoid arthritis patients with knee synovitis: a controlled, randomized, double-blinded trial. Clin Rheumatol. 2011;30:77-85
52. Heuft-Dorenbosch LL, de Vet HC, van der Linden S. Yttrium radiosynoviorthesis in the treatment of knee arthritis in rheumatoid arthritis: a systematic review. Ann Rheum Dis. 2000;59:583-6
53. Jones G. Yttrium synovectomy: a meta-analysis of the literature. Aust N Z J Med. 1993;23:272-5
54. Klett R, Lange U, Haas H, Voth M, Pinkert J. Radiosynoviorhesis of medium-sized joints with

rhenium-186-sulphide colloid: a review of the literature. Rheumatology. 2007;46:1531-7
55. van der Zant FM, Boer RO, Moolenburgh JD, Jahangier ZN, Bijlsma JW, Jacobs JW. Radiation synovectomy with (90)Yttrium, (186)Rhenium and (169)Erbium: a systematic literature review with meta-analyses. Clin Exp Rheumatol. 2009;27:130-9
56. van der Zant FM, Knol RJ, Broos WA. Radiosynoviorthesis: almost seventy years of experience but still somewhat fameless. Q J Nucl Med Mol Imaging. 2022;66:293-303. doi: 10.23736/S1824-4785.22.03470-7. Epub 2022 Jun 16
57. van der Zant FM, Jahangier ZN, Moolenburgh JD, van der Zee W, Boer RO, Jacobs JW. Radiation synovectomy of the ankle with 75 MBq colloidal 186rhenium-sulfide: effect, leakage, and radiation considerations. J Rheumatol. 2004;31:896-901
58. Goetz M, Klug S, Gelse K, Swoboda B, Carl HD. Combined arthroscopic and radiation synovectomy of the knee joint in rheumatoid arthritis: 14-year follow-up. Arthroscopy. 2011;27:52-9
59. Szentesi M, VAN DEN Wyngaert T, Géher P, Farbaky Z, Takács E, Csőre G, Kampen WU. Long-term clinical results from 10 years follow-up after radiosynoviorthesis: a prospective observational study. Q J Nucl Med Mol Imaging. 2022;66:324-33
60. Blower PJ. A nuclear chocolate box: the periodic table of nuclear medicine. Dalton Trans. 2015;44:4819-44
61. Poty S, Francesconi LC, McDevitt MR, Morris MJ, Lewis JS. α-Emitters for Radiotherapy: From Basic Radiochemistry to Clinical Studies-Part 2. J Nucl Med. 2018;59:1020-7
62. Kratochwil C, Bruchertseifer F, Giesel FL, Weis M, Verburg FA, Mottaghy F, Kopka K, Apostolidis C, Haberkorn U, Morgenstern A. 225Ac-PSMA-617 for PSMA-Targeted α-Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer. J Nucl Med. 2016;57:1941-44

Lutetium-177 PSMA for prostate cancer; current developments and challenges

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Abstract

[^{177}Lu]Lu-PSMA has shown to be effective and safe in patients with metastatic castration resistant prostate cancer (mCRPC), leading to Food and Drugs Authorization (FDA) approval in the United States of America for [^{177}Lu]Lu-PSMA-617 in March 2022 and to European Medical Agency (EMA) approval in December 2022. In the Netherlands, [^{177}Lu]Lu-PSMA-I&T is reimbursed since August 2021 for the same indication. This illustrates that a lot has happened since our initial report on [^{177}Lu]Lu-PSMA in the previous therapy special edition of Tijdschrift voor Nucleaire Geneeskunde, five years ago. This review will summarize recent scientific developments on [^{177}Lu]Lu-PSMA radioligand therapy. The most notable and impactful prospective trials included the TheraP-, and VISION-trial investigating [^{177}Lu]Lu-PSMA-617 in mCRPC patients. They will be discussed in more detail. Furthermore, several technical aspects of this novel therapy, relevant to the nuclear medicine community will be discussed. As [^{177}Lu]Lu-PSMA is a relatively new therapy, many unknowns concerning patient selection, imaging biomarkers and response monitoring still exist. This review will provide a summary on these aspects and stresses the need for additional prospective validation studies.

Introduction

Most patients with prostate cancer can be treated with curative intent. However, the survival rates of prostate cancer depend on the stage of disease. Although the five-year survival rate for localized prostate cancer is 100%, it drops to 31% if distant metastases are present (1). Treatment options for men with advanced or metastatic castration resistant prostate cancer (mCRPC) mostly exist of new hormonal agents (e.g. enzalutamide and abiraterone) and chemotherapy (e.g. docetaxel and cabazitaxel). However, these therapies are associated with substantial side effects and in some patients it is contraindicated or not tolerated. Therefore, novel therapeutic strategies with improved outcomes and less side effects are desired.

With the introduction of the radioligand prostate specific membrane antigen (PSMA) a new 'theranostic' agent became available for prostate cancer. PSMA is a type II membrane glycoprotein (also called folate hydrolase I or glutamate carboxypeptidase II (GCPII)). The expression of PSMA is 100-1000 fold higher in prostate cancer cells in comparison to healthy tissue (2). This makes it an interesting target for both diagnostics and therapeutics. The first application using PSMA-ligands labelled with positron emitting isotopes allowed molecular imaging in vivo with PET(/CT), generally referred to as PSMA PET. Over the years, PSMA PET has proven to be more accurate in prostate cancer imaging with a higher diagnostic accuracy than conventional imaging (CT and skeletal scintigraphy) for the detection of prostate cancer lymph nodes and bone metastases: 92% (95% CI 88-95%) versus 65% (95% CI 60-69%), respectively (3). As a second step, PSMA-ligands were labelled with therapeutic isotopes, including ^{177}Lu. Radioligand therapy with [^{177}Lu]Lu-PSMA has shown to be effective and safe in patients with mCRPC in different multi-center, open-label, (randomized) trials (4-6). This led to the Food and Drugs Authorization (FDA) approval in the United states of America of [^{177}Lu]Lu-PSMA-617 (^{177}Lu-vipivotide teraxetan, PluvictoTM, Advanced Accelerator Applications USA, Inc. (AAA, a Novartis company; Millburn, NJ, USA)) for the treatment of metastatic prostate cancer since March 2022. Marketing authorization for the drug has been granted in August 2022 in the United Kingdom. In December 2022, the European medicines agency (EMA) approved [^{177}Lu]Lu-PSMA-617. In the Netherlands, despite the EMA

approval, PSMA-617 is currently not yet available for clinical use, while approval for reimbursement by health insurance companies is awaited. As an alternative and likely temporary solution, the comparable radiopharmaceutical, [^{177}Lu]Lu-PSMA-I&T has been reimbursed for men with mCRPC since August 2021 (figure 1). This review will summarize different leading developments on PSMA radioligand therapy and discuss further aspects of this novel therapy, with emphasis on current clinical and scientific efforts in the Netherlands.

Indication

Following the EANM procedure guidelines (7), patients are eligible for [^{177}Lu]Lu-PSMA if they have: 1) mCRPC and are exhausted or are ineligible for approved alternative options, 2) adequate organ function and, 3) show adequate radiotracer uptake on PSMA PET/CT prior to [^{177}Lu]Lu-PSMA therapy. The latter is fiercely debated, as it is based on previous literature on neuroendocrine tumour theranostics, in which uptake in de tumour sites must at least be higher than the physiological uptake in normal organs, including the liver. At present however, this will remain the key criterion on imaging for patient selection based on the VISION trial results. Table 1 represents the contraindications following the EANM guidelines.

Efficacy

Five years ago, in the previous edition of this journal's special issue (8), many small retrospective studies were available and since then numerous studies have been published. In the Netherlands the first clinical experience with small molecule [^{177}Lu]Lu-PSMA radioligand therapy was in 2016 at the Utrecht University Medical Center (9). Thirty consecutive patients with metastatic castration resistant prostate cancer (mCRPC) received 1-6 therapy cycles with 6 GBq [^{177}Lu]Lu-PSMA-617. After the first cycle, in 45% of the patients the analgesics could be decreased. During treatment, 57% of the patients had a maximum PSA decline of ≥ 50% and 24% of the patients even ≥ 90%. Toxicity was limited to Common Terminology Criteria for Adverse Events (CTCAE) grade I-II, most commonly xerostomia (17%). Median overall survival (OS) starting from the first therapy cycle was 11.3 (range 1.4-32.3) months during a median follow-up of 13.7 (9.8-32.3) months. Later, several multi-center prospective phase II and III trials followed, and the number of studies on [^{177}Lu]Lu-PSMA-617 rapidly increased

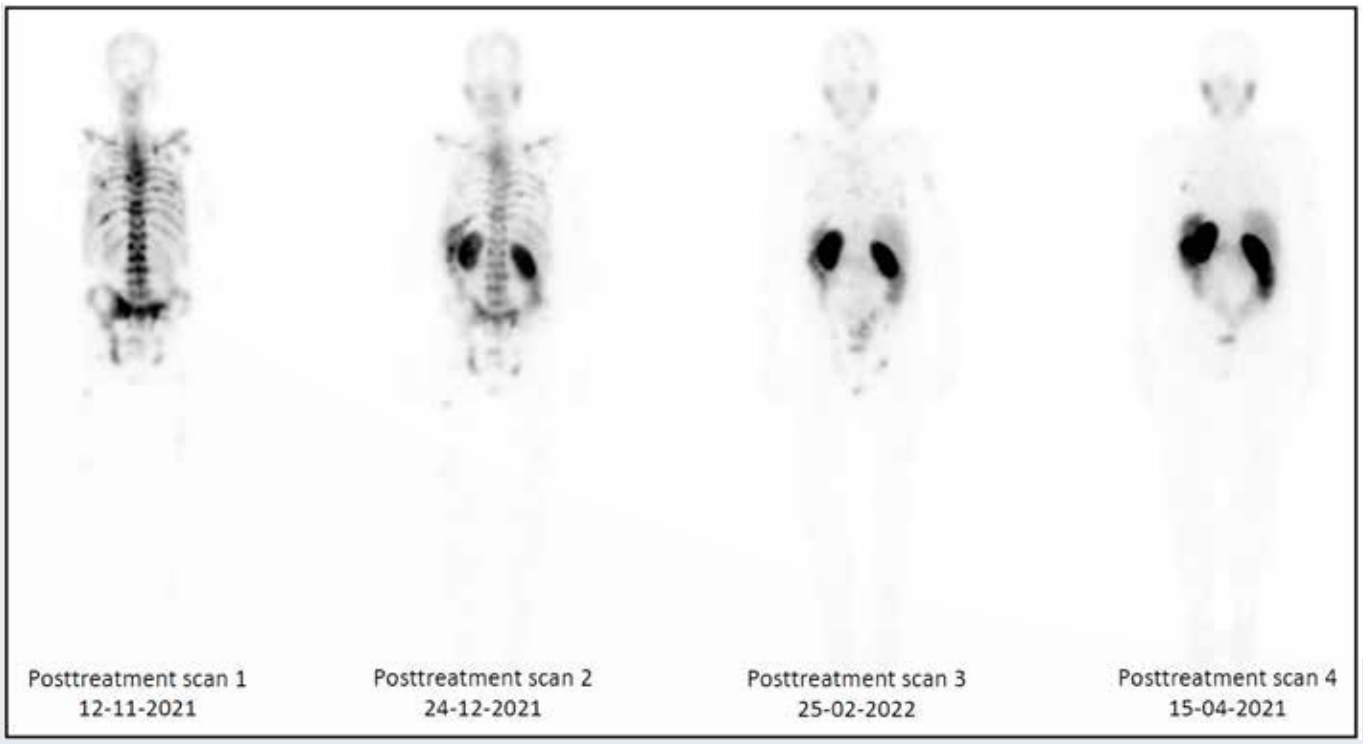

Figure 1. Example of response during [^{177}Lu]Lu-PSMA-I&T as shown on post-treatment scintigraphy. A 62 years old metastatic castration resistant prostate cancer (mCRPC) patient with baseline prostate specific antigen (PSA) of 399 ng/mL, received four cycles of 7.4 GBq [^{177}Lu]Lu-PSMA-I&T. He had a very good clinical response and was free of pain after his first treatment, which enabled him to start his work full-time again. A PSA decline to 1.6 ng/mL was observed.

Table 1. Contraindications for [^{177}Lu]Lu-PSMA therapy according to the EANM guidelines

1	Life expectancy < 6 months (ECOG performance status > 2); unless the main objective is alleviation of disease-related symptoms.
2	Unacceptable medical or radiation safety risk for isolation on a nuclear medicine therapy unit (if required by national regulations).
3	Unmanageable urinary tract obstruction or hydronephrosis. In patients with diagnosed or who are at high risk of urinary retention, [^{99m}Tc]Tc-MAG3 or [^{99m}Tc]Tc-DTPA renal scintigraphy should be considered as a baseline exam.
4	Progressive deterioration of organ function (GFR < 30 mL/min or creatinine > 2-fold upper limit of normal (ULN); liver enzymes > 5-fold ULN).
5	Myelosuppression: a. Total white cell count less than 2.5 × 10^9/L b. Platelet count less than 75 × 10^9/L
6	Conditions that require timely interventions (i.e. radiation therapy, surgery), e.g. spinal cord compression and unstable fractures. [^{177}Lu]Lu-PSMA may be performed afterwards upon patient's condition. Borderline cases should be evaluated within the multidisciplinary tumour board for the individual benefit-to-risk ratio.

after Novartis acquired Endocyte.

TheraP-trial

The first prospective, multi-center, open-label, randomized phase II study (TheraP) investigated the activity and safety of [^{177}Lu]Lu-PSMA-617 in men with mCRPC and PSMA PET positive disease, for whom cabazitaxel was considered the next appropriate standard treatment (6). Patients were randomly assigned in a 1:1 ratio. The intervention arm consisted of up to 6 cycles of 6.0-8.5 GBq [^{177}Lu]Lu-PSMA-617 every 6 weeks, the control arm received cabazitaxel (20 mg/m^2 intravenously every 3 weeks to a maximum of 10 cycles). A total of 200 men were randomly assigned, 101 patients in the intervention arm and 99 patients in the control arm. The intervention arm had similar median PSA-based progression-free survival (PFS) (interval from randomization to first evidence of > 25% PSA-progression and at least 2 ng/mL after 12 weeks) of 5.1 months. However, a delayed PSA-based progression was observed in the intervention arm (HR 0.60; 95% CI 0.44-0.83; p = 0.0017). Similar benefits were found for radiographic progression on CT according to the response evaluation criteria in solid tumours version 1.1 (RECIST 1.1) and prostate cancer clinical trials working group 3 criteria (PCWG3) (10) for bone lesions at skeletal scintigraphy (HR 0.64; 95% CI 0.46-0.88; p = 0.0070). Objective response according to RECIST 1.1 was observed in 49% (95% CI 33-56) in the [^{177}Lu]Lu-PSMA-617 arm versus 24% (95% CI 11-38) in the cabazitaxel arm (p = 0.019). A PSA-response of ≥ 50% PSA decline was noted in 66% (95% CI 56-75%) in the intervention arm versus 37% (95% CI 27-46%) in the control arm.

Three years later at ASCO 2022, the survival analysis was presented, in which OS in both arms were similar, approximately 19 months (HR 0.97; 95% CI 0.70-1.4; p = 0.99) (11). However, during follow up a high number of crossover and post-protocol therapies were reported.

VISION-trial

Largely in parallel, an international multi-center, open-label, randomized, phase III study (VISION-trial) investigated the efficacy and safety of [^{177}Lu]Lu-PSMA-617 plus protocol-permitted standard of care (ppSoC) in patients previously treated for mCRPC (with at least either enzalutamide or abiraterone, and a taxane; i.e. docetaxel or cabazitaxel), with a positive PSMA PET (4). Patients were randomly assigned in a 2:1 ratio. The intervention arm consisted of intravenous infusions of 7.4 GBq once every 6 weeks for four cycles and ppSoC, the control arm included ppSoC alone. ppSOC included hormonal treatment, not restricted to the approved hormonal treatments (e.g. abiraterone and enzalutamide), bisphosphonates, radiation therapy, denosumab, or glucorticoids. Treatment could be expanded up to a total of six cycles, in case patients showed evidence of response. A total of 831 patients were included, 551 patients in the intervention group and 280 patients in the control group. The intervention arm had a significant better median radiographic PFS of 8.7 months versus 3.4 months, defined according to PCWG3 (10) (HR 0.40; 99.2% CI 0.29-0.57; p < 0.001) and median OS of 15.3 months versus 11.3 months (HR 0.62; 95% CI 0.52-0.74; p < 0.001). Complete response rate according to RECIST 1.1 was 9.2% in the intervention arm and none in the control arm, a partial objective

response was noted in 41.8% in the intervention arm and 3% in the control arm. In comparison to TheraP-trial a lower PSA-response (≥ 50% PSA decline) was noted, 46.0% of the intervention arm and 7.1% in the control arm, caused by differences in patient selection. A PSA-response of ≥ 80% was noted in 33% of the intervention arm and 2% in the control arm.

PSMA I&T

The described studies applied the PSMA-617 ligand. At the same time, the alternative and largely comparable PSMA-I&T ligand was also evaluated in other studies. For [^{177}Lu]Lu-PSMA-I&T existing data consisted of retrospective studies only. Currently, an international, multi-center, phase III RCT is enrolling patients (SPLASH; NCT04647526; to be discussed in the final section).

Safety

Results from earlier retrospective studies were confirmed in the two above-mentioned prospective studies, in which the TheraP-trial revealed 33% grade 3-4 adverse events (according to CTCAE) in the intervention arm and 53% in the control arm. The most common side effects reported included fatigue (75%), dry mouth (60%), nausea (41%) and bone marrow suppression (thrombocytopenia (29%), anaemia (27%), neutropenia (11%), and leukopenia (11%)). No death was attributed to [^{177}Lu]Lu-PSMA-617 in the TheraP-trial.

In contrast to the TheraP-trial, in the VISION-trial, the incidence of adverse events of ≥ grade 3 was higher within the intervention arm (52.7% versus 38.0%). However, quality of life was not adversely affected. The most common adverse events in the intervention arm included fatigue (43.1%), dry mouth (38.8%), nausea (35.3%), and bone marrow suppression (thrombocytopenia (17.2%), anaemia (31.8%), lymphopenia (14.2%) and, leukopenia (12.5%)). Five adverse events that led to death were considered related to [^{177}Lu]Lu-PSMA-617 in the VISION-trial (bone marrow failure, subdural hematoma, intracranial hemorrhage, and pancytopenia in two patients).

Dosimetry

Biodistribution of [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T are quite similar, with high physiological accumulation in the lacrimal and salivary glands, kidneys, and small intestine; medium to low accumulation in the liver and spleen. Both are predominantly renally excreted. However, retention of [^{177}Lu]Lu-PSMA-617 is higher than of [^{177}Lu]Lu-PSMA-I&T, whilst they have a similar effective whole-body half-life, [^{177}Lu]Lu-PSMA-617 42 hours versus [^{177}Lu]Lu-PSMA-I&T 35 hours (12).

In a sub study of the VISION-trial, dosimetry was performed in 29 mCRPC patients who received up to six cycles of 7.4 GBq [^{177}Lu]Lu-PSMA-617 plus ppSoC every six weeks. SPECT/CT was preformed of the upper and lower abdomen at 2, 24, 48 and 168 hours after first administration (13). Blood and urine samples were collected throughout cycle one. Absorbed dose per unit activity (Gy/GBq) and cumulative estimated absorbed dose (Gy) over all 6 cycles (44.4 GBq cumulative activity) extrapolated from cycle one data were reported. The lacrimal glands received the highest absorbed dose per administered activity of 2.10 (±0.47) Gy/GBq, followed by the salivary glands and kidneys at 0.63 (±0.36) Gy/GBq and 0.43 (±0.16) Gy/GBq, respectively. These results are in line with earlier retrospective studies. Even though absorbed dose in lacrimal glands is the highest, incidence of related clinical toxicity is very low or non-existent, thus both salivary glands and kidneys are considered to be the dose limiting organs for [^{177}Lu]Lu-PSMA-617 treatment. For [^{177}Lu]Lu-PSMA-I&T a ~1.5x higher median kidney dose was observed in comparison to [^{177}Lu]Lu-PSMA-617 (14). However, reported clinically relevant toxicities remain similar (15). Fortunately, toxicity of salivary glands and kidneys is relatively low and predominantly transient, not affecting quality of life. Tumour dosimetry was not assessed in the sub-study of the VISION-trial.

Previous studies did investigate tumour dosimetry and a potential correlation to treatment outcome (biochemical response </≥ 50%). Violet et al. reported their results from a prospective cohort of 30 mCRPC patients, who received up to four cycles of [^{177}Lu]Lu-PSMA-617 (16). All patients had a screening [^{68}Ga]Ga-PSMA-11 PET/CT and SPECT/CT at 4, 24, and 96 hours after [^{177}Lu]Lu-PSMA-617. Administered [^{177}Lu]Lu-PSMA-617 dose was variable; based on tumour burden, patient's weight and renal function (mean 7.5 GBq/cycle range 4.4-8.7, SD 1.0). Non-responding patients had a significantly lower tumour dose of ~4 Gy than responders, ~12 Gy ($p < 0.01$). Regarding the administered dose, a pre-VISION single-center analysis evaluated two different administered doses of [^{177}Lu]Lu-PSMA-617 (6 GBq and 7.4 GBq) on safety and efficacy (5). No significant difference was found in change of kidney, liver, and blood cell parameters and no significant difference in PSA decline > 50% (35% vs. 54%, $p = 0.065$) or best PSA response (40.2% vs. 57.8%, $p = 0.329$). The median estimated survival and PSA-PFS also did not significantly differ between the 6.0 GBq and 7.5 GBq regimen (11.3 vs. 12.7 months, $p = 0.384$; and 9.5 vs. 12.3 months, $p = 0.258$). However, to date, prospective studies performing prospective dosimetry are lacking.

Discussion

This recap of recent developments (last 5 years) on PSMA radioligand

therapy has shown rapid adoption of a theranostic therapy by the (uro-) oncology community. Prior to [^{177}Lu]Lu-PSMA, all available therapies were either taxane-based or androgen receptor targeted treatments, thus the need for a new therapeutic mechanism was felt. In this respect, the TheraP- and VISION-trial had the most notable impact. [^{177}Lu]Lu-PSMA-617 has been proven to be safe, generally well tolerated and an effective therapy for men with mCRPC.
However, even though both trials provided paramount data, some issues are still debated. One issue to our interest, was the use of [^{68}Ga]Ga-PSMA-11 PET/CT for patient selection. In the VISION-trial 87% of all screened patients met the inclusion criterion (tumour uptake on [^{68}Ga]Ga-PSMA-11 PET > liver), which raised the question if pre-treatment PSMA PET/CT is worth the added effort and costs (17). Patients were excluded if they showed PSMA negative lesions (PSMA uptake ≤ liver parenchyma in any lymph node with a short axis of ≥ 2.5 cm, or in any metastatic solid-organ lesion with a short axis of ≥ 1.0 cm, or in any metastatic bone lesion with a soft tissue component with a short axis of ≥1.0). By using these criteria, VISION included 'predominant PSMA positive disease' patients. Thus, the scientific question remains whether patients with non-predominant PSMA positive disease with one or several PSMA negative lesion(s) could still benefit from [^{177}Lu]Lu-PSMA-617 therapy (figure 2). Patient selection in VISION was based on PSMA expression on [^{68}Ga]Ga-PSMA-11 PET/CT. In a sub-study of the VISION-trial, including the 551 patients from the intervention arm, high whole-body SUV_{mean} was the only consistent imaging parameter with improved outcomes across all clinical endpoints (i.e. only the quartile of patients with highest SUV_{mean} results). Unfortunately, imaging reconstruction and acquisition was non-standardized, thus many technical limitations were also present (17) (figure 3).
Hotta et al. investigated this particular issue in an international, multi-center retrospective study, in 301 patients with mCRPC treated with [^{177}Lu]Lu-PSMA-617 and divided the cohort in three 'expression groups' based on visual scores and semi-quantitative measures: high (> 80% of the lesions show higher uptake than the parotid glands), intermediate (neither "low" nor "high"), and low PSMA expression (> 80% of the lesions < uptake than the parotid glands) based on the [^{68}Ga]Ga-PSMA-11 PET/CT (18). The high accumulation group outperformed the intermediate and low groups regarding biochemical response (PSA decline ≥ 50%) 69.6%, 38.7%, and 16.7% (semi-quantitative measures: $p < 0.001$) in the high, intermediate, and low expression groups, respectively, and OS with

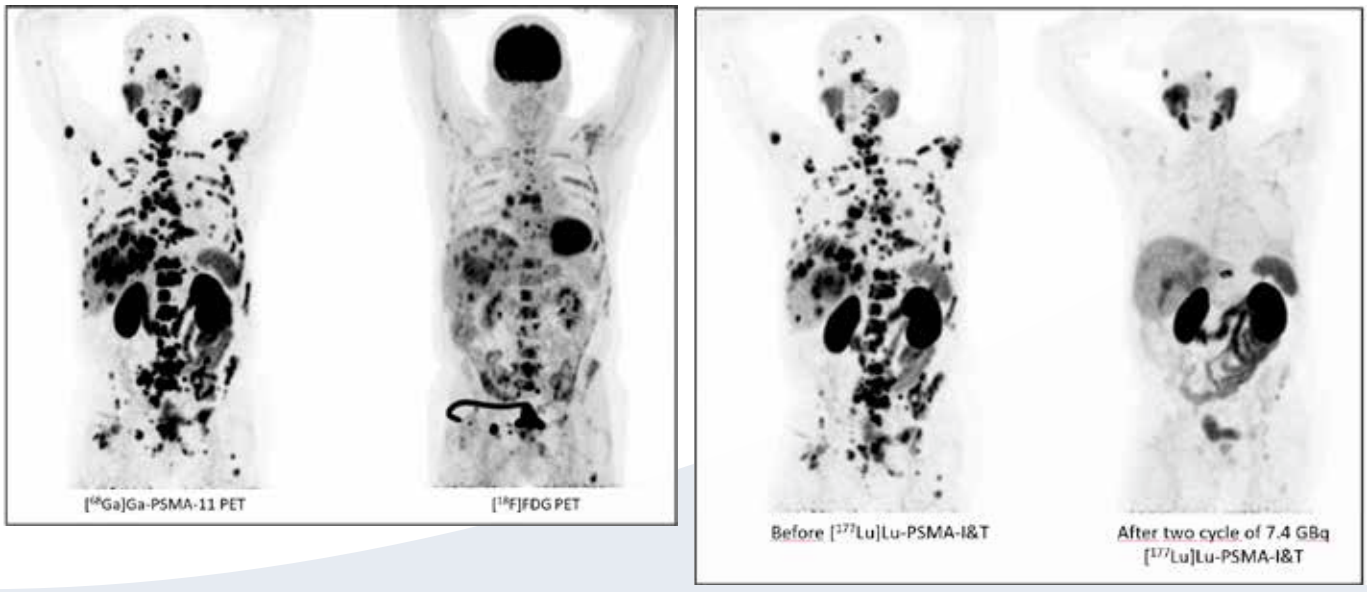

Figure 2. Maximum intensity projections pre- and post-treatment.
Maximum intensity projections (MIP) of a [^{68}Ga]Ga-PSMA-11 PET and [^{18}F]FDG-PET/CT in a 69 year old metastatic castration resistant prostate cancer (mCRPC) patient with baseline prostate specific antigen (PSA) of 105 ng/mL. The PET scans show high uptake of PSMA and moderate to low uptake of FDG.
[^{68}Ga]Ga-PSMA-11 MIP of the same patient before and after two cycles of 7.4 GBq [^{177}Lu]Lu-PSMA-I&T. The patient had a PSA decline to 0.91, a pain reduction from 8 to 1 following the VAS (visual analoque scale) pain score, and a quality-of-life gain of two points (5 to 7).

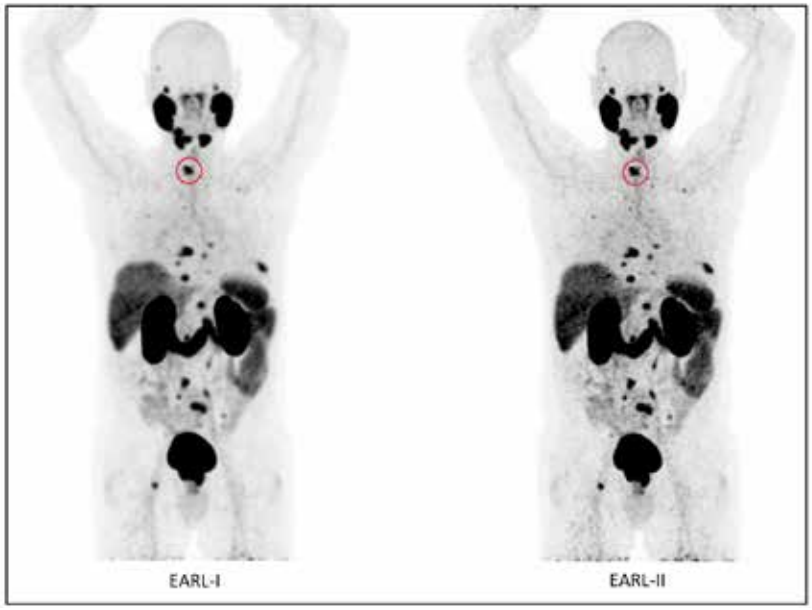

Figure 3. Follow-up [^{68}Ga]Ga-PSMA-11 PET in a 73 year old patient with metastatic castration resistant prostate cancer (mCRPC) and raising prostate specific antigen (PSA). Example of the influence of different reconstruction parameters and its effect on semi-quantitative measurements. Left: EARL-I reconstruction maximum intensity projection (MIP), with a maximum standardized uptake value corrected for lean body mass (SUL_{max}) of 5.41 of the indicated bone lesion (red circle). Right: EARL-II reconstruction MIP with a SUL_{max} of the same bone lesion of 6.81.

15.0 months in the high expression group versus 11.7 months in the intermediate plus low expression group (semi-quantitative measures: p = 0.013). These results suggest that uptake might be a valuable prognostic and predictive imaging-based biomarker, and that not all mCRPC disease within a patient has to be highly PSMA expressing. Additionally, the used visual and semi-quantitative measurements likely missed PSMA-negative disease, as visual assessments were based on maximum intensity projections only and semi-quantitative measures did not take PSMA-negative disease into account. To date, only one study pursued a lesion-based analysis, besides the general patient-based analyses that supported this hypothesis (19).

Van der Sar et al. found a clear accumulation-response relationship on a lesion-level (primary tumour, lymph node, bone or visceral metastasis) for $SUV_{peak/max}$ on pre-treatment [^{68}Ga]Ga-PSMA-11 PET/CT (reconstructed according to EARL1) in men with mCRPC receiving two cycles of [^{177}Lu]Lu-PSMA-617 treatment. Patients with a higher mean SUV_{peak} (> 14.87) at baseline had a better imaging-based response (based on PERCIST-like criteria) (p < 0.001), except for complete response, where a lower accumulation was found. The latter was probably a result of smaller lesions with less counts impaired by partial volume effects. The findings of van der Sar et al. strengthen the suggestion that mCRPC patients with some low uptake lesions could also benefit from [^{177}Lu]Lu-PSMA-617 therapy. In the study by van der Sar et al., no clear PSMA-negative disease was included (19).

Although most evidence on patient selection is based on [^{68}Ga]Ga-PSMA-11, not all centres have access to this radioactive isotope. There are currently several Fluor-18-based PSMA-ligands available for PET imaging that are in wide use in the Netherlands, including [^{18}F]PSMA-1007, [^{18}F]DCFPyL and [^{18}F]JK-PSMA-7. For these tracers, the uncertainty on thresholds that can predict response are even larger.

Considering PSMA-negative disease, some suggest using [^{18}F]FDG-PET/CT as an addition or surrogate for CT or MRI. Chen et al. (20) retrospectively evaluated the added value of [^{18}F]FDG-PET/CT compared to [^{68}Ga]Ga-PSMA-11 PET/CT in an in-patients comparison of 56 CRPC patients. [^{68}Ga]Ga-PSMA-11 PET/CT showed a higher detection rate and a higher number of positive lesions in comparison to [^{18}F]FDG-PET/CT, especially in patients with higher risk features (Gleason score ≥ 8 and PSA ≥ 7.9 ng/mL). However, in 23.2% (13/56) of the patients at least one lesion observed on the [^{18}F]FDG-PET/CT was not observed on the [^{68}Ga]Ga-PSMA-11 PET/CT. The clinical relevance of the increased detection rate however, remained unclear. Some suggested that patients with a PSMA-negative, but FDG-positive lesion will not have added value of [^{177}Lu]Lu-PSMA treatment (21). Khreish et al. (22) showed in a retrospective cohort of mCRPC patients that patients with at least one mismatch PSMA-/FDG+ lesion (17/29, 59%) had a significant shorter overall survival compared with patients without mismatch lesions (3.3 versus 6 months; p = 0.008). However, PSMA-/FDG+ mismatch in this study was determined on [^{18}F]FDG-PET/CT and [^{68}Ga]Ga-PSMA-11 PET with an interval of 4 weeks, and images were acquired after the second cycle of therapy (not at baseline, i.e. prior to initiation of [^{177}Lu]Lu-PSMA). Furthermore, patients were only selected for this analysis if they had

biochemically or clinically progressive disease after the second treatment (selection bias). Seifert et al. (23) concluded that less than 5% (3/98, 3%) of the mCRPC patients referred to [^{177}Lu]Lu-PSMA-617 therapy had a mismatch finding on pre-treatment PSMA-PET and [^{18}F]FDG-PET/CT. This raises the question if the combination of pre-treatment PSMA PET and FDG PET is really needed. Pathmanandavel et al. (24) recently reported the data from the phase I/II LuPIN-trial, including 65 mCRPC patients receiving up to six cycles of [^{177}Lu]Lu-PSMA-617 and a potential sensitizer (NOX66). In their study, [^{18}F]FDG-PET/CT did not have added value as prognostic factor for OS, whilst increased total tumour volume on [^{68}Ga]Ga-PSMA-11 PET/CT and PSA progression after treatment did (6 weeks after completing [^{177}Lu]Lu-PSMA-617 or when treatment ceased earlier because of clinical progression).

In the VISION-trial, the choice was made not to include [^{18}F]FDG-PET/CT for patient selection, in order to prevent potential operational complexity and costs (17). On the other hand, the TheraP trial excluded patients with PSMA-/FDG+ mismatch and metastatic disease was assessed semi-quantitatively (SUVmax > 10), which resulted in exclusion of one-third of screened patients (91/291). A small patient study (n=14) by Aberts et al. (25) showed that it is feasible to combine [^{18}F]FDG-PET/CT and [^{68}Ga]Ga-PSMA-11 PET/CT as part of a same day imaging protocol. However, with the data from Seifert et al. (23) in mind (<5% has PSMA-/FDG+ mismatch), cost-effectiveness is questionable and undetermined at this time.

Summarizing, pre-treatment PSMA PET can give added value for predicting [^{177}Lu]Lu-PSMA treatment response. Combining FDG PET with PSMA PET gives a higher detection rate of PSMA negative metastases, however the clinical relevance and cost-effectiveness for patient selection needs further investigation (26).

The second issue to our interest is the response evaluation. PSA for response evaluation has always been under debate for different lines of CRPC treatment (e.g. ^{223}Ra). Even with [^{177}Lu]Lu-PSMA not all patients with tumour progression show PSA progression (27). Both discussed trials (i.e. VISION and TheraP) used RECIST 1.1 and PCWG3 for radiological response assessment, being the most commonly used criteria, but subject to known flaws and limitations. Thus, new response criteria are eagerly being investigated. For molecular imaging with PSMA PET, several options are available for response evaluation: Positron Emission Tomography Response Criteria in Solid Tumours (aPERCIST), the PSMA PET Progression (PPP), and the Response Evaluation Criteria In PSMA-Imaging (RECIP) 1.0. A retrospective comparison study comparing all these different response criteria concluded that RECIP 1.0 identified the fewest patients with progressive disease and achieved the highest risk of death by progressive disease versus no progressive disease (28). The authors suggested that other classification methods tend to overcall progression. However, prospective validation studies evaluating the different response criteria are lacking (28) and these criteria have not been endorsed by the urogenital oncological community. The predominant reason is that response evaluation on PSMA PET alone is considered too limited, as low to intermediately active PSMA lesions may have responded, but are not account for in the response evaluation, while PSMA negative lesions might be missed.

Currently, there are six trials registered that investigate [^{177}Lu]Lu-PSMA in prostate cancer patients in the Netherlands, in various settings. These studies will be briefly described:

First, PROQURE (NCT05162573), a national, multi-center, phase I study, investigating tolerability of concurrent external beam radiotherapy and [^{177}Lu]Lu-PSMA-617 for node-positive prostate cancer in treatment naïve patients. The study opened in 2021 and is actively recruiting.

Second, PSMAddition (NCT04720157), an international, multi-center, open-label, randomized, phase III study investigating [^{177}Lu]Lu-PSMA-617 combined with androgen deprivation therapy (ADT) in hormone sensitive prostate cancer patients in comparison to standard of care. The study opened in 2021 and is actively recruiting.

Third, PSMAfore (NTC04689828), an international, multi-center, open-label, randomized, phase III study investigating [^{177}Lu]Lu-PSMA-617 in men with mCRPC, who already received ADT, but did not yet receive chemotherapy. The study opened in 2021 and recruitment has been closed.

Fourth, Bullseye 2 (NCT04443062) (29, 30), a multi-center, randomized, open-label, phase II study, investigating [^{177}Lu]Lu-PSMA-617 in men with recurrent hormone sensitive prostate cancer who are eligible for ADT. The study opened in 2020 and is actively recruiting.

Lastly, SPLASH (NCT04647526), an international, multi-center, open-label, randomized, phase III study, investigating [^{177}Lu]Lu-PSMA-I&T in men with mCRPC after second-line ADT. This study opened in 2021 and is actively recruiting.

The next step for PSMA radioligand therapy is the use of alpha emitters, e.g. actinium-225 PSMA ([^{225}Ac]Ac-PSMA). The high linear energy transfer in PSMA positive lesions causes more double-strand breaks and thereby potentially a higher efficacy than beta emitters (31). Currently, a single-center, phase I study is investigating [^{225}Ac]Ac-PSMA-I&T in mCRPC patients in the Netherlands (31).

Conclusion

[^{177}Lu]Lu-PSMA has shown to be safe and effective. It is reimbursed in the Netherlands in the salvage setting in mCRPC. Results of the currently recruiting studies in different settings are eagerly awaited. Furthermore, more evidence is needed for patient selection, imaging-based biomarkers and response monitoring.

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References

1. 1. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Niksic M, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 2018;391(10125):1023-75
2. 2. Silver DA, Pellicer I, Fair WR, Heston WD, Cordon-Cardo C. Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res. 1997;3:81-5
3. 3. 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, multi-centre study. Lancet. 2020;395(10231):1208-16
4. 4. Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2021;385:1091-103
5. 5. Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, et al. [(177)Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol. 2018;19:825-33
6. 6. Hofman MS, Emmett L, Sandhu S, Iravani A, Joshua AM, Goh JC, et al. [(177)Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. Lancet. 2021;397(10276):797-804
7. 7. Kratochwil C, Fendler WP, Eiber M, Baum R, Bozkurt MF, Czernin J, et al. EANM procedure guidelines for radionuclide therapy with (177)Lu-labelled PSMA-ligands ((177)Lu-PSMA-RLT). Eur J Nucl Med Mol Imaging. 2019;46:2536-44
8. 8. Braat AJAT, Ahmadzadehfar H. Lutetium-177 labelled PSMA ligands for the treatment of metastatic castrate-resistant prostate cancer. Tijdschrift voor nucleaire geneeskunde 2016;4:1627-34
9. 9. van Kalmthout L, Braat A, Lam M, van Leeuwaarde R, Krijger G, Ververs T, et al. First Experience With 177Lu-PSMA-617 Therapy for Advanced Prostate Cancer in the Netherlands. Clin Nucl Med. 2019;44:446-51
10. 10. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016;34:1402-18
11. 11. Hofman MS, Emmett L, Sandhu S, Iravani A, Joshua AM, Goh JC, et al. Thera P: 177Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic castrationresistant prostate cancer (mCRPC) progressing after docetaxel-Overall survival after median follow-up of 3 years (ANZUP 1603). J Clin Oncol. 2022;40(16)
12. 12. Schuchardt C, Zhang J, Kulkarni HR, Chen X, Muller D, Baum RP. Prostate-Specific Membrane Antigen Radioligand Therapy Using (177)Lu-PSMA I&T and (177)Lu-PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer: Comparison of Safety, Biodistribution, and Dosimetry. J Nucl Med. 2022;63:1199-207
13. 13. Herrmann K, Rahbar K, Eiber M, Krause BJ, Lassmann M, Jentzen W, et al. Dosimetry of 177Lu-PSMA-617 for the treatment of metastatic castration-resistant prostate cancer: results from the VISION trial sub-study. J Clin Oncol. 2022;40:S97
14. 14. Uijen MJM, Prive BM, van Herpen CML, Westdorp H, van Gemert WA, de Bakker M, et al. Kidney absorbed radiation doses for [177 Lu]Lu-PSMA-617 and [177 Lu]Lu-PSMA-I&T determined by 3D clinical dosimetry. Nucl Med Commun. 2023;44:270-5
15. 15. Hartrampf PE, Weinzierl FX, Buck AK, Rowe SP, Higuchi T, Seitz AK, et al. Matched-pair analysis of [(177)Lu]Lu-PSMA I&T and [(177)Lu]Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging. 2022;49:3269-76
16. 16. Violet J, Jackson P, Ferdinandus J, Sandhu S, Akhurst T, Iravani A, et al. Dosimetry of (177)Lu-PSMA-617 in Metastatic Castration-Resistant Prostate Cancer: Correlations Between Pretherapeutic Imaging and Whole-Body Tumor Dosimetry with Treatment Outcomes. J Nucl Med. 2019;60:517-23
17. 17. Kuo PH, Benson T, Messmann R, Groaning M. Why We Did What We Did: PSMA PET/CT Selection Criteria for the VISION Trial. J Nucl Med. 2022;63:816-8
18. 18. Hotta M, Gafita A, Murthy V, Benz MR, Sonni I, Burger I, et al.

Predicting the outcome of mCPRC patients after Lu-177 PSMA therapy using semi-quantitative and visual criteria in baseline PSMA PET: An international multicenter retrospective study. J Clin Oncol. 2022;40:(6_ suppl)32-32
19. 19. van der Sar ECA, Kuhr AJS, Ebbers SC, Henderson AM, de Keizer B, Lam M, et al. Baseline Imaging Derived Predictive Factors of Response Following [(177)Lu]Lu-PSMA-617 Therapy in Salvage Metastatic Castration-Resistant Prostate Cancer: A Lesion- and Patient-Based Analysis. Biomedicines. 2022;10(7):1575
20. 20. Chen R, Wang Y, Zhu Y, Shi Y, Xu L, Huang G et al. The added value of 18F-FDG PET/CT compared to 68Ga-PSMA PET/CT in patients with castration-resistant prostate cancer. J Nucl Med. 2021; jnumed.121.262250. Online ahead of print
21. 21. Calais J, Czernin J. PSMA Expression Assessed by PET Imaging Is a Required Biomarker for Selecting Patients for Any PSMA-Targeted Therapy. J Nucl Med. 2021;62:1489-91
22. 22. Khreish F, Ribbat K, Bartholoma M, Maus S, Stemler T, Hierlmeier I, et al. Value of Combined PET Imaging with [(18)F]FDG and [(68)Ga]Ga-PSMA-11 in mCRPC Patients with Worsening Disease during [(177)Lu]Lu-PSMA-617 RLT. Cancers (Basel). 2021;13(16)
23. 23. Seifert R, Telli T, Hadaschik B, Fendler WP, Kuo PH, Herrmann K. Is (18)F-FDG PET needed to assess (177)Lu-PSMA Therapy Eligibility? A VISION-like, Single-Center Analysis. J Nucl Med. 2022;jnumed.122.264741. Online ahead of print
24. 24. Pathmanandavel S, Crumbaker M, Nguyen A, Yam AO, Wilson P, Niman R, et al. The Prognostic Value of Posttreatment (68)Ga-PSMA-11 PET/CT and (18)F-FDG PET/CT in Metastatic Castration-Resistant Prostate Cancer Treated with (177)Lu-PSMA-617 and NOX66 in a Phase I/II Trial (LuPIN). J Nucl Med. 2023;64:69-74
25. 25. Alberts I, Schepers R, Zeimpekis K, Sari H, Rominger A, Afshar-Oromieh A. Combined [68 Ga]Ga-PSMA-11 and low-dose 2-[18F]FDG PET/CT using a long-axial field of view scanner for patients referred for [177Lu]-PSMA-radioligand therapy. Eur J Nucl Med Mol Imaging. 2023;50:951-6
26. 26. Jadvar H. The VISION Forward: Recognition and Implication of PSMA-/(18)F-FDG+ mCRPC. J Nucl Med. 2022;63:812-5
27. 27. Manafi-Farid R, Harsini S, Saidi B, Ahmadzadehfar H, Herrmann K, Briganti A, et al. Factors predicting biochemical response and survival benefits following radioligand therapy with [(177)Lu]Lu-PSMA in metastatic castrate-resistant prostate cancer: a review. Eur J Nucl Med Mol Imaging. 2021;48:4028-41
28. 28. Gafita A, Rauscher I, Fendler WP, Murthy V, Hui W, Armstrong WR, et al. Measuring response in metastatic castration-resistant prostate cancer using PSMA PET/CT: comparison of RECIST 1.1, aPCWG3, aPERCIST, PPP, and RECIP 1.0 criteria. Eur J Nucl Med Mol Imaging. 2022;49:4271-81
29. 29. Prive BM, Janssen MJR, van Oort IM, Muselaers CHJ, Jonker MA, van Gemert WA, et al. Update to a randomized controlled trial of lutetium-177-PSMA in Oligo-metastatic hormone-sensitive prostate cancer: the BULLSEYE trial. Trials. 2021;22:768
30. 30. Prive BM, Janssen MJR, van Oort IM, Muselaers CHJ, Jonker MA, de Groot M, et al. Lutetium-177-PSMA-I&T as metastases directed therapy in oligometastatic hormone sensitive prostate cancer, a randomized controlled trial. BMC Cancer. 2020;20:884
31. 31. Hooijman EL, Chalashkan Y, Ling SW, Kahyargil FF, Segbers M, Bruchertseifer F, et al. Development of [(225)Ac]Ac-PSMA-I&T for Targeted Alpha Therapy According to GMP Guidelines for Treatment of mCRPC. Pharmaceutics. 2021;13:715

Radium-223 bij gemetastaseerd castratieresistent prostaatcarcinoom

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Abstract
Behandeling met [^{223}Ra]$RaCl_2$ is veilig en effectief bij patiënten met gemetastaseerd castratieresistent prostaatkanker (mCRPC) met symptomatische botmetastasen. Het huidige onderzoek richt zich op het vinden van predictieve parameters voor respons op de behandeling en op de mogelijkheid de ^{223}Ra-behandeling te combineren met andere (reeds goedgekeurde) vormen van therapie bij mCRPC.

Introductie

Radium-223 ([^{223}Ra]$RaCl_2$, Xofigo®, Bayer Healthcare) is een alfastraler die zich specifiek richt op (osteoblastische) botmetastasen. [^{223}Ra]$RaCl_2$ is sinds 2013 in de Europese Unie geregistreerd als behandeling bij gemetastaseerd castratieresistent prostaatkanker (mCRPC) met symptomatische botmetastasen (1). [^{223}Ra]$RaCl_2$ is een zogenaamd calcium-mimeticum. Dit betekent dat het door het lichaam op eenzelfde manier wordt gedistribueerd als calcium. Dat betekent onder andere dat [^{223}Ra]$RaCl_2$ actief wordt getransporteerd naar locaties met een hoge botaanmaak en -afbraak. In het botweefsel heeft [^{223}Ra]$RaCl_2$ een tweeledig effect. Enerzijds remt [^{223}Ra]$RaCl_2$ de door de tumor geïnduceerde osteoblastische groei en beschermt het normale botstructuur. Anderzijds induceert [^{223}Ra]$RaCl_2$ dubbelstrengs breuken in het DNA van de tumorcellen (2).

Dosisschema's

Het bewijs voor de effectiviteit en veiligheid van ^{223}Ra-therapie bij mCRPC is geleverd in de ALSYMPCA-studie, een gerandomiseerde placebogecontroleerde fase 3-studie met patiënten met mCRPC en symptomatische skeletmetastasen, maar geen aangetoonde viscerale metastasen (3). Deze studie toonde een significante overlevingswinst bij behandeling met [^{223}Ra]$RaCl_2$, ongeacht of patiënten eerder docetaxel hadden gehad of niet (4). De incidentie van bijwerkingen in de met [^{223}Ra]$RaCl_2$ behandelde patiëntengroep was lager dan in de placebogroep (3). Daarnaast was behandeling met [^{223}Ra]$RaCl_2$ geassocieerd met een verbetering van de kwaliteit van leven in vergelijking met placebo (5).
In 2020 zijn de uitkomsten gepubliceerd van een onderzoek waarin verscheidene dosisschema's van [^{223}Ra]$RaCl_2$ werden geanalyseerd. Het effect van een behandeling bestaand uit 6 cycli met standaarddosis van 55 kBq/kg werd vergeleken met het effect van 6 cycli met een hogere dosis (88 kBq/kg) en met het effect van 12 cycli met de standaarddosis van 55 kBq/kg. De studie toonde aan dat noch de verhoogde dosis, noch de langere behandeling met de standaarddosis leidt tot een beter resultaat (6).

Immunologische respons

Het immunologisch effect van [^{223}Ra]$RaCl_2$ is onderzocht in diverse studies. Uit een onderzoek met een in vitro behandeling van humane long-, borst- en prostaattumoren met sub-lethale doses van [^{223}Ra]$RaCl_2$ (4 tot 10 Gy) bleek dat antigeen specifieke CD8+ T-lymfocyten een rol spelen bij de cytolyse van tumorcellen na blootstelling aan [^{223}Ra]$RaCl_2$ (7). Een in vivo studie bij 15 patiënten met een indicatie voor een behandeling met [^{223}Ra]$RaCl_2$ liet zien dat één injectie [^{223}Ra]$RaCl_2$ leidt tot een afname van PD-1-positieve CD8+ T-cellen (8). De Nederlandse, multicenter RadiumINSIGHT-studie doet momenteel nader onderzoek naar de immunologische respons bij een behandeling met [^{223}Ra]$RaCl_2$.

Herbehandeling

Ook naar herbehandeling met [^{223}Ra]$RaCl_2$ is onderzoek gedaan. De tweejaars-follow-up resultaten van een fase 1-2-studie lieten zien dat behandeling met een tweede serie van zes injecties ^{223}Ra goed werd verdragen met minimale hematologische toxiciteit (9). De studie werd uitgevoerd bij een groep zorgvuldig geselecteerde patiënten die een positieve response vertoonden op een eerdere behandeling met [^{223}Ra]$RaCl_2$. De patiënten (met botmetastasen) hadden bij behandelingen met [^{223}Ra]$RaCl_2$ geen chemotherapie ondergaan. Momenteel loopt in Nederland de RE-RAD (RE-treatment of metastatic castration-resistant prostate cancer patients with RAdium-223 therapy in Daily practise) studie onder leiding van Maarten van der Doelen (Radboudumc) en Dirk Wyndaele (Catharina Ziekenhuis). Deze studie voert een retrospectieve analyse uit bij patiënten die in Nederland voor

een tweede of volgende keer zijn behandeld met ^{223}Ra.

Combinatietherapie

[^{223}Ra]$RaCl_2$ is dankzij de aangetoonde overlevingswinst, het gunstige veiligheidsprofiel en het positieve effect op de kwaliteit van leven potentieel aantrekkelijk voor toepassing in combinatie met andere levensverlengende behandelopties bij mCRPC-patiënten, hetzij sequentieel, hetzij gelijktijdig.
Over het gebruik van [^{223}Ra]$RaCl_2$ en [^{177}Lu]Lu-PSMA in sequentie wordt steeds meer duidelijk. In de retrospectieve RaLu-studie zijn de veiligheid en effectiviteit onderzocht van een behandeling met [^{177}Lu]Lu-PSMA bij mCRPC-patiënten (n=49) die eerder met [^{223}Ra]$RaCl_2$ zijn behandeld. De auteurs concludeerden dat sequentieel gebruik van [^{223}Ra]$RaCl_2$ en [^{177}Lu]Lu-PSMA goed wordt verdragen door patiënten en leidt tot beperkte myelosuppressie (10).

Abirateron

De bekendste studie waarbij [^{223}Ra]$RaCl_2$ gelijktijdig werd gegeven met andere medicatie is de ERA-233-studie. In deze fase 3-studie werden 806 patiënten met mCRCP met botmetastasen gerandomiseerd naar een behandeling met abirateron/prednison of abirateron/prednison/^{223}Ra. De blindering van de studie werd voortijdig verbroken toen bleek dat het fractuurrisico in de combinatiegroep hoger was dan in de abiraterongroep (11). Er was op dat moment sprake van een toename van skelet gerelateerde voorvallen (skeletal related events, SRE) en geen verbetering van de totale overleving (OS) in de combinatiegroep. Deze resultaten hebben geleid tot aanpassing van de indicatiestelling voor [^{223}Ra]$RaCl_2$ door de EMA.
[^{223}Ra]$RaCl_2$ is sindsdien geïndiceerd als monotherapie of in combinatie met een LHRH-analoog voor volwassen patiënten met mCRPC, symptomatische botmetastasen en geen bekende viscerale metastasen, die progressief zijn na tenminste twee voorafgaande systemische therapielijnen voor mCRPC (andere dan LHRH-analoga) of die niet in aanmerking komen voor een beschikbare systemische mCRPC-behandeling (1).
Latere studies, waaronder PEACE-3 (NCT02194842), hebben uitgewezen dat de verslechterde SRE-vrije overleving niet te wijten is aan de behandeling met [^{223}Ra]$RaCl_2$. Het toevoegen van botbeschermende medicatie (zoledroninezuur of denosumab) vermindert namelijk het risico op SRE's, zowel in de arm met als in de arm zonder [^{223}Ra]$RaCl_2$ (12).

Andere combinaties

Momenteel lopen er diverse klinische studies bij patiënten met mCRPC naar het effect van de combinatie van [^{223}Ra]$RaCl_2$ met andere medicatie, waaronder docetaxel (DORA-studie, NCT03574571), niraparib (NIRARAD-studie, NCT03076203), olaparib (COMRADE-studie, NCT03317392) en [^{177}Lu]Lu-PSMA-I&T (AlphaBet-studie, NCT05383079). Ook bij patiënten met hormoongevoelig, gemetastaseerd prostaatkanker (mHSPC) wordt de effectiviteit van combinatietherapieën met ^{223}Ra onderzocht. Hieronder enkele studies die [^{223}Ra]$RaCl_2$ combineren met radiotherapie, zoals de SAXON-PC- (NCT05133440), de RAVENS- (NCT04037358), de RROPE- (NCT03304418), en de City of Hope-studie (NCT03361735). De Nederlandse DUET-I studie behandelt oligometastatische patiënten met een sequentiële combinatie van [^{223}Ra]$RaCl_2$ en [^{177}Lu]Lu-PSMA-I&T. In deze fase 1-studie krijgen de patiënten 55 kBq/kg [^{223}Ra]$RaCl_2$ in week 0, 4 en 8 en 7,4 GBq [^{177}Lu]Lu-PSMA-I&T in week 6 en 12. De primaire uitkomstmaat van deze studie is haalbaarheid en veiligheid van de combinatie.

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Referenties

1. www.ema.europa.eu/en/documents/product-information/xofigo-epar-product-information_nl.pdf Geraadpleegd 28 maart 2023
2. Suominen MI, Fagerlund KM, RisannenJP, et al. Radium-223 Inhibits Osseous Prostate Cancer Growth by Dual Targeting of Cancer Cells and Bone Microenvironment in Mouse Models. Clin Cancer Res. 2017;23:4335-46
3. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter Radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213-23
4. Hoskin P, Sartor O, O'Sullivan JM, et al. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. Lancet Oncol. 2014;15:1397-406
5. Parker C, Coleman RE, Vogelzang N, et al. Updated survival, quality of life(QOL),and safety data of radium-223 chloride (RA-223) in patients with castration-resistant prostate cancer (CRPC)with bone metastases from the phase 3 double blind, randomized, multinational study (ALSYMPCA). Ann Oncol. 2012;23(Suppl 9):ix296
6. Sternberg CN, Saad F, Graff JN, et al. A randomised phase II trial of three dosing regimens of radium-223 in patients with bone metastatic castration-resistant prostate cancer. Ann Oncol. 2020;31:257-65
7. Malamas AS, Gameiro SR, Knudson KM, et al. Sublethal exposure to alpha radiation (223Ra dichloride) enhances various carcinomas' sensitivity to lysis by antigen-specific cytotoxic T lymphocytes

through calreticulin-mediated immunogenic modulation. Oncotarget 2016;7:86937-47
8. Kim JW, Shin MS, Kam Y, et al. Immune analysis of Radium-223 in patients with metastatic prostate cancer. Clin Genitour Cancer. 2017;16:e469-e476
9. Sartor O, Heinrich D, Mariados N, et al. Re-treatment with radium-223: 2-year follow-up from an international, open-label, phase 1/2 study in patients with castration resistant prostate cancer and bone metastases. Prostate. 2019;79:1683-91
10. Rahbar K, Essler M, Pabst KM, et al. Safety and survival outcomes of Lutetium-177-Prostate-Specific Membrane Antigen therapy in patients with metastatic castration-resistant prostate cancer with prior Radium-223 treatment: The RALU Study. J Nucl Med. 2022;27 Oct (jnumed.122.264456)
11. Smith M, Parker C, Saad F, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, doubleblind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20:408-19
12. Gillessen S, Choudhury A, Rodriguez-Vida A, et al. Decreased fracture rate by mandating bone protecting agents in the EORTC 1333/PEACE-3 trial combining Ra-223 with enzalutamide versus enzalutamide alone: an updated safety analysis. J Clin Oncol. 2021;39(suppl 15): abstract 5002

Radioembolization: An update on current practice and recent developments

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Introduction

Since the 1950s, when it became clear that hepatic tumors derive their blood supply primarily from the hepatic artery and normal hepatic parenchyma primarily receives it blood from the portal vein, there has been growing interest into hepatic artery-directed treatments (1).
Dr. Irving Ariel was the first to describe the technique of radioembolization in 1965. Via a groin puncture and femoral artery access, ^{90}Y loaded ceramic microspheres were administered through a catheter in the celiac artery (2). This therapy provided symptomatic improvements, but was not without complications. One patient experienced paresis of the right leg, while another patient became paraplegic. Five decades later and after the publication of multiple large multicenter studies, this technique eventually evolved into radioembolization and has become mainstream clinical practice performed in hospitals worldwide.
To date three types of microspheres have gained European CE market approval. Resin ^{90}Y-microspheres in 2002 (SIR-Spheres, SIRTeX Medical Ltd., Australia), glass ^{90}Y-microspheres in 2006 (TheraSphere, Boston Scientific, US) and ^{166}Ho-microspheres in 2015 (QuiremSpheres, Quirem Medical, The Netherlands).
Since the last review on radioembolization in this journal in 2016, data from large randomized multicenter trials have been published that have changed the playing field (3). Based on these data, guidelines have been adjusted that confirm that radioembolization is a valuable tool in treatment of hepatic malignancies. This paper will give an overview and future outlook of the current state of radioembolization treatment for three types of tumors.

Microspheres

^{90}Y-microspheres

In the early beginnings of radioembolization, non-selective tracer distribution and subsequent non-target microsphere deposition in distal organs caused major side effects, including gastrointestinal ulceration, radiation cholecystitis and radiation pneumonitis (liver-lung shunts). Myelotoxicity was also a major side effect reported. This was due to the unstable binding of the isotope ^{90}Y to the microspheres and detrimental leaching of ^{90}Y from the plastic or ceramic spheres used at that time (4). This eventually led to the development of new generation glass and resin ^{90}Y-microspheres in the early 1980's. In phase I trials and subsequent dose escalation studies the safety and early efficacy of glass ^{90}Y-microspheres in patients with hepatocellular carcinoma (HCC) and resin ^{90}Y-microspheres in patients with metastatic colorectal cancer (mCRC) was demonstrated (5). As a result of these studies (and subsequent studies), both glass and resin ^{90}Y-microspheres are currently approved for treatment of unresectable liver tumors on the European market.

^{166}Ho-microspheres

A relatively new type of microspheres used for radioembolization are ^{166}Ho-microspheres that are radioactive loaded bio-resorbable poly-L-lactic acid (PLLA) microspheres containing the isotope ^{166}Ho (see also table 1). These microspheres were initially developed at the UMC Utrecht in the Netherlands and are now a commercial product (Quiremspheres™, Terumo). Like ^{90}Y, ^{166}Ho is a high-energy beta-emitting isotope that can be used for tumor irradiation. Furthermore, it has imaging properties, through the emission of gamma photons and due to its paramagnetic properties. This allows visualization of its distribution in the liver and quantification of the absorbed tumor on SPECT/CT and MRI. In comparison with ^{90}Y-microspheres the half-life of ^{166}Ho-microspheres is shorter, 27 hours versus 64 hours, thus to achieve the same absorbed dose more activity is needed.
The first human trial, Holmium Embolization Particles for Arterial Radiotherapy (HEPAR I trial), in 2011, was performed in patients with unresectable, chemorefractory liver metastases who were treated with ^{166}Ho-microspheres. This trial concluded that ^{166}Ho-microspheres radioembolization was safe and feasible with an aimed whole liver absorbed dose of 60 Gy (6). This study was followed by the HEPAR II trial, a phase II study examining the efficacy of ^{166}Ho-microspheres radioembolization in salvage patients with liver metastases. It demonstrated that radioembolization with ^{166}Ho-microspheres induced a tumor response with an acceptable toxicity profile (7).

Table 1. Radioembolization microspheres characteristics.

Characteristics	SIR-Spheres®	TheraSphere®	QuiremSpheres®
Material	Resin	Glass	Poly-L-lactic acid
Particle size and range (μm)	30 (20–60)	25 (20–30)	30 (15–60)
Embolic effect	Moderate	Mild	Moderate
Activity per sphere (Bq)	40–70	4534 *	200–400
Specific gravity (g/dL)	1.6	3.7	1.4
Activity available (GBq)	3 #	3–20 ^ "	"
Handling for dispensing	Required	Not required	Not required
Multiple dosing from one vial	Possible	Not possible	Not possible

Note. From " EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds" by Weber, M., Lam, M., Chiesa, C. et al. EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds. Eur J Nucl Med Mol Imaging 49, 1682-99 (2022). https://doi.org/10.1007/s00259-021-05600-z

Direct measure by Pasciak et al. (8) at calibration, the IFU provide a value of 2500 Bq. The value is variable according to physical decay depending on the day and time of treatment.
Prescribed activity should be withdrawn on site. The FLEXdose option allows injection 3 days before calibration, when the vial activity is 10 GBq at higher specific activities.
^ Vials of 3-20 GBq in steps of 0.5 GBq, calibrated at noon on the Sunday before treatment with a shelf-life of 12 days.
" Patient-specific activity is calibrated at the day and time of treatment.

Radioembolization technique

Overall, ^{90}Y-microspheres radioembolization and ^{166}Ho-microspheres radioembolization are comparable in many aspects.
A standard radioembolization procedure of unresectable liver tumors, can be summarized in four steps.

Step 1. Patient selection
It is strongly recommended that patients referred for radioembolization are discussed in a multidisciplinary tumor board. All locoregional (e.g. resection, ablation, radioembolization, chemoembolization, radiotherapy) or systemic options (e.g. chemotherapy, immunotherapy) should preferably be available. The indication for radioembolization can vary from salvage treatment in advanced stage disease (typically lobar or whole liver treatment), bridging for transplantation (selective treatment) or in a neoadjuvant setting for resection (typically radiation lobectomy or radiation segmentectomy). The inclusion criteria vary depending on the treatment intent. In broad terms, patients should at least have liver-only or liver dominant disease; a life expectancy of at least 3 months; accessible liver vasculature; adequate liver functional reserve; and a favorable scout dose distribution to receive radioembolization. For an overview of indications and contraindications for radioembolization with ^{166}Ho-microspheres and ^{90}Y-microspheres, see table 2.

Step 2. Work-up procedure
Pre-operative CTA is advised to assess the hepatic arterial vasculature and possible anatomical variations. The work-up procedure consists of catheterization of the liver vasculature under angiography and selecting the injection position(s) for the scout dose. The goal of this procedure is to 1) detect any unintended gastrointestinal deposition of activity, 2) calculate the lung shunt fraction, 3) predict the intrahepatic distribution of the microspheres (tumor and non-tumor absorbed doses), and 4) allow for treatment planning (calculate the required activity for treatment). Performing C-arm CT during the work-up procedure is essential. A C-arm CT with transcatheter contrast injection should at the very minimum be performed at every intended injection position. This helps to timely recognize non-target vessels causing extrahepatic deposition, select the tumor feeding arteries and recognize

Table 2. Recommendations and contraindications for radioembolization.

Indications	Contraindications
1. Unresectable primary or metastatic hepatic disease with liver-only or liver dominant tumor burden 2. Life expectancy > 3 months 3. An eastern cooperative oncology group (ECOG) status ≤ 2 4. In case of (suspected) cirrhosis; Child–Pugh score ≤ B7 5. Preoperative radioembolization for: (a) Downstaging (b) Bridge to transplant (c) Hypertrophy induction	1. Pretreatment scan demonstrating (a) The potential of > 30 Gy radiation exposure to the lung (b) Flow to the gastrointestinal tract that cannot be corrected by catheter techniques 2. Limited hepatic reserve (a) Irreversibly elevated bilirubin levels (> 2.0 mg/dl) (b) Reduced albumin (< 3 g/dl) 3. Prior external beam radiation therapy involving the liver in the treatment field of view. Systemic radionuclide treatments are allowed (e.g., [^{177}Lu]Lu-dotatate) 4. Severe contrast allergy, not manageable or responsive to prophylaxis

Note. From "Holmium-166 Radioembolization: Current Status and Future Prospective" by Stella et al. Cardiovascular Interventional Radiology 2022 Nov;45(11):1634-45. doi: 10.1007/s00270-022-03187-y.

potential parasitic tumor feeders. In general, a scout dose of technetium-99m macroaggregated albumin ([^{99m}Tc]Tc-MAA) is used. It acts as a surrogate particle and emits gamma radiation (with minimal radiation exposure to the patient), which can be visualized on planar imaging and SPECT/CT.
Alternatively, a scout dose of ^{166}Ho-microspheres (QuiremscoutTM, Terumo) can be used instead of [^{99m}Tc]Tc-MAA. The ^{166}Ho-microspheres scout dose consists of the exact same microspheres as used for ^{166}Ho-microspheres therapy. Only the number of microspheres and specific activity per microsphere is lower. [^{99m}Tc]Tc -MAA differs greatly in shape, size and density from ^{90}Y- or ^{166}Ho-microspheres. By using a ^{166}Ho-microspheres scout dose, the possible discrepancy between planning and treatment is greatly reduced in comparison to [^{99m}Tc]Tc -MAA. Disadvantages of ^{166}Ho-microspheres scout include that it is more costly, takes more time to administer (same administration system as for the treatment procedure itself) and comes with a low amount of beta radiation. However, data from the first trials have shown that the absorbed dose of encountered extrahepatic depositions are insufficient to cause any complications (6,9,10). Furthermore, ^{166}Ho-microspheres scout has been proven to be superior in its predictive value for intrahepatic distribution and in assessing possible lung dose in comparison with [^{99m}Tc]Tc-MAA (11,12). Development of a ^{90}Y-microspheres scout is underway with the first prospective single-arm clinical trial, utilizing 0.56 GBq resin scout ^{90}Y-microspheres, reporting superior results in biodistribution in comparison with [^{99m}Tc]Tc-MAA for non-segmental therapies (13).

Step 3. Treatment planning
Treatment planning is the most important step of the entire treatment. Data from the work-up procedure and scout dose SPECT-CT are used to determine a plan, including the number of injection positions, activity per injection position, time frame for treatment (instance e.g. whole liver treatment in one session or sequential treatment). Calculating the required amount of activity should be dosimetry based. Dosimetry can roughly be divided into three models: Single compartment model, a multi-compartment model or a voxel-based model. In the single compartment model, there is no distinction between the tumor and the normal liver parenchyma, and a mean dose is calculated for the entire perfused volume. In the multi-compartment model (also known as partition model), doses are evaluated separately for the tumor and the normal perfused liver. In voxel-based dosimetry, dosimetry is evaluated for each reconstructed voxel with predefined volumes of interest. Recent guidelines by the European Association of Nuclear Medicine recommend using multi-compartment dosimetry, whenever tumor segmentation is feasible. Clinical data support tumoricidal doses and maximum tolerated doses for each product used (14). When multi-compartment dosimetry is not possible, single compartment dosimetry can be used as an alternative.

Step 4. Treatment procedure
One to two weeks after the scout dose ([^{99m}Tc]Tc -MAA or ^{166}Ho scout) the radioembolization is performed based on the scout procedure. Depending

on the treatment plan (whole liver, unilobar or segmental) the catheter is placed at the same position(s) as in the scout dose.
Since all currently used microspheres emit beta radiation, they are delivered in a vial that is positioned centrally in a Perspex administration box for radiation shielding. The vial is connected to the intra-arterially placed catheter through the tubing of the administration system. Administration of glass ^{90}Y-microspheres is performed by semi-continuous infusion controlled by a single syringe. This differs from resin ^{90}Y-microspheres and ^{166}Ho-microspheres for which the administration is performed intermittently to check for stasis and possible backflow. Finally, to quantify delivery after radioembolization, either SPECT or MRI can be used for ^{166}Ho-microspheres and either PET or Bremsstrahlung-SPECT can be used for ^{90}Y-microspheres. Radioembolization can be performed as an outpatient treatment depending on the local radiation safety regulations. In many centers, patients stay in the hospital for one night (15,16).

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy, accounting for 80-90% of all primary hepatic malignancies. HCC has a 5-year survival rate of approximately 70% with early-stage HCC, which decreases to a median overall survival of 1-1.5 years for symptomatic advanced-stage cases treated with systemic therapies (17,18).
Several trials examining ^{90}Y-microspheres radioembolization in HCC have been published over the last few years. There have been three major trials that have compared ^{90}Y-microspheres radioembolization with sorafenib (multikinase inhibitor approved for treatment of HCC) in locally advanced HCC: SARAH trial, SIRveNIB trial and SORAMIC trial. Although radioembolization was proven to be safe, there was no significant difference in overall survival

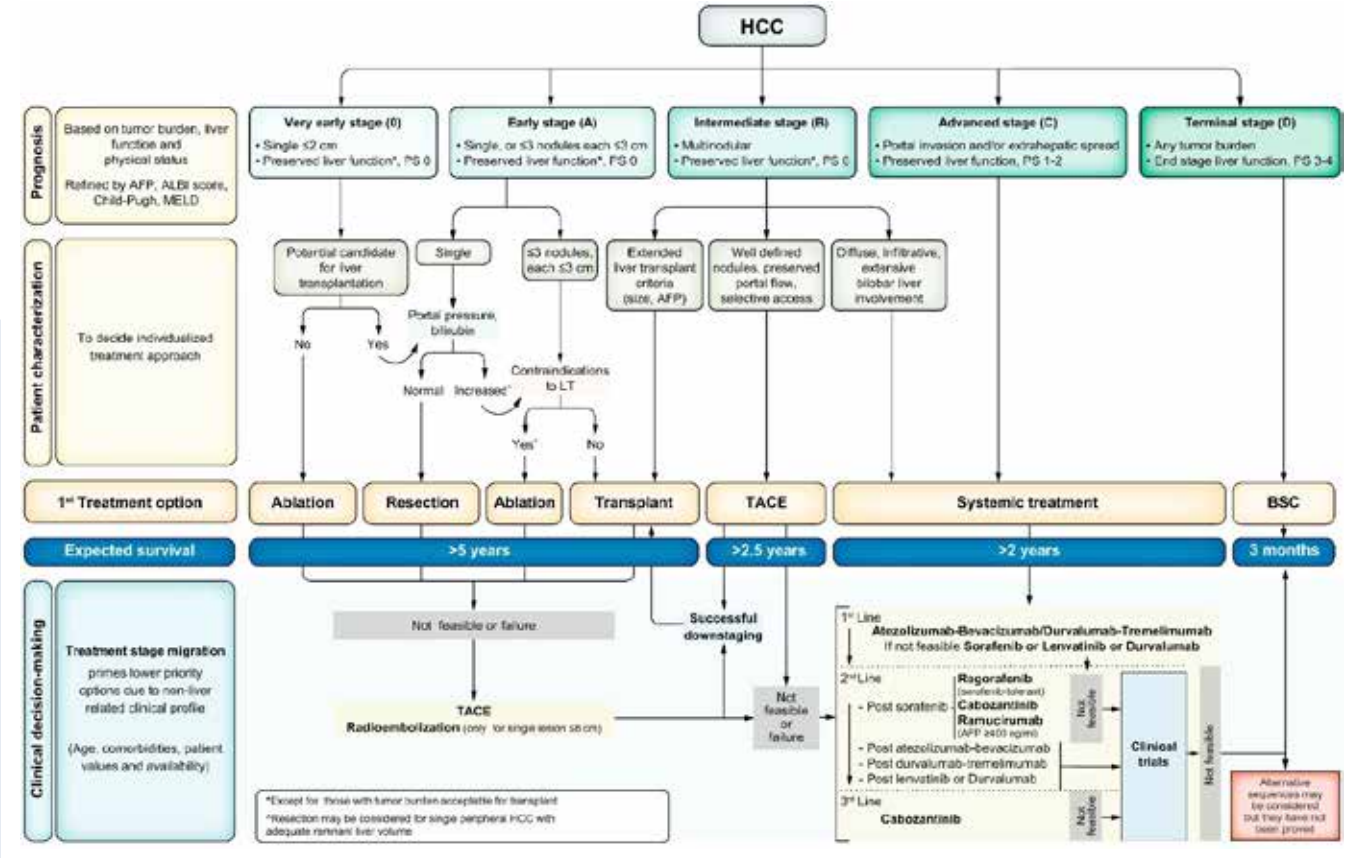

Figure 1. BCLC staging and treatment strategy in 2022.
Note. From "BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update" by Reig et al. J Hepatol 2022 Mar;76 (3):681-693.

either when performed in addition to sorafenib or in comparison with sorafenib (19-21). However, since the publication of the IMbrave trial, sorafenib is rarely implemented anymore. The IMbrave trial compared a combination of atezolizumab (anti-programmed death-ligand 1 (PD-L1) antibody) and bevacizumab (VEGF-A-targeting monoclonal antibody) with sorafenib in patients with unresectable HCC. This combination resulted in a significantly improved overall survival and progression-free survival (PFS) compared to sorafenib (22). Since then, the combination of atezolizumab and bevacizumab, as well as several other immunotherapeutics, are incorporated in the Barcelona Clinic Liver Cancer (BCLC) staging system (see figure 1).
In the same period, the first data on ^{166}Ho-microspheres radioembolization for HCC were reported. This HEPAR Primary study demonstrated in 31 patients with liver-dominant HCC that ^{166}Ho-microspheres radioembolization is a safe treatment with unacceptable toxicity occurring in 10% of patients (23). There was complete or partial response for 84% of the target liver lesions at 6 months follow-up and median overall survival was 14.9 months.

Above mentioned prospective studies all provided valuable information on safety and efficacy of radioembolization in HCC, however it was the retrospective LEGACY study that made the largest impact in terms of guideline adjustments. The LEGACY study was a single-arm, retrospective study that included all eligible, consecutive patients with HCC treated with radioembolization with eligibility criteria that included solitary HCC ≤ 8 cm, Child-Pugh A cirrhosis and ECOG performance 0-1.
A total of 162 patients were included and median tumor size was 2.7 cm (range 1-8 cm).
Median follow-up time was 29.9 months by reverse Kaplan-Meier.
ORR (best response) was 88.3% (CI: 82.4-92.4), with 62.2% (CI: 54.1-69.8) exhibiting a duration of response ≥ 6 months. Three-year overall survival was 86.6% in all patients. For patients with neoadjuvant therapy with resected or transplanted liver overall survival was 92.8% (24).
Based on these results, radioembolization was included as a treatment option in the updated 2022 BCLC strategy. Based on this updated version, radioembolization could be considered in patients with single nodules up to 8 cm in very early stage (BCLC 0) ,early stage (BCLC A) and intermediate stage (BCLC B) if not suitable for resection or ablation (see figure 1) (25). The aforementioned 8 cm limit is somewhat remarkable as there were no tumors included in the LEGACY study above 8 cm and the large majority were much smaller than 8 cm with a median of 2.7 cm (range 1.0 - 8.0). Furthermore, there is no scientific data indicating that radioembolization would not be efficacious in tumors larger than 8 cm.

Another landmark study was the Dosisphere-01 trial which was a randomized, multicenter, open-label phase II trial. In this trial the usage of multi-compartment dosimetry in comparison with single compartment dosimetry significantly improved the ORR in patients with locally advanced HCC (p=0.01).
Furthermore, there was no increase in the toxicity profile and an improvement in overall survival was observed with a median OS of 26.6 months vs. 10.7 months in the single compartment dosimetry group (26).
These results made it clear that multi-compartment dosimetry should become the standard-of-care method for radioembolization treatment planning.
Moreover, these results confirm that the absence of multi-compartment dosimetry limits the value of study results, as confirmed by the SARAH post-hoc analysis (27).

Metastatic colorectal cancer

Metastatic colorectal carcinoma (mCRC) is the most prevalent type of hepatic metastases, accounting for 35% of patients with hepatic metastases (28). Radioembolization is an established treatment option for mCRC patients in a salvage setting. This was in part due to an RCT published in 2010 that demonstrated that radioembolization with resin ^{90}Y-microspheres in patients with liver-limited metastases failing the available chemotherapeutic options prolonged time to tumor progression and time to liver progression (29). Positive results were also reported in the MORE study, a retrospective analysis of 606 patients with unresectable colorectal liver metastases treated with radioembolization using resin ^{90}Y-microspheres. Authors concluded that resin ^{90}Y-microspheres radioembolization offers favorable survival benefits for patients with unresectable metastatic colorectal cancer, even among patients who received three or more prior lines of chemotherapy with a median OS of 10.0 months (95% CI: 9.2-11.8 months) (30).
In first line however, data were less favorable. A combined analysis of three multicenter, randomized, phase III trials (Sirflox, Foxfire, FoxFire Global) failed to show benefit in overall survival when first-line FOLFOX chemotherapy was supplemented with radioembolization in comparison with FOLFOX alone (31). However, data from the Sirflox trial suggested that radioembolization may be most beneficial in liver-limited or liver predominant disease. In this trial radioembolization with resin ^{90}Y-microspheres gave significantly better 'liver-specific-PFS' but failed to show an overall PFS benefit, with 45% of patients having their primary tumor in place and 40% with extrahepatic disease (32). One potential subgroup

with a distinct benefit consisted of patients with right-sided primary tumors (33).

In second line, a recent large phase III (EPOCH) trial comparing second-line chemotherapy alone with second-line chemotherapy plus glass ^{90}Y-microspheres radioembolization in 428 patients with liver-dominant or liver-only disease was recently published (2021). In this trial a significant improvement in PFS was reported with an ORR of 34% with second-line chemotherapy augmented with ^{90}Y-microspheres radioembolization compared to 21.1% in only second-line chemotherapy. Further subgroup analysis identified possible factors that might improve PFS benefit, patients with fewer than three lesions, resected primary tumor, lower tumor burden, left primary tumor location (PTL) and a KRAS mutation (34).
^{166}Ho-microspheres radioembolization for chemorefractory mCRC patients has been studied in the HEPAR I, II and SIM trials, which confirmed safety and efficacy with a reported median OS of 14.5 months in the HEPAR II trial (35).

Based on these performed trials, radioembolization as a first-line treatment in patients with mCRC was not recommended. Current radioembolization should be considered in patients with mCRC when available chemotherapeutic agents fail (36). However, data on radioembolization in mCRC is limited by the absence of prospective multi-compartment dosimetry studies (37).

Neuroendocrine liver metastasis

Neuroendocrine neoplasms (NEN) are a rare (2% of all malignancies) and very heterogenous group of tumors (38,39). A well-established negative prognostic factor for NEN patients is the presence of neuroendocrine liver metastases (NELM) with one quarter of NEN patients having distant metastases at presentation with the liver being the most affected (40,41). Since the majority (60-70%) of NELM patients have diffuse liver disease, which does not allow for surgical resection, there is a clinical need for liver-directed treatments in light of the limited systemic options for NENs. The large majority of data regarding radioembolization come from retrospective studies with heterogenous study populations and primarily in a salvage setting. These studies confirmed safety and efficacy of radioembolization of NELM in a salvage setting with reported median OS of 28.5-39 months (42). Only one retrospective study specifically investigated radioembolization in a second-line setting. In this study a median hepatic PFS of 18.6 months and median global PFS of 18.8 months was reported. These results are slightly better than the results obtained in a salvage setting. Furthermore, median OS was prolonged compared to the salvage setting group, 44.8 vs. 30.6 months respectively (43), however biased by subsequent treatments.

In order to boost the benefit for patients suffering from high intrahepatic tumor burden, several studies have examined the possible synergy between radioembolization and systemic treatments. To date, three small studies have been performed, the first by Soulen et al. in which resin ^{90}Y-microspheres radioembolization was combined with systemic chemotherapy capecitabin plus temozolomide (CAPTEM) in patients with NELM of different origins who were primarily treated in a second-line setting. In this study high response rates and long survival were reported suggesting a synergistic effect (44). Only one patient of 21 in total developed hepatic failure due to radioembolization-induced liver disease (REILD). Kim et al. examined the combination of everolimus and pasitreotide augmented with ^{90}Y-microspheres radioembolization in a phase 1b study, where everolimus dosage was escalated whilst pasitreotide and radioembolization were standardized. This treatment was safe and no additional hepatotoxicity was identified (45). The first combination study with ^{166}Ho-microspheres radioembolization came with the HEPAR plus trial. In this trial peptide receptor radionuclide therapy (PRRT) was combined with ^{166}Ho-microspheres radioembolization, by adding radioembolization within 20 weeks after the fourth cycle of PRRT (46). The combination treatment was proven to be safe and effective with only one case of REILD.
Above mentioned studies further confirm the added value of radioembolization as a local treatment option in NELM. Furthermore, in the European Neuroendocrine Tumor Society (ENETS) guideline from 2016 and the European Society for Medical Oncology (ESMO) guideline from 2020 the role of radioembolization has been extended, including early application as a tumor debulking treatment or as a salvage treatment in selected cases, after the failure of systemic treatments (47,48).
However, like with mCRC, data on radioembolization in NELM is limited by the absence of prospective multi-compartment dosimetry-based studies. Especially since clear dose-response and dose-survival relationships have been reported in NELM (42).

Future Directions

As mentioned earlier one of the great limitations of the published studies was the lack of multi-compartment dosimetry. As demonstrated in the Dosisphere-01 trial, multi-compartment dosimetry is superior to single compartment dosimetry. Multi-compartment dosimetry requires a reliable scout particle for predicting microsphere distribution

and it requires understanding of dose-response relationships. ^{166}Ho-microspheres scout has proven to be a more reliable predictor than [^{99m}Tc]Tc -MAA. Dose-response relationships are now studied for the different types of microspheres and for different tumor types, which will help us develop more patient tailored treatments with better outcome and less toxicity. Moving forward, there will be more attention to dosimetry, not only in clinical trials but also in clinical practice.

Another shift in the treatment paradigm will be the choice of type of radioembolization or treatment strategy. Instead of whole liver radioembolization for all, the emphasis will be put more on (super) selective radioembolization or radiation lobectomy in preparation for surgical liver resection. The main benefits of these approaches are the reduced healthy liver toxicity, improved disease control and the potential for curation, either directly or after surgery (49). Immunotherapy has had a huge impact on how HCC patients are being treated today. In the coming years, the position of radioembolization relative to immunotherapies must be established. Since radioembolization significantly enhances intra-tumor immune infiltrates, combining immunotherapy with radioembolization may have a synergistic effect (37).

Lastly, ^{166}Ho-microspheres are gradually gaining a foothold in the radioembolization landscape. Data on ^{166}Ho-microspheres radioembolization is still scarce compared to ^{90}Y-microspheres radioembolization but there are many clinical studies ongoing or in preparation. The first randomized clinical trial on ^{166}Ho-microspheres radioembolization recently started in the Netherlands: CAIRO7 (NCT05092880). This study will investigate if ^{166}Ho-microspheres radioembolization is an effective alternative, better tolerated and more cost-effective treatment option in elderly or frail patients compared to chronic systemic treatment with comparable progression-free survival.

Conclusion

Hepatic radioembolization is a safe and effective treatment in primary and secondary hepatic malignancies. The position of radioembolization for these indications has changed due to new evidence and alternative treatment options like immunotherapy. The field of radioembolization is evolving, driven amongst other things by multi-compartment dosimetry, more reliable scout particles and combination treatments.

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References

1. Breedis C, Young G. The blood supply of neoplasms in the liver. Am J Pathol. 1954;30:969-77
2. Ariel IM. TREATMENT OF INOPERABLE PRIMARY PANCREATIC AND LIVER CANCER BY THE INTRA-ARTERIAL ADMINISTRATION OF RADIOACTIVE ISOTOPES (Y90 RADIATING MICROSPHERES). Ann Surg. 1965;162:267-78
3. Lam MGEH. Advances in Nuclear Therapy. Tijdsch Nucl Geneesk. 2016;4:1612.
4. Ehrhardt GJ, Day DE. Therapeutic use of 90Y microspheres. Int J Rad Appl Instrum B. 1987;14(3):233-42
5. Spyridonidis T, Spyridonidis J, Papathanasiou N, Katsanos K. History and development of radioembolization: an old idea with modern applications. Nucl Med Comm. 2019;40:684-92.
6. Smits ML, Nijsen JF, van den Bosch MA, Lam MGEH, Vente MA, Mali WP, et al. Holmium-166 radioembolization in patients with unresectable, chemorefractory liver metastases (HEPAR trial): a phase 1, dose-escalation study. Lancet Oncol. 2012;13:1025-34
7. Prince JF, van den Bosch M, Nijsen JFW, Smits MLJ, van den Hoven AF, Nikolakopoulos S, et al. Efficacy of Radioembolization with (166)Ho-Microspheres in Salvage Patients with Liver Metastases: A Phase 2 Study. J Nucl Med. 2018;59:582-8
8. Pasciak AS, Bourgeois AC, McKinney JM, Chang TT, Osborne DR, Acuff SN, et al. Radioembolization and the Dynamic Role of (90)Y PET/CT. Front Oncol. 2014;4:38
9. Prince JF, van Rooij R, Bol GH, de Jong HW, van den Bosch MA, Lam MG. Safety of a Scout Dose Preceding Hepatic Radioembolization with 166Ho Microspheres. J Nucl Med. 2015;56:817-23
10. Braat A, Prince JF, van Rooij R, Bruijnen RCG, van den Bosch M, Lam M. Safety analysis of holmium-166 microsphere scout dose imaging during radioembolization work-up: A cohort study. Eur Radiol. 2018;28:920-8
11. Smits MLJ, Dassen MG, Prince JF, Braat A, Beijst C, Bruijnen RCG, et al. The superior predictive value of (166)Ho-scout compared

with (99m)Tc-macroaggregated albumin prior to (166)Ho-microspheres radioembolization in patients with liver metastases. Eur J Nucl Med Mol Imaging. 2020;47:798-806
12. Elschot M, Nijsen JF, Lam MG, Smits ML, Prince JF, Viergever MA, et al. (^{99}m)Tc-MAA overestimates the absorbed dose to the lungs in radioembolization: a quantitative evaluation in patients treated with ^{166}Ho-microspheres. Eur J Nucl Med Mol Imaging. 2014;41:1965-75
13. Kokabi N, Webster LA, Elsayed M, Switchenko JM, Chen B, Brandon D, et al. Accuracy and Safety of Scout Dose Resin Yttrium-90 Microspheres for Radioembolization Therapy Treatment Planning: A Prospective Single-Arm Clinical Trial. J Vasc Interv Radiol. 2022;33:1578-87.e5
14. Weber M, Lam M, Chiesa C, Konijnenberg M, Cremonesi M, Flamen P, et al. EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds. Eur J Nucl Med Mol Imaging. 2022;49:1682-99
15. van Roekel C, Harlianto NI, Braat AJAT, Prince JF, van den Hoven AF, Bruijnen RCG, et al. Evaluation of the Safety and Feasibility of Same-Day Holmium-166 -Radioembolization Simulation and Treatment of Hepatic Metastases. Journal of Vascular and Interventional Radiology. 2020;31:1593-9
16. Tong AK, Kao YH, Too CW, Chin KF, Ng DC, Chow PK. Yttrium-90 hepatic radioembolization: clinical review and current techniques in interventional radiology and personalized dosimetry. Br J Radiol. 2016;89(1062):20150943
17. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021;7:6
18. Villanueva A. Hepatocellular Carcinoma. N Engl J Med. 2019;380(15):1450-62
19. Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux G-P, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol. 2017;18:1624-36
20. Chow PKH, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, et al. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. J Clin Oncol. 2018;36:1913-21
21. Ricke J, Klümpen HJ, Amthauer H, Bargellini I, Bartenstein P, de Toni EN, et al. Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. J Hepatol. 2019;71:1164-74
22. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020;382:1894-905
23. Reinders MTM, van Erpecum KJ, Smits MLJ, Braat A, Bruijne J, Bruijnen R, et al. Safety and Efficacy of (166)Ho Radioembolization in Hepatocellular Carcinoma: The HEPAR Primary Study. J Nucl Med. 2022;63:1891-8
24. Salem R, Johnson GE, Kim E, Riaz A, Bishay V, Boucher E, et al. Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable HCC: The LEGACY Study. Hepatology. 2021;74:2342-52
25. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022;76:681-93
26. Garin E, Tselikas L, Guiu B, Chalaye J, Edeline J, de Baere T, et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. Lancet Gastroenterol Hepatol. 2021;6:17-29
27. Hermann AL, Dieudonné A, Ronot M, Sanchez M, Pereira H, Chatellier G, et al. Relationship of Tumor Radiation-absorbed Dose to Survival and Response in Hepatocellular Carcinoma Treated with Transarterial Radioembolization with (90)Y in the SARAH Study. Radiology. 2020;296:673-84
28. de Ridder J, de Wilt JH, Simmer F, Overbeek L, Lemmens V, Nagtegaal I. Incidence and origin of histologically confirmed liver metastases: an explorative case-study of 23,154 patients. Oncotarget. 2016;7:55368-76
29. Hendlisz A, Van den Eynde M, Peeters M, Maleux G, Lambert B, Vannoote J, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol. 2010;28:3687-94
30. Kennedy A, Cohn M, Coldwell DM, Drooz A, Ehrenwald E, Kaiser A, et al. Updated survival outcomes and analysis of long-term survivors from the MORE study on safety and efficacy of radioembolization in patients with unresectable colorectal cancer liver metastases. Journal of Gastrointestinal Oncology. 2017;8:614-24
31. Wasan HS, Gibbs P, Sharma NK,

Taieb J, Heinemann V, Ricke J, et al. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol. 2017;18:1159-71
32. van Hazel GA, Heinemann V, Sharma NK, Findlay MP, Ricke J, Peeters M, et al. SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) Versus mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients With Metastatic Colorectal Cancer. J Clin Oncol. 2016;34:1723-31
33. Gibbs P, Heinemann V, Sharma NK, Taieb J, Ricke J, Peeters M, et al. Effect of Primary Tumor Side on Survival Outcomes in Untreated Patients With Metastatic Colorectal Cancer When Selective Internal Radiation Therapy Is Added to Chemotherapy: Combined Analysis of Two Randomized Controlled Studies. Clin Colorectal Cancer. 2018;17:e617-e29
34. Mulcahy MF, Mahvash A, Pracht M, Montazeri AH, Bandula S, Martin RCG, 2nd, et al. Radioembolization With Chemotherapy for Colorectal Liver Metastases: A Randomized, Open-Label, International, Multicenter, Phase III Trial. J Clin Oncol. 2021;39:3897-907
35. Stella M, Braat AJAT, van Rooij R, de Jong H, Lam MGEH. Holmium-166 Radioembolization: Current Status and Future Prospective. Cardiovasc Intervent Radiol. 2022;45:1634-45
36. Cervantes A, Adam R, Roselló S, Arnold D, Normanno N, Taïeb J, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34:10-32
37. Ramdhani K, Smits MLJ, Lam MGEH, Braat AJAT. Combining Selective Internal Radiation Therapy with Immunotherapy in Treating Hepatocellular Carcinoma and Hepatic Colorectal Metastases: A Systematic Review. Cancer Biother Radiopharm. 2023. Online ahead of print
38. Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing But NET: A Review of Neuroendocrine Tumors and Carcinomas. Neoplasia. 2017;19:991-1002
39. Basu B, Sirohi B, Corrie P. Systemic therapy for neuroendocrine tumors of gastroenteropancreatic origin. Endocr Relat Cancer. 2010;17:R75-90
40. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncology. 2017;3:1335-42
41. Riihimäki M, Hemminki A, Sundquist K, Sundquist J, Hemminki K. The epidemiology of metastases in neuroendocrine tumors. Int J Cancer. 2016;139:2679-86
42. Ramdhani K, Braat AJAT. The Evolving Role of Radioembolization in the Treatment of Neuroendocrine Liver Metastases. Cancers (Basel). 2022;14(14)
43. Schaarschmidt BM, Wildgruber M, Kloeckner R, Nie J, Steinle V, Braat AJAT, et al. ⁹⁰Y Radioembolization in the Treatment of Neuroendocrine Neoplasms: Results of an International Multicenter Retrospective Study. J Nucl Med. 2022;63:679
44. Soulen MC, van Houten D, Teitelbaum UR, Damjanov N, Cengel KA, Metz DC. Safety and Feasibility of Integrating Yttrium-90 Radioembolization With Capecitabine-Temozolomide for Grade 2 Liver-Dominant Metastatic Neuroendocrine Tumors. Pancreas. 2018;47:980-4
45. Kim HS, Shaib WL, Zhang C, Nagaraju GP, Wu C, Alese OB, et al. Phase 1b study of pasireotide, everolimus, and selective internal radioembolization therapy for unresectable neuroendocrine tumors with hepatic metastases. Cancer. 2018;124:1992-2000
46. Braat AJAT, Kwekkeboom DJ, Kam BLR, Teunissen JJM, de Herder WW, Dreijerink KMA, et al. Additional hepatic (166)Ho-radioembolization in patients with neuroendocrine tumors treated with (177)Lu-DOTATATE; a single center, interventional, non-randomized, non-comparative, open label, phase II study (HEPAR PLUS trial). BMC Gastroenterol. 2018;18:84
47. Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Neuroendocrinology. 2016;103:172-85
48. Pavel M, Öberg K, Falconi M, Krenning EP, Sundin A, Perren A, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31:844-60
49. Gabr A, Riaz A, Mouli S, Desai K, Thornburg B, Salem R, et al. Modified Radiation Lobectomy: An Evolving Paradigm to Convert Patients to Liver Resection Candidacy. Semin Intervent Radiol. 2019;36:343-8

Beeldgestuurd behandelen – Holmium-166 therapie geleid door CT en MRI

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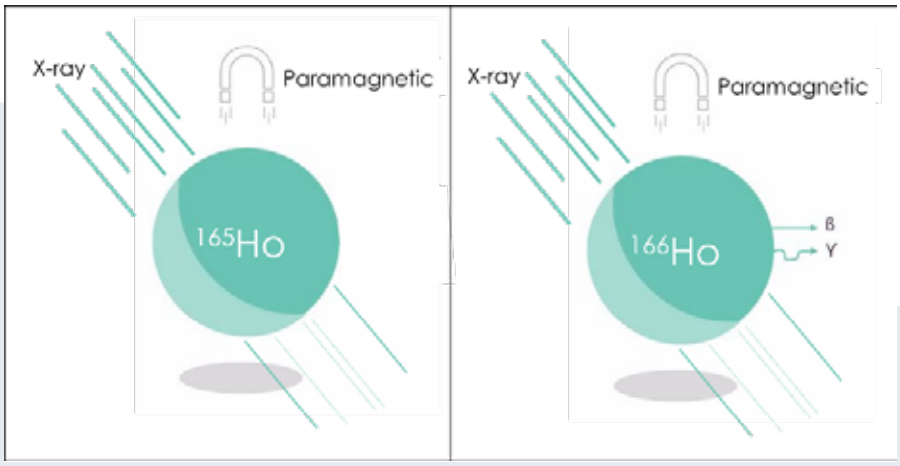
Ontwikkeling van holmium-166 therapieën

Holmium-166 microsferen (HoMS) vonden hun oorsprong in 1991 (1), en al snel werd de ontwikkeling van de microsferen met deze bèta$^-$- (β^-) en gamma-emitter (γ) doorgezet binnen fundamenteel en preklinisch onderzoek in het UMC Utrecht (2-5). Er gingen jaren overheen voor de optimale vorm van de microsferen werd gevonden (6). Het eindproduct, holmiumacetylacetonaat in een matrix van polymelkzuur met een gemiddelde diameter van 30 µm, werd in 2009 voor het eerst gebruikt ter behandeling van patiënten met verscheidene typen levertumoren zonder verdere behandelopties (7). De behandeling is gelijk aan de behandeling met de in 2001 op de markt verschenen yttrium-90 (^{90}Y) microsferen, en wordt zowel selectieve interne radiotherapie (SIRT) als transarteriële radioembolisatie (TARE) genoemd.
In de jaren daarna vond de valorisatie plaats, waardoor deze therapie breder ingezet kon worden. Gezien patiënten met levermaligniteiten vaak pas laat gediagnosticeerd worden is er vaker sprake van uitgebreide ziekte binnen de lever. Lokale behandelopties zoals chirurgie of ablatie zijn dan niet meer mogelijk, en systemische therapieën hebben vaak veel negatieve bijeffecten. Voor patiënten met uitgebreide leverziekte en slechtere conditie is TARE vaak nog een laatste laag-invasieve behandeling, maar de uitkomsten variëren van totale respons tot verwaarloosbare respons. Tegenwoordig is de holmium onderzoeksgroep onder leiding van Frank Nijsen verbonden aan de MAGIC en Nucmed onderzoeksgroepen van het Radboudumc. Hierin voeren wij onderzoek uit naar de verbetering van TARE en naar mogelijk nieuwe toepassingen, zoals intratumorale behandeling binnen andere lokale tumoren met HoMS. Waarin we fundamenteel, preklinisch en klinisch onderzoek verrichten.

Nucleaire beeldvorming met SPECT, CT en MRI

Een groot voordeel van de HoMS zijn de verschillende beeldvormingsmogelijkheden (figuur 1). Naast β^--straling heeft ^{166}Ho ook laag-energetische γ-straling die kan worden gevisualiseerd en gekwantificeerd met behulp van single photon emission computed tomography (SPECT). HoMS hebben een relatief hoge dichtheid wat een sterke verzwakking van röntgenstraling veroorzaakt, waardoor holmium hyperintens (wit) zichtbaar wordt op computed tomography (CT). Ook MRI kan gebruikt worden om de HoMS zichtbaar te maken, en is in de afgelopen jaren geoptimaliseerd voor klinisch gebruik met CE gemarkeerde software. Door de paramagnetische eigenschappen van holmium zal het MR-signaal sneller uitdoven, wat met de huidige MRI-systemen nauwkeurig gemeten kan worden met een multi-gradiënt echo scan. De snelheid van het uitdoven van het MR-signaal kan vertaald worden naar een dosisverdeling zoals we die kennen van de SPECT, maar met een veel kortere acquisitietijd (ca. 3 minuten) en een hoge resolutie (2x2x4 mm). Afhankelijk van de beschikbaarheid van de beeldvormingsmodaliteit, de uitvoer van de therapie en de patiëntenpopulatie, wordt er binnen



Figuur 1. Illustratieve weergave van de beeldvorming karakteristieken van holmium-165 en holmium-166 microsferen.

de verschillende behandelmethoden, trans arterieel en intratumoraal, een keuze gemaakt tussen gebruik van SPECT, CT of MRI, of een combinatie hiervan.

Dosimetrie binnen TARE

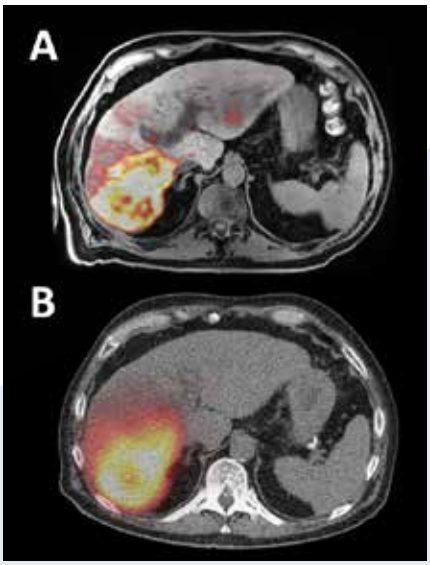
Doordat intraprocedureel de microsferen niet in beeld kunnen worden gebracht, en de proefbolus die tijdens een voorbereidende procedure wordt gegeven om de dosisverdeling preoperatief in te schatten niet 1 op 1 hetzelfde is als de behandeling, is voorzichtigheid geboden bij het maken van de dosisplanning om genoeg vitaal leverweefsel te sparen. Recente literatuur pleit daarbij voor een hoge tumordosis met daarbij een lage dosis op het gezonde leverweefsel. De SARAH en DOSIPHERE-1 studie hebben laten zien dat het optimaliseren van de tumordosis een langere progressievrije en algemene overleving laten zien (8,9). Retrospectief werd bij de studiepatiënten van de SARAH studie een mediane overleving van 14,1 maanden gevonden bij een tumordosis hoger dan 100 Gy, terwijl voor patiënten met een lagere tumordosis de mediane overleving 6,1 maanden was (8). Naast dosimetrie op de gemiddelde tumordosis is ook tumorheterogeniteit een belangrijke factor die genoemd wordt in de literatuur, maar waar weinig invloed op uitgeoefend kan worden tijdens TARE (10). Gelimiteerde dosimetrie na behandeling en het gebrek aan dosimetrie tijdens de behandeling kan verklaren dat in de tot nu toe uitgevoerde gerandomiseerde studies TARE geen toegevoegde waarde laten zien ten opzichte van de standaardbehandeling (11). Ondanks de brede toepassing van beeldvorming tijdens TARE kan het afbeelden van de microsfeerverdeling tijdens de behandelprocedure nog geoptimaliseerd worden, waarbij MRI een belangrijke rol kan vervullen.

De EMERITUS studies

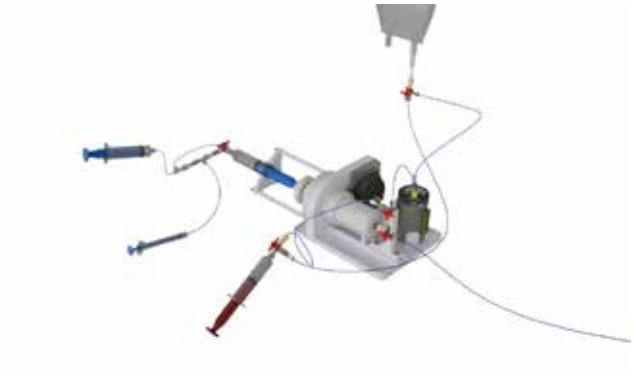
De eerste publicatie over de vertaling van MRI naar geabsorbeerde dosis om ^{166}Ho-radioembolisatie te beoordelen komt uit 2012 (12), en al snel volgde de toepassing op patiënten in 2013 (13) om de therapie te evalueren en te vergelijken met de klassieke SPECT-beeldvorming. Vanaf vorig jaar heeft de ontwikkeling van MRI-dosimetrie opnieuw een vlucht gekregen vanwege een vernieuwde toepassing, waarbij MRI- dosimetrie al tijdens de behandeling een rol krijgt in een tussentijdse evaluatie van de microsfeerverdeling (figuur 2). De eerste toepassing hiervan werd onderzocht in de vorig jaar gepubliceerde EMERITUS studie, waaruit bleek dat het veilig was om TARE uit te voeren onder een 3T MRI-scanner (14). Daarnaast liet deze studie de mogelijke meerwaarde van MRI-geleide TARE zien, maar gaf ook een kritische blik op de huidige methode en (on)nauwkeurigheid van MRI-dosimetrie. Deze inzichten hebben bijvoorbeeld geleid tot de ontwikkeling van een nieuw algoritme voor dosisberekening op basis van MR-beelden, de zogeheten voxelwise subtractiemethode (15).

Om naar een volledig MRI-geleide behandeling te gaan is het noodzakelijk om de HoMS fractioneel te kunnen toedienen. Op die manier kan naar aanleiding van de perioperatieve dosimetrie ter plekke een beslissing worden gemaakt over de toe te dienen activiteit voor een volgende MRI-scan gemaakt wordt. Om dit te kunnen verwezenlijken is door Quirem Medical een MR-conditioneel toediensysteem ontwikkeld voor MRI-geleide TARE (figuur 3). Dit systeem wordt momenteel binnen de CONTROL studie onderzocht om de veiligheid en validiteit van het systeem *in vivo* te testen. De eerste studiepatiënten zijn reeds succesvol behandeld met dit systeem. Daarnaast is de toedientijd ten opzichte van de toediening zoals die tijdens EMERITUS werd gedaan meer dan gehalveerd.

Met deze recente ontwikkelingen binnen de MRI-dosimetrie en optimalisatie van de workflow komt er ook ruimte voor de eerste studie waarin TARE daadwerkelijk op geleide van MRI uit wordt gevoerd. In de EMERITUS-2 studie, die gepland staat om in mei 2023 te starten worden intraprocedureel op basis van MRI-dosimetrie op verschillende tijdspunten beslissingen gemaakt over de toe te dienen activiteit bij patiënten met hepatocellulair carcinoom. De voornaamste doelen van de studie zijn de veiligheid van het intraprocedureel beoordelen van de dosis en het vinden van de tolereerbare dosis van het vitale leverweefsel. Hierbij wordt er een maximale gezonde leverdosis



Figuur 2. Eén van de studiepatiënten van de EMERITUS studie. De dosisverdeling na de behandeling met HoMS kan zowel met MRI (A) als met SPECT (B) goed zichtbaar worden gemaakt.



Figuur 3. Het nieuw ontwikkelde toediensysteem. In de witte afscherming bevindt zich een spuit met HoMS, welke door motoraandrijving draait om de microsferen in suspensie te houden. De blauwe spuiten worden door de nucleair geneeskundige gebruikt om door middel van druk de microsferen toe te dienen in fracties. De rode spuit wordt gebruikt om te flushen tussen de fracties door.

gehanteerd van 40, 60 of 80 Gy (op max 2/3 van het levervolume), maar geen limiet op de tumordosis. Beide worden tijdens de behandeling over de tijd gemonitord, om zo tot de optimale TARE behandeling voor de individuele patiënt te komen. Uitgangspunt van de studie is om gecontroleerd een zo hoog mogelijke tumordosis te bereiken en de gehele tumor te behandelen zonder het vitale leverweefsel in gevaar te brengen.

De toekomst voor MRI-geleide radioembolisatie

Waar de huidige studieopzet geoptimaliseerd is voor het onderzoeken van de veiligheid en mogelijk toegevoegde waarde van MRI-geleide radioembolisatie is het nog geen opzet die op grote schaal kan worden uitgevoerd. De combinatie van fluoroscopie en MRI in naastgelegen ruimtes (figuur 4) is schaars en tijdrovend. Daarom wordt er binnen het recent gestarte DELIVR project in samenwerking met verschillende bedrijven onderzoek gedaan om de volledige procedure onder MRI uit te kunnen voeren. Onderdeel hiervan zijn het ontwikkelen van MR-safe instrumentarium, en tracking software om ook de plaatsing van de katheter onder MRI-geleiding mogelijk te maken. Op dit moment wordt er hard gewerkt aan translatie naar de kliniek, met als ultieme doel het aantonen van de toegevoegde waarde voor de patiënt en het breed beschikbaar maken van deze therapie.

Bredere inzet van holmium microsferen, intratumorale behandeling

Om de HoMS breder in te zetten is er in 2018 een subsidie door NWO-TTW verstrekt voor het ontwikkelen van een behandeling voor hersentumoren door middel van een intratumorale injectie met HoMS. Deze behandeling wordt microbrachytherapie genoemd. Aanleiding voor deze subsidieaanvraag waren studies waarbij free handed injecties zijn geplaatst in verschillende typen tumoren in veterinaire patiënten. De behandeling van deze patiënten vond plaats op de afdeling Diergeneeskunde van de Universiteit Utrecht. Het ging hierbij om honden en katten met tumoren in het mondgebied (plaveiselcelcarcinoom), op de poot (melanoom, osteosarcoom), op de flank (weke delen tumor), maar ook in de hersenen (16-20).
In totaal werden ruim veertig dieren behandeld door middel van het injecteren van HoMS in de tumor. Door

Figuur 4. Het MITeC in het Radboudumc waarin de EMERITUS studies worden uitgevoerd. Een hybride OK uitgerust met de ARTIS pheno (Siemens) staat in direct contact met de OK waarin een 3T Siemens MRI staat.

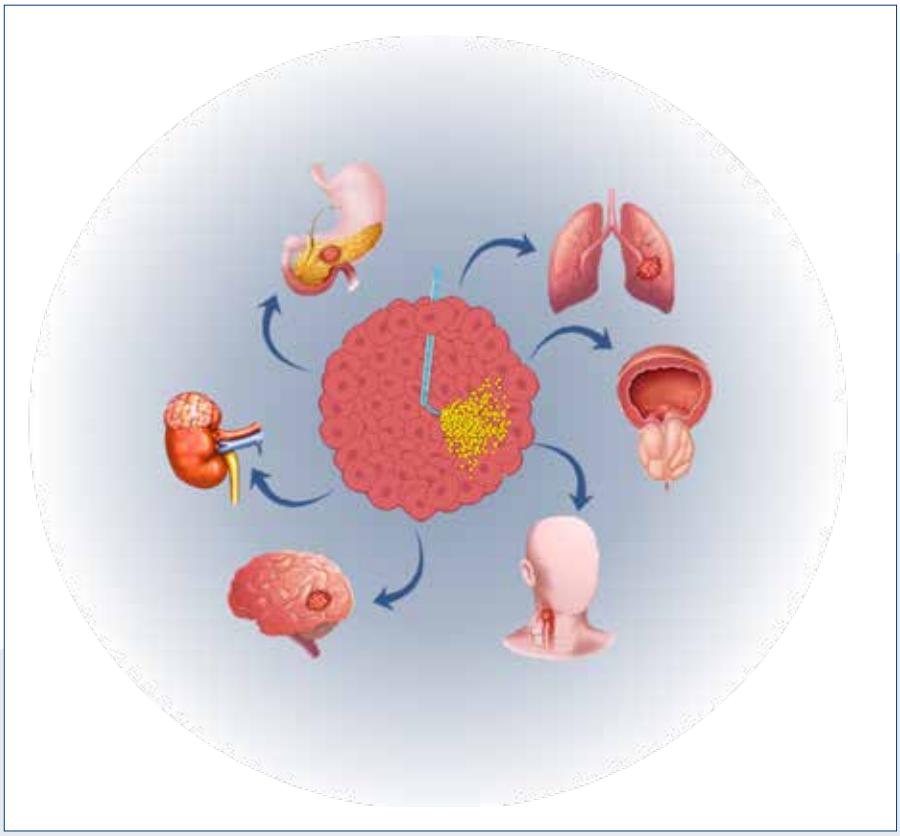
heel gericht injecties in de tumor te kunnen plaatsen bleek voor de helft van de patiënten de behandeling curatief, wat het potentieel van deze nieuwe type behandeling liet zien. Een belangrijke bevinding in deze studies was dat een goede verdeling van de microsferen in de tumor noodzakelijk is voor een complete respons van de tumor.
Beeldvorming kan gebruikt worden om de verdeling van de microsferen in de tumor nauwkeurig te observeren. Door gebruik te maken van perioperatieve beeldvorming kan tijdens de behandeling direct worden geëvalueerd of het behandelde gebied voldoende dosis zal krijgen om een therapeutisch effect te induceren. Mocht dit niet het geval zijn dan kan door het gebruik van de beeldvorming de behandeling direct worden bijgestuurd door meer activiteit toe te dienen op de plaatsen waar dat nodig is. De mogelijkheid om van twee verschillende beeldvormingsmodaliteiten gebruik te kunnen maken zorgt voor een bredere toepassing en bereikbaarheid van de behandeling in verschillende centra aangezien niet overal een MRI voorhanden is op de OK of interventieruimte.

Intratumorale behandeling van hersentumoren

Microbrachytherapie kan gezien worden als platformtechniek die toegepast kan worden op verschillende typen tumoren die met een naald te bereiken zijn (figuur 5). Hersentumoren zijn mogelijk ook goed benaderbaar voor microbrachytherapie.
Behandeling van deze tumoren met de reguliere therapieën is vaak lastig door de ligging in kwetsbaar gebied. De injectie van HoMS direct in de tumor kan daar een uitkomst in bieden door de relatief korte dracht (± 2,8 mm) van ^{166}Ho in combinatie met het relatief hoge dosis tempo (21). Deze korte dracht en hoge dosis tempo zorgen ervoor dat lokaal een hoge dosis kan worden afgegeven terwijl het omliggende weefsel gespaard wordt. Om deze behandeling gecontroleerd uit te kunnen voeren zijn er naast beeldgeleiding ook een aantal andere parameters die van belang zijn. Zo is het belangrijk om de microsferen te injecteren terwijl er minimale schade aan het gezonde weefsel wordt toegebracht. In samenwerking met de TU Delft is een injectiesysteem met een gebogen naaldtip ontwikkeld waarmee de hele tumor behandeld kan worden via één injectiekanaal, terwijl er minimale schade aan het gezonde weefsel wordt toegebracht (22). Ook het type microsferen en de injectievloeistof zijn belangrijke parameters voor het verkrijgen van een totale dosisdekking in de tumor.

Van muis naar mens

Om een stap te zetten richting de humane kliniek zijn we begonnen met toxiciteitstudies in muizen. Hierbij is gekeken naar de toxische reacties die optreden in de acute (drie dagen) tot en met de chronische fase (één jaar) na het injecteren van de nieuwe en bekende microsferen en de geoptimaliseerde injectievloeistof. Tot heden zijn er geen aanwijsbare toxische effecten gezien en kon de volgende stap in het onderzoek worden gezet.
Voor de translatie naar de humane kliniek zijn er studies opgezet in een groot proefdiermodel. Hierbij is gekozen voor een varkensmodel door de vele paralellen met het humane brein. In de eerste studie is



Figuur 5. Microbrachytherapie kan gezien worden als een platformtechniek voor tumoren in organen die met een naald te bereiken zijn. Hierbij kan gedacht worden aan hersenen, longen, pancreas, hoofd hals, prostaat en nieren.

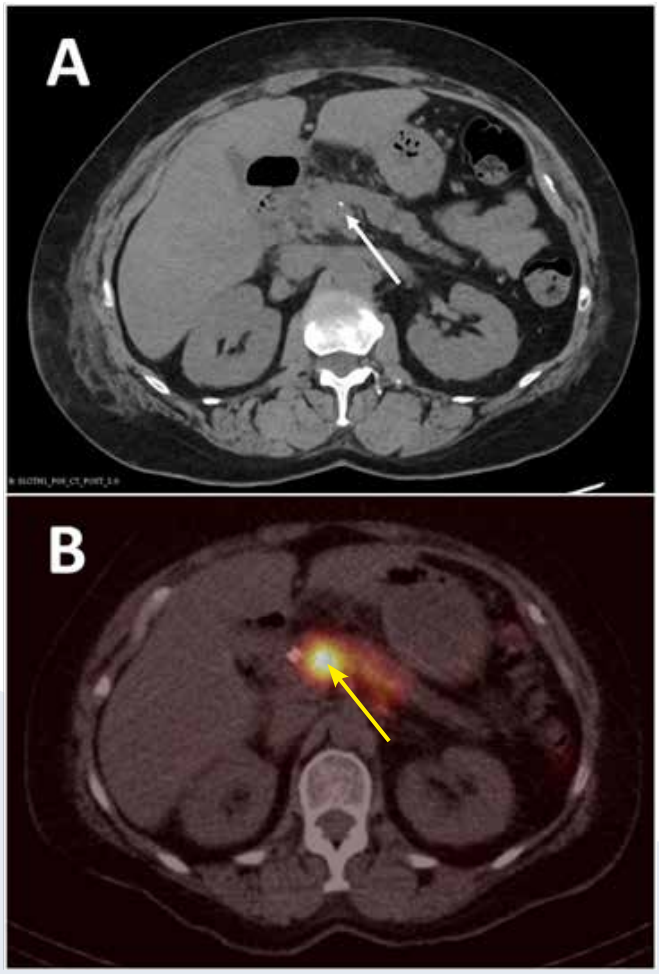
een suspensie van injectievloeistof en microsferen geïnjecteerd in gezonde varkensbreinen om de veiligheid en uitvoerbaarheid te testen. Ook hier werd geen toxiciteit aangetoond, waarna in een vervolgstudie een tumormodel in het varkensbrein is ontwikkeld. Dit tumormodel zal worden gebruikt om te testen of een MRI-geleide behandeling in de hersenen, gebruikmakende van het ontwikkelde injectiesysteem, geoptimaliseerde toedieningsvloeistof en de microsferen met hogere holmium concentratie, veilig en uitvoerbaar is. Indien de geplande studies een positief resultaat laten zien zal de stap worden gezet naar de humane kliniek. Op dit moment wordt er nagedacht over de studie-opzet van de eerste klinische trial in mensen, die naar verwachting binnen twee jaar van start zal gaan.

CT-geleide intratumorale behandeling van pancreaskanker

Naast hersentumoren is de intratumorale behandeling ook toe te passen in patiënten met een pancreas ductaal adenocarcinoom (PDAC). PDAC is met 3000 diagnoses per jaar de meest voorkomende vorm van pancreaskanker en zorgt voor 6,5% van alle kankersterfte in Nederland (24). Standaardtherapieën zoals chemotherapie (FOLFIRINOX) en chirurgie zijn zeer intensief en veroorzaken veel bijwerkingen. Patiënten met een slechte conditie of comorbiditeit komen vaak niet in aanmerking voor deze therapieën en volgen een palliatief of best-supportive-care traject.
CT-geleide intratumorale behandeling met HoMS zou een mogelijke minimaal invasieve uitkomst kunnen bieden voor patiënten met een lokaal uitgebreide PDAC of die door deze ziekte in een palliatief traject zitten. Ook hier geldt dat het relatief hoge dosis tempo en de korte dracht van de β^--straling een snelle, doeltreffende en veilige therapie zou kunnen vormen voor deze patiëntengroepen. Binnen het Radboudumc, op de afdeling medische beeldvorming, begon in maart 2020 het SLOTH-project, een overkoepelend onderzoeksproject om de klinische toepassing van HoMS voor PDAC te onderzoeken.

Preklinisch onderzoek (SLOTH *ex vivo*)

De eerste stap was de uitvoering van fundamenteel onderzoek waarbij injecties met homogene HoMS suspensies in fantomen en *ex vivo* pancreastumoren werden getest. In de preklinische experimenten is gebruik gemaakt van holmium-165, de non-radioactieve variant van holmium-166 met, behalve SPECT, dezelfde beeldvormingskarakteristieken (figuur 1). Vanuit de *ex vivo* studie konden de mogelijkheden en limieten van intratumorale injectie in PDAC in kaart worden gebracht. De beeldvorming, zowel CT en MRI zijn geoptimaliseerd, net als de manier van injecteren van HoMS, naaldkeuze, naaldplaatsing, microsfeer concentraties en injectievolumes. Dit gaf de 'proof-of-concept' die nodig was voor de volgende fase, de pilotstudie van het SLOTH-project.



Figuur 6. Postoperatieve CT (A) en SPECT (B) van een SLOTH-1 patiënt met een HoMS depositie (gele pijl) centraal in de pancreastumor.

Eerste pancreaskanker patiënten behandeld met HoMS (SLOTH-1)

Het doel van de SLOTH-1 studie was het testen van de haalbaarheid en veiligheid van intratumorale HoMS injecties in patiënten met irresectabel PDAC.Patiënten die worden gepland voor een chirurgische resectie van de tumor, worden in zeldzame situaties tijdens de operatie irresectabel verklaard vanwege onverwachte metastasen of vaatbetrokkenheid. Deze patiënten ontvingen in dat geval intratumorale HoMS injecties door middel van echogeleide naaldplaatsing in een open-chirurgische setting. Bij deze patiënten is primair gekeken naar dosimetrie m.b.v. SPECT en het monitoren van bijwerkingen (CTCAE v4.0) tijdens een follow-up van 12 weken.
Ten tijde van schrijven zijn twee van de drie patiënten op deze wijze behandeld. Er waren geen peroperatieve complicaties. Een gemiddelde tumordosis van 8,9 Gy en 71,5 Gy zijn behaald. Verspreiding van de HoMS naar lever en longen via de bloedbaan en naar de darmen via de ductus pancreaticus zijn geïdentificeerd en resulteerde in een gemiddelde orgaandosis van 0,1-0,3 Gy. De holmiumtherapie werd goed verdragen met twee procedure-gerelateerde bijwerkingen na 12 weken (pancreatitis en misselijkheid). Verder werden er 23 graad 1-2 en 5 graad 3 niet-gerelateerde bijwerkingen gezien, waarschijnlijk ten gevolge van de open-buik operatie en tumorprogressie op afstand. Op postoperatieve CT is centrale depositie van de HoMS in de tumor goed zichtbaar in vergelijking met het contrast van de SPECT, alhoewel lagere concentraties niet identificeerbaar lijken (figuur 6).

Minimaal invasieve CT-geleide HoMS injectie (SLOTH-2a)

De SLOTH-2a omvat opnieuw een haalbaarheid en veiligheidsstudie voor een nieuwe, minimaal invasief beoogde, injectiemethode middels CT-geleiding. CT-geleiding is binnen de interventieradiologie reeds een veel toegepaste techniek voor bijvoorbeeld puncties of biopten van PDAC. Voor deze interventie hoeven patiënten niet meer naar de OK en kan met behulp van de CT de naald naar de juiste locatie binnen de tumor worden geleid. Een ander groot voordeel van de CT is de mogelijkheid tot perioperatieve beeldvorming, met directe feedback van behandel nauwkeurigheid en beoogd effect (figuur 7). Tijdens de SLOTH-2a studie zullen zes patiënten met palliatief bevonden pancreascarcinoom worden geïncludeerd. Zij worden behandeld met CT-geleide percutane HoMS injecties onder algehele anesthesie, gevolgd door een ziekenhuisopname ter monitoring van eventuele bijwerkingen. Primair zal hierbij gekeken worden naar dosimetrie m.b.v. SPECT en het monitoren van bijwerkingen tijdens een follow-up van 16 weken. Als exploratieve uitkomsten wordt er gekeken naar response (RECIST 1.1), pijn-scores, en kwaliteit van leven. De studie is reeds goedgekeurd door de METC en zal in het tweede kwartaal van 2023 beginnen met includeren van patiënten.

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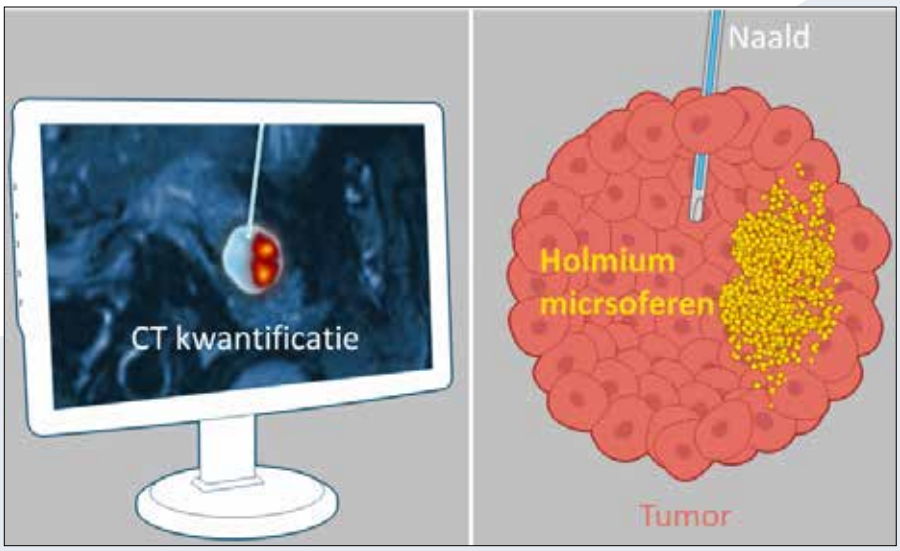
Referenties

1. Mumper R.J., Ryo U.Y., Jay M. Neutron-activated holmium-166-poly (L-lactic acid) microspheres: a potential agent for the internal radiation therapy of hepatic tumors. J Nucl Med. 1991;32:2139-43
2. Nijsen J.F., van Steenbergen M.J., Kooijman H. et al. Characterization of poly(L-lactic acid) microspheres loaded with holmium acetylacetonate. Biomaterials 2001;22:3073-81
3. Vente M.A., Nijsen J.W.F., de Roos R. et al., Neutron activation of holmium poly(L-lactic acid) microspheres for hepatic arterial radio-embolization: a validation study. Biomed Microdevices 2009;11:763-72
4. Nijsen J.F.W., Seppenwoolde J.H.,Havenith T. et al., Liver



Figuur 7. Illustratieve weergave van het gebruik van CT voor naald-geleiding en holmium kwantificatie voor intra-tumorale HoMS injecties in een tumor.

tumors: MR imaging of radioactive holmium microspheres--phantom and rabbit study. Radiology, 2004;231:491-9
5. Seppenwoolde J.H., Bartels L.W.,van der Weide R. et al. Fully MR-guided hepatic artery catheterization for selective drug delivery: a feasibility study in pigs. J Magn Reson Imaging 2006;23:123-9
6. Nijsen F., van het Schip F., Zonnenberg B. De historie van een Nederlandse ontwikkeling voor de behandeling van levertumoren - Van radioactieve holmiumbol tot QuiremSpheres. Tijdschr Nucl Geneesk. 2018;4:2100-5
7. Smits M.L., Nijssen J.F.W., van den Bosch M.A.A.J. et al. Holmium-166 radioembolisation in patients with unresectable, chemorefractory liver metastases (HEPAR trial): a phase 1, dose-escalation study. Lancet Oncol. 2012;13:1025-34
8. Hermann A.L., Dieudonné A., Ronot M. et al. Relationship of Tumor Radiation-absorbed Dose to Survival and Response in Hepatocellular Carcinoma Treated with Transarterial Radioembolization with (90)Y in the SARAH Study. Radiology. 2020;296:673-84
9. Garin E., Tselikas L, Guiu B et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. Lancet Gastroenterol Hepatol. 2021;6:17-29
10. Roosen J., Klaassen N.J.M., Westlund Gotby L.E.L. et al. To 1000 Gy and back again: a systematic review on dose-response evaluation in selective internal radiation therapy for primary and secondary liver cancer. Eur J Nucl Med Mol Imaging. 2021;48:3776-90
11. . van Hazel G.A., Heinemann V., Sharma N.K.et al. SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) Versus mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients With Metastatic Colorectal Cancer. J Clin Oncol. 2016;34:1723-31
12. Seevinck P.R., van de Maat G.H., de Wit T.C. et al. Magnetic resonance imaging-based radiation-absorbed dose estimation of 166Ho microspheres in liver radioembolization. Int J Radiat Oncol Biol Phys. 2012;83:e437-44
13. van de Maat G.H., Seevinck P.R., Elschot M et al. MRI-based biodistribution assessment of holmium-166 poly(L-lactic acid) microspheres after radioembolisation. Eur Radiol. 2013;23: 827-35
14. Roosen J., Westlund Gotby L.E.L., Arntz M.J. et al. Intraprocedural MRI-based dosimetry during transarterial radioembolization of liver tumours with holmium-166 microspheres (EMERITUS-1): a phase I trial towards adaptive, image-controlled treatment delivery. Eur J Nucl Med Mol Imaging. 2022;49:4705-15
15. Roosen J., van Wijk M.W.M., Westlund Gotby L.E.L. et al. Improving MRI-based dosimetry for holmium-166 transarterial radioembolization using a nonrigid image registration for voxelwise DeltaR2 * calculation. Med Phys. 2023;50:935-46
16. Morsink N.C., Klaassen N.J.M., Meij B.P. et al. Case Report: Radioactive Holmium-166 Microspheres for the Intratumoral Treatment of a Canine Pituitary Tumor. Front Vet Sci. 2021;8:748247
17. van Nimwegen S.A., Bakker R.C., Kirpensteijn J. et al. Intratumoral injection of radioactive holmium ((166) Ho) microspheres for treatment of oral squamous cell carcinoma in cats. Vet Comp Oncol. 2018;16:114-24
18. Van de Bovenkamp C.G., Meij B. Stassen Q.E.M. et al. [Administration of radioactive holmium-166 microsphere in domestic animals with inoperable tumors]. Tijdschr Diergeneeskd. 2009;1:532-3
19. Bult W., Vente M.A., Vandermeulen E. et al. Microbrachytherapy using holmium-166 acetylacetonate microspheres: a pilot study in a spontaneous cancer animal model. Brachytherapy. 2013;12:171-7
20. Morsink N.C., Nijsen J.F.W., Grinwis G.C.M. et al. Intratumoral injection of holmium-166 microspheres as neoadjuvant therapy of soft tissue sarcomas in dogs. Front Vet Science. 2022;9:1015248
21. Klaassen N.J.M., Arntz M., Gil Arranja A. et al. The various therapeutic applications of the medical isotope holmium-166: a narrative review. EJNMMI Radiopharm Chem. 2019;4:19
22. de Vries M., Klaassen N.J.M., Morsink N.C. et al. Dedicated holmium microsphere administration device for MRI-guided interstitial brain microbrachytherapy. Med Eng Phys. 2021;96:13-21
23. Arranja A., Hennink W.E., Chassagne C. et al., Preparation and characterization of inorganic radioactive holmium-166 microspheres for internal radionuclide therapy. Mat Sci Eng C Mater Biol Appl. 2020;106:110244
24. Integraal Kankercentrum Nederland, IKNL. Verkregen middels iknl.nl/Kankersoorten, op 21 maart 2023

De-escalating Thyroid Cancer Treatment: Indications for Thyroid Remnant Ablation and Adjuvant I-131 Therapy after Surgery for Differentiated Thyroid Cancer

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Abstract

Patients with differentiated thyroid cancer have an excellent prognosis. After the diagnosis of differentiated thyroid cancer most patients undergo a total thyroidectomy followed by radioiodine therapy. In recent years it has become evident that not all patients need extensive surgical treatment and post-operative radioiodine therapy. This article describes the current indications for radioiodine therapy after thyroidectomy for differentiated thyroid cancer.

Introduction

In the Netherlands, approximately 900 patients are diagnosed with thyroid cancer yearly, the most common form being differentiated thyroid cancer (DTC), which makes up around 85% of new cases (1). Patients with DTC generally have a favorable prognosis, with most cases being in TNM stage 1 or 2, with a 10-year disease-specific survival rate of over 90%. The standard treatment for DTC involves surgical removal of the thyroid gland, usually followed by post-operative radioiodine therapy, which is a non-invasive treatment.

Radioiodine therapy involves the oral administration of an activity of radioactive iodine (^{131}I), which is then eventually absorbed by thyroid cells through the sodium-iodide transporter. ^{131}I treatment is a targeted therapy that is effective in treating thyroid cancer and metastatic disease, although it can have side effects such as fatigue and nausea, and may also increase the risk of damage to the salivary glands and secondary neoplasms over the long term. The goal of ^{131}I treatment, as stated in the Martinique criteria, is to postoperatively destroy remaining normal thyroid tissue, to facilitate follow-up and to diagnose and treat microscopic disease and therefore increase recurrence-free survival (2). There are three distinct indications for ^{131}I treatment: i) remnant ablation, to destroy post-thyroidectomy residual thyroid tissue to facilitate thyroglobulin (Tg) follow-up and improve future radioiodine imaging, ii) adjuvant treatment, to destroy subclinical microscopic tumor deposits, for which the risk is high enough to justify ^{131}I therapy to improve disease-specific and overall survival, and iii) treatment of known disease, to destroy post-operatively remaining DTC foci or to treat persistent or recurrent DTC during follow-up.

Despite its use for over eight decades, there are still many controversies surrounding the use of ^{131}I, including which patients would benefit from the treatment, what activity to use and which method of thyroid stimulating hormone (TSH) stimulation to employ. Here we describe the current available evidence for de-escalating DTC treatment and the recommendations of different international guidelines.

Thyroid nodule diagnosis

The Thyroid Imaging Reporting and Data System (TI-RADS) classification is increasingly being used to make the decision for further pathological investigation of thyroid nodules. TI-RADS is an ultrasound-based risk stratification system for thyroid nodules that was published in 2009, although a number of other varieties also exists (3-6). The implementation of TI-RADS has led to fewer fine needle biopsies being performed, resulting in a smaller, and more selected group of patients undergoing surgery. With the implementation of TI-RADS a reduction of unnecessary biopsies of malignant nodules of 20-47% has been described (7). This means that less, but more selected patients undergo surgery, and thus radioiodine treatment.

The guidelines on incidental findings have also changed in recent years (8). There is a more restrictive work-up for incidental thyroid nodules detected on CT or MRI, which also leads to less patients receiving surgery and I-131.

Current guidelines

In 2015, the American Thyroid Association (ATA) provided guidance on the use of ^{131}I for DTC in its guidelines on the management of thyroid nodules and DTC (9). The

European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (NMMI) did not endorse these guidelines (10). In 2019, a joint, multilateral statement was developed during the Martinique meeting (2).

This statement provides updated guidance on the indications for ^{131}I in treating DTC. An overview of the guidelines published since 2015 are summarized in table 1. The guidelines differ in the specific recommendations on indications and prescribed activity.

However, they do all emphasize the importance of individualizing treatment based on the patient's specific clinical characteristics.

Randomized controlled trials

In recent years, four large randomized

Table 1. Guidelines on ^{131}I therapy after thyroidectomy.

	ATA (2015)(9)	Dutch Thyroid Cancer Guideline (2015) (11)	ESMO (2019) (12){Filetti, 2019 #656}	Martinique consensus (2019) (2)	ETA (2022) (13)	EANM/ SNNMI (2022) (14)
Microcarcinoma	Not routinely recommended	N/A	No ^{131}I	Based on individual basis; shared-decision making	No ^{131}I	N/A
Low risk	Not routinely recommended	1.1 GBq	Intensive scientific debate (no ^{131}I vs. 1.1 GBq ^{131}I), should be based on the presence of individual risk modifiers.	Based on individual basis; shared-decision making	Intensive scientific debate (no ^{131}I vs. 1.1 GBq ^{131}I), should be based on the presence of individual risk modifiers.	Indicated, risk-based approach
Intermediate risk	Should be considered	Patient-tailored	Patient-tailored	Based on individual basis; shared-decision making	Patient-tailored	Indicated, risk-based approach
High risk	Routinely recommended	Patient-tailored	All patients, >3700 MBq	Based on individual basis; shared-decision making	All patients, >3700 MBq	Indicated, risk-based approach
rhTSH vs. THW	rhTSH is an acceptable alternative in low-risk or intermediate-risk without nodal involvement; and may be considered an alternative in intermediate-risk with nodal involvement	Low-risk: THW or rhTSH Other: THW	THW or rhTSH	N/A	rhTSH should be the preferred method of preparation	rhTSH or THW; THW for metastatic disease

ATA = American Thyroid Association; ESMO = European Society for Medical Oncology; ETA = European Thyroid Association; EANM = European Association of Nuclear Medicine; Society of Nuclear Medicine and Molecular Imaging; N/A = Not Available; GBq = Gigabecquerel; rhTSH = Recombinant Thyroid-Stimulating Hormone; THW = Thyroid Hormone Withdrawal.

controlled trials have been conducted on the use of ^{131}I for DTC in the setting of thyroid remnant ablation: ESTIMABL (15,16), ESTIMABL2 (17), Hi-LO (18,19) and IoN (20), with a total of 2464 included patients. An overview of the trials is shown in table 2.

The primary focus of the ESTIMABL1 and HiLo trials was to determine whether 1.1 GBq ^{131}I therapy was non-inferior to 3.7 GBq for remnant ablation in low-risk and intermediate risk patients, and whether recombinant TSH (rhTSH) was non-inferior to thyroid hormone withdrawal (THW), in a 1:1:1:1 study design. The results of both trials showed that 1.1 GBq and rhTSH were as effective as 3.7 GBq and THW for remnant ablation in low-risk and intermediate-risk patients. The ESTIMABL2 and IoN trials built upon this conclusion and investigated whether no ^{131}I versus 1.1 GBq ^{131}I was non-inferior in low-risk patients. The ESTIMABL2 trial concluded that no ^{131}I was as effective as 1.1 GBq ^{131}I in low-risk patients. The results of the IoN trial have not yet been published.

Which patients are candidates for ^{131}I treatment?

Generally, guidelines agree that the decision to administer ^{131}I for DTC should be based on the patients' risk of recurrence following surgery and not risk of cancer related mortality. This is different from most other malignancies where treatment is primarily based on the TNM classification of malignant tumors (23). The 2015 ATA guidelines provided a risk stratification system to categorize patients into three groups based on their likelihood of structural disease recurrence: low-risk, intermediate-risk and high-risk, which is illustrated in figure 1 (9). Patients with intrathyroidal DTC and less than 5 lymph node micrometastases (<0.2 cm) are considered low-risk. Patients with aggressive histology, minor thyroidal extension, vascular invasion or more than 5 involved lymph nodes (0.2-3.0 cm) are categorized as intermediate-risk. Patients with gross extrathyroidal extension, incomplete tumor resection, distant metastases or lymph nodes larger than 3 cm are considered high-risk. The patient group with >10 mm DTC without metastases is currently the subject of debate. However, the 2019 joint statement does add that optimal patient selection requires consideration and evaluation of multiple factors beyond postoperative disease status and risk stratification (2). These include post-operative risk assessment, impact on outcomes of interest, side effect profile, patient values and preferences, improved initial staging, facilitate sensitive follow-up, availability and quality of ultrasound, radioiodine imaging, thyroglobulin (Tg) assays and an experienced thyroid surgeon, the presence of anti-Tg antibodies and the preferences of the local disease management team. While some may debate the specific details of the risk assessment criteria mentioned earlier, the fundamental principle remains unchanged: if a patient has multiple

Table 2. Randomized controlled trials on radioiodine therapy for differentiated thyroid cancer.

Study	Trial	Number of patients	Aim	Patient group	Dose administered	Method of TSH stimulation	Conclusion
Schlumberger et al. (2012) (short-term) (15) Schlumberger et al. (2018) (long-term) (16)	ESTIMABL1	726	Remnant ablation	Low risk patients	1.1 and 3.7 GBq	rhTSH and THW	1.1 GBq + rhTSH was as effective as 3.7 GBq + THW
Mallick et al. (2012) (short-term) (21) Dehbi et al. (2019) (long-term) (22)	HiLo trial	438	Remnant ablation	Low- and intermediate risk patients	1.1 and 3.7 GBq	rhTSH and THW	1.1 GBq + rhTSH was as effective as 3.7 GBq + THW
Leboulleux et al. (2022) (17)	ESTIMABL2	730	Remnant ablation	Low-risk patients	No I-131 and 1.1 GBq I-131	rhTSH	No I-131 was as effective as 1.1 GBq I-131
Mallick et al. (2012) (study protocol) (20)	IoN trial	570	Remnant ablation	Low-risk patients	No I-131 and 1.1 GBq I-131	Unknown	Not published yet

GBq = Gigabecquerel; DFS = Disease-Free Survival; TSH = Thyroid-Stimulating Hormone; rhTSH = Recombinant Thyroid-Stimulating Hormone; THW = Thyroid Hormone Withdrawal.

and more severe characteristics that increase the risk of cancer recurrence or thyroid cancer-related death, the indication for post-operative ^{131}I treatment is more strongly recommended.

Patients with unifocal papillary microcarcinoma

For patients with unifocal papillary microcarcinoma (i.e. <10 mm), ^{131}I should be avoided as it leads to overtreatment of disease without any beneficial effect on recurrence and mortality rates, as shown by several retrospective studies (24-27).

Patients with low-risk of structural disease recurrence

Most thyroid cancer patients present with low-risk disease. The benefit of the administration of ^{131}I to low-risk patients after total thyroidectomy remains controversial. Adverse events associated with ^{131}I therapy, such as salivary gland destruction, bone marrow dysfunction and cardiovascular effects, support the trend towards less aggressive treatment for low-risk patients. However, in low-risk patients I-131 can be useful for ablation of thyroid tissue and/or residual disease, allowing for interpretation of serum Tg levels. The ESTIMABL2 trial demonstrated that no radioiodine treatment was as effective as 1.1 GBq ^{131}I in low-risk patients in a three-year follow-up study (17). When further considering that modern high-resolution ultrasound and high sensitivity Tg measurement have superseded diagnostic radioiodine scanning during follow-up, there really does not appear to be any good medical reason left for performing radioiodine therapy for thyroid remnant ablation in this setting. The current trend toward de-escalation of low-risk patients is also present in the surgical management of thyroid cancer. Specifically, hemithyroidectomy is being chosen more frequently over total thyroidectomy in low-risk patients. It is important to note that this approach limits the use of ^{131}I, as not all thyroid tissue is removed.

Patients with intermediate-risk of structural disease recurrence

For patients with intermediate-risk of structural disease recurrence, it is important to consider their individual factors when deciding whether to administer ^{131}I. For patients with a higher-intermediate risk of structural disease recurrence, ^{131}I therapy is shown to be beneficial. However, the available retrospective studies report a wide variety of results regarding the efficacy of ^{131}I. A study that involved 532 patients found that individuals who are over 45 years of age, have tumors that are smaller than 4 cm in size, without extrathyroidal extension any nodal metastases can undergo surgery without ^{131}I safely, advocating for de-escalation of radioiodine therapy (28). On the other hand, a recent retrospective study (n=1487) investigated the correlation between ^{131}I therapy and serum Tg levels (29). The study concluded that ^{131}I is effective in reducing the recurrence in intermediate-risk patients with unstimulated Tg ≤1 ng/mL, or stimulated Tg ≤10 ng/mL. Recurrence was present in 6/1349 (0.4%) of patients in the I-131-group, and 5/138 (3.6%) in the non-^{131}I therapy group. The patients with recurrence (n=11) all had recurrence in the cervical lymph nodes. Another large study (n=21870) also concluded that adjuvant ^{131}I therapy was associated with an improved overall survival in intermediate-risk patients (30). In the prospective HiLo trial, intermediate-risk patients were included, however no clear subgroup analysis was performed on these patients (18).

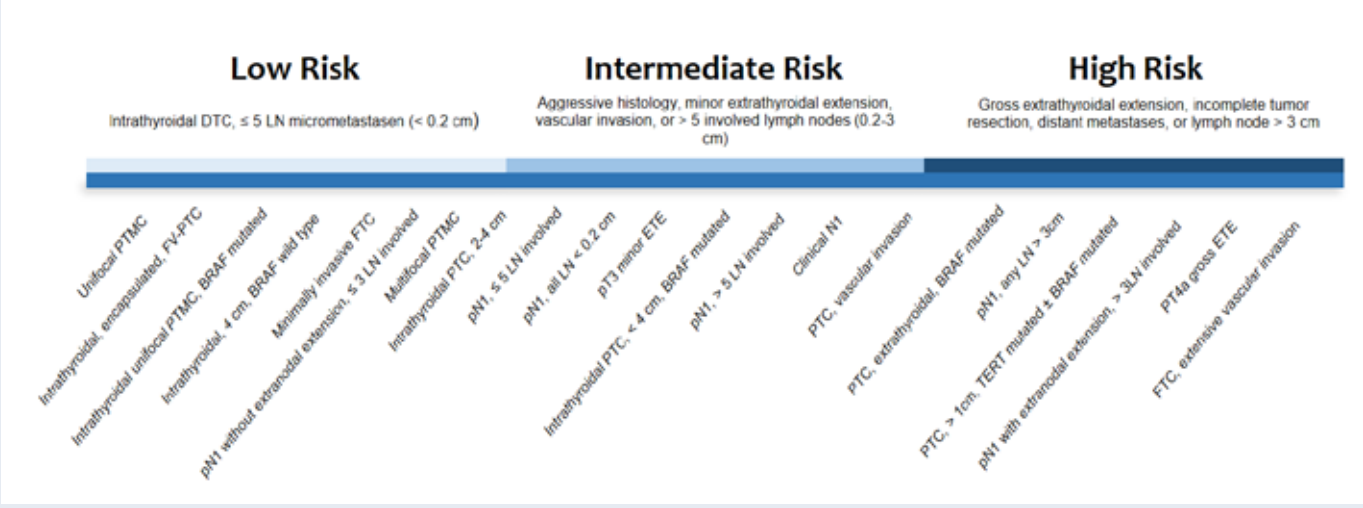

Figure 1. Risk of Structural Disease Recurrence as formulated by the 2015 ATA guidelines.

Certainly, in the intermediate risk patients, the inhomogeneity of evidence does not warrant a hard "yes" or "no" to I-131 treatment. In these patients, the process of shared decision can be of great value.

Patients with high-risk of structural disease recurrence and distant metastases

For high-risk patients and/or patients with distant metastases the use of I-131 is recommended by all guidelines.

Which activities of ^{131}I should be used?

In the context of remnant ablation, patients who are categorized as low-risk can be given an activity of 1.1 GBq after the injection of rhTSH. However, considering that there appears to be no good justification left for performing ^{131}I therapy with thyroid remnant ablation as the only goal, the question is whether there is any role left for this activity level.

On the other hand, for patients with intermediate and high-risk disease in the adjuvant setting, the recommended activity is 5.5 GBq, which should be administered after withdrawal of thyroid hormone, depending on the precise stage of the patient as well as any relevant co-morbidities. For treatment of known disease, an activity of 7.4 GBq or more is typically administered, with the exact amount depending among others on the patient's weight and age; for very high activities well exceeding 7.4 GBq dosimetry is advisable.

What method of TSH-stimulation should be used?

Stimulation with rhTSH is a safe option associated with reduced side effects of ^{131}I and better quality of life. The current recommendations are summarized in table 1. The efficacy of rhTSH for thyroid remnant ablation appears to be equivalent to withdrawal in both the HiLo and ESTIMABL studies. There is lack of prospective studies examining the use of rhTSH in adjuvant treatment, and clinicians should carefully consider its use in this context. Legal regulations permit the use of rhTSH in Europe for initial treatment in patients without distant metastases, but its off-label use in patients with metastatic disease should be evaluated on a case-by-case basis on conjunction with any morbidity the patient may have precluding safe thyroid hormone withdrawal.

Despite the limited evidence, clinicians and patients should have an open conversation to make a shared decision about the best TSH stimulation modality based on their preferences and experiences. Further prospective studies are necessary to evaluate the effectiveness of rhTSH in both the adjuvant setting and the treatment of known disease.

Conclusion

There have been several recent developments in de-escalating thyroid cancer management, with the aim to reduce patient burden without compromising long-term outcomes. In this manuscript we have presented a short overview of latest literature and recent guidelines concerning the use of ^{131}I. The treatment of DTC used to be quite extensive with a total thyroidectomy followed by a high activity of ^{131}I for almost all patients. However, most patients with DTC have an excellent prognosis and this extensive treatment is not necessary for all patients with low and intermediate risk DTC.

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References

1. Integraal Kankercentrum Nederland. Incidentie schildklierkanker 2022 [Available from: https://iknl.nl/kankersoorten/schildklierkanker/registratie/incidentie
2. Tuttle RM, Ahuja S, Avram AM, Bernet VJ, Bourguet P, Daniels GH, et al. Controversies, consensus, and collaboration in the use of 131I therapy in differentiated thyroid cancer: a joint statement from the American Thyroid Association, the European Association of Nuclear Medicine, the Society of Nuclear Medicine and Molecular Imaging, and the European Thyroid Association. Thyroid. 2019;29:461-70
3. Horvath E, Majlis S, Rossi R, Franco C, Niedmann JP, Castro A, et al. An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical management. J Clin Endocrinol Metab. 2009;94:1748-51
4. Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L. European Thyroid Association guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: the EU-TIRADS. Eur Thyroid J. 2017;6:225-37
5. Shin JH, Baek JH, Chung J, Ha EJ, Kim J-h, Lee YH, et al. Ultrasonography diagnosis and imaging-based management of thyroid nodules: revised Korean Society of Thyroid Radiology consensus statement and recommendations. Korean J Radiol. 2016;17:370-95
6. Tessler FN, Middleton WD, Grant EG, Hoang JK, Berland LL, Teefey SA, et al. ACR thyroid imaging, reporting and data system (TI-RADS): white paper of the ACR TI-RADS committee. J Am Coll Radiol. 2017;14:587-95
7. Hoang JK, Middleton WD, Tessler FN. Update on ACR TI-RADS: successes, challenges, and future directions, from the AJR special series on radiology reporting and data systems. Am J Roentgenol. 2021;216:570-8
8. Hoang JK, Langer JE, Middleton WD, Wu CC, Hammers LW,

Cronan JJ, et al. Managing incidental thyroid nodules detected on imaging: white paper of the ACR Incidental Thyroid Findings Committee. J Am Coll Radiol. 2015;12:143-50
9. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26:1-133
10. Verburg FA, Aktolun C, Chiti A, Frangos S, Giovanella L, Hoffmann M, et al. Why the European Association of Nuclear Medicine has declined to endorse the 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. Eur J Nucl Med Mol Imaging. 2016;43:1001-5
11. Federatie Medisch Specialisten. Schildkliercarcinoom: Richtlijnendatabase; 2015 [Available from: https://richtlijnendatabase.nl/richtlijn/schildkliercarcinoom/algemeen.html
12. Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30:1856-83
13. Pacini F, Fuhrer D, Elisei R, Handkiewicz-Junak D, Leboulleux S, Luster M, et al. 2022 ETA Consensus Statement: What are the indications for post-surgical radioiodine therapy in differentiated thyroid cancer? Eur Thyroid J. 2022;11:e210046
14. Avram AM, Giovanella L, Greenspan B, Lawson SA, Luster M, Van Nostrand D, et al. SNMMI Procedure Standard/EANM Practice Guideline for Nuclear Medicine Evaluation and Therapy of Differentiated Thyroid Cancer: Abbreviated Version. J Nuclear Med. 2022;63:15N-35N
15. Schlumberger M, Catargi B, Borget I, Deandreis D, Zerdoud S, Bridji B, et al. Strategies of radioiodine ablation in patients with low-risk thyroid cancer. New Engl J Med. 2012;366:1663-73
16. Schlumberger M, Leboulleux S, Catargi B, Deandreis D, Zerdoud S, Bardet S, et al. Outcome after ablation in patients with low-risk thyroid cancer (ESTIMABL1): 5-year follow-up results of a randomised, phase 3, equivalence trial. Lancet Diabetes Endocrinol. 2018;6:618-26
17. Leboulleux S, Bournaud C, Chougnet CN, Zerdoud S, Al Ghuzlan A, Catargi B, et al. Thyroidectomy without radioiodine in patients with low-risk thyroid cancer. New Engl J Med. 2022;386:923-32
18. Mallick U, Harmer C, Yap B, Wadsley J, Clarke S, Moss L, et al. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. New Engl J Med. 2012;366:1674-85
19. Dehbi HM, Mallick U, Wadsley J, Newbold K, Harmer C, Hackshaw A. Recurrence after low-dose radioiodine ablation and recombinant human thyroid-stimulating hormone for differentiated thyroid cancer (HiLo): long-term results of an open-label, non-inferiority randomised controlled trial. Lancet Diabetes Endocrinol. 2019;7:44-51
20. . Mallick U, Harmer C, Hackshaw A, Moss L. Iodine or Not (IoN) for low-risk differentiated thyroid cancer: the next UK National Cancer Research Network randomised trial following HiLo. Clin Oncol. 2012;24:159-61
21. Mallick U, Harmer C, Yap B, Wadsley J, Clarke S, Moss L, et al. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. New Engl J Med. 2012;366:1674-85
22. Dehbi H-M, Mallick U, Wadsley J, Newbold K, Harmer C, Hackshaw A. Recurrence after low-dose radioiodine ablation and recombinant human thyroid-stimulating hormone for differentiated thyroid cancer (HiLo): long-term results of an open-label, non-inferiority randomised controlled trial. Lancet Diabetes Endocrinol. 2019;7:44-51
23. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67:93-9
24. Kim HJ, Kim NK, Choi JH, Kim SW, Jin SM, Suh S, et al. Radioactive iodine ablation does not prevent recurrences in patients with papillary thyroid microcarcinoma. Clin Endocrinol. 2013;78:614-20
25. Al-Qahtani KH, Al Asiri M, Tunio MA, Aljohani NJ, Bayoumi Y, Fatani H, et al. Adjuvant Radioactive iodine 131 ablation in papillary microcarcinoma of thyroid: Saudi Arabian experience. J Otolaryngol Head Neck Surg. 2015;44:1-9
26. Lin HW, Bhattacharyya N. Survival impact of treatment options for papillary microcarcinoma of the thyroid. Laryngoscope. 2009;119:1983-7
27. Kwon H, Jeon MJ, Kim WG, Park S, Kim M, Kim TY, et al. Lack of efficacy of radioiodine remnant ablation for papillary thyroid microcarcinoma: verification using inverse probability of treatment weighting. Ann Surg Oncol. 2017;24:2596-602

28. Nixon IJ, Patel SG, Palmer FL, DiLorenzo MM, Tuttle RM, Shaha A, et al. Selective use of radioactive iodine in intermediate-risk papillary thyroid cancer. Arch Otolaryngol Head Neck Surg. 2012;138:1141-6
29. Tian T, Qi Z, Huang S, Wang H, Huang R. Radioactive iodine therapy decreases the recurrence of intermediate-risk PTC with low thyroglobulin levels. J Clin Endocrinol Metab. 2023:dgad045. Online ahead of print
30. Ruel E, Thomas S, Dinan M, Perkins JM, Roman SA, Sosa JA. Adjuvant radioactive iodine therapy is associated with improved survival for patients with intermediate-risk papillary thyroid cancer. J Clin Endocrinol Metab. 2015;100(4):1529-36

Understanding the radiobiology of therapeutic medical radionuclides (UNRANU)

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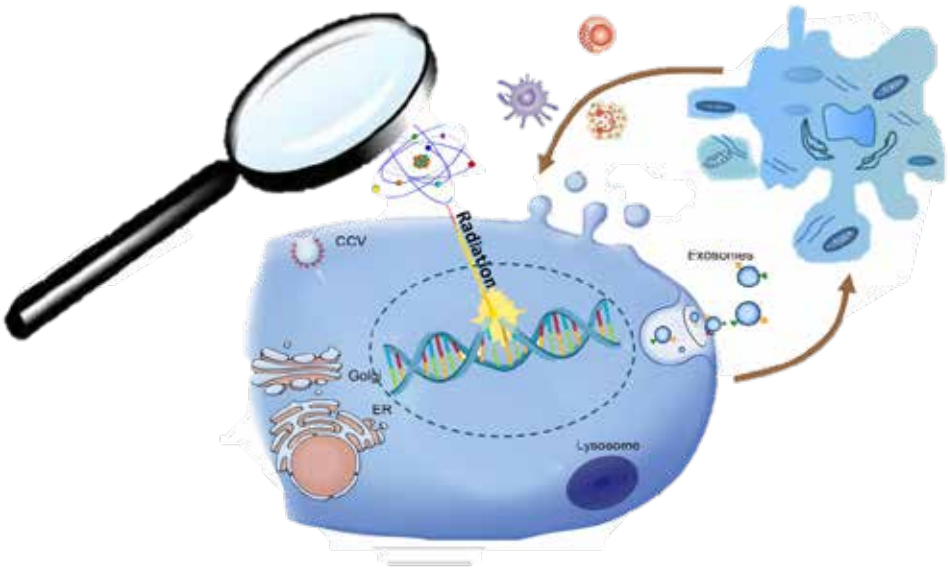

Introduction

December 14th, 2022, the UNRANU research proposal was awarded by the Dutch Research Council (NWO) within the *Perspectief* program. This *Perspectief* funding instrument supports projects that contribute to the creation of economic opportunities within the societal challenges and key technologies of the Mission-driven Innovation Policy of NWO. Within UNRANU, we aim to improve the radiobiological knowledge and accessibility of therapeutic isotopes for radionuclide therapy (RNT). Ultimately, this would improve the availability of RNT, contribute to more rationalized treatment selection and/or treatment planning, with the final goal to help more cancer patients with a better disease outcome.

The consortium

UNRANU is a Dutch consortium consisting of the initiators Frank Nijsen, Sandra Heskamp (Radboudumc), Antonia Denkova (TU Delft) and Julie Nonnekens (Erasmus MC) and various industry partners, peripheral hospitals, patient associations and knowledge institutes. Eight researchers (post-docs and PhD students) will be allocated across Radboudumc, TU Delft and Erasmus MC. The other participating institutions are Oncode, RIVM, Meander Medisch Centrum, Nederlandse Leverpatiënten Vereniging, Nederlandse Vereniging van Nucleaire Geneeskunde, Prostaatkanker Stichting, Reinier de Graaf Ziekenhuis, Stichting Darmkanker, Wetenschapsknooppunt. The involved companies are AlfaRIM, HUB Organoids, MILabs, NRG, PALLAS, Quirem Medical (Terumo), RTM, Siemens Healthineers, TerThera, URENCO, Von Gahlen and VSL. A multidisciplinary advisory board consisting of Prof. Dr. F. Verburg, Dr. J. Nagarajah, Prof. Dr. J. Bussink, Dr. R. de Blois, Prof. Dr. A. Glaudemans, and Prof. Dr. J. Zeevaart has been established, which ensures up-to-date knowledge, critical thinking and analysis of the project and its results. The project will run for 5 years starting in Q4 2023.

Project background and scientific challenge

Cancer is a major challenge in healthcare and leading cause of death worldwide, accounting for nearly 10 million deaths in 2020. Despite numerous developments, most patients with metastasized disease cannot be cured. Successful clinical trials such as NETTER-1 and VISION have shown that RNT can significantly improve survival of cancer patients. NETTER-1 showed that [^{177}Lu]Lu-DOTATATE (Luthatera, Novartis) significantly improves overall survival of patients with somatostatin receptor (SSTR) positive neuroendocrine tumors, while VISION demonstrated that [^{177}Lu]Lu-PSMA-617 (Pluvicto, Novartis) improves outcome of castrate-resistant metastatic prostate cancer patients (1,2) These studies led to the FDA approval of Luthatera and Pluvicto for the afore mentioned patient populations. In addition to systemic applications, RNT has been successfully applied locally, for example through transarterial radioembolization (TARE) with

radioactive labelled microspheres with yttrium-90 or holmium-166 (3,4). Despite these initial successes, most patients cannot be cured with the current treatment regimen and the application of RNT in clinical practice is still limited to a few cancer types and small cohorts of patients, thereby not fully exploiting its potential. This outcome can be explained by the fact that the choice of radionuclides and RNT schedule are currently suboptimal, due to limited fundamental knowledge of the biological effects of different radionuclides, resulting in inferior therapeutic efficacy. Furthermore, for many patients RNT is not fully accessible yet, and therefore it is only applied in selected patient populations.

In the UNRANU program we have defined three main objectives:

1) To determine the radiobiological and immunological effects of therapeutic radionuclides with different physical properties in vitro and in vivo.

2) To improve the availability of selected radionuclides by developing new or improving existing production routes.

3) To transfer this knowledge to clinicians, society, patients, industry, and policy makers.

For objective 1, we will tighten the knowledge gap on the biological responses of tumors when treated with different radionuclides. Current scientific developments in RNT are typically related to research on new targeting agents to achieve high tumor uptake with little accumulation in non-target tissues. However, seeing that results are still far from optimal, it is essential to implement additional research strategies. High tumor uptake of the targeting agent is important, but it does not guarantee tumor elimination. Tumor cell killing efficiency also depends on other factors including the radionuclides' distribution within the tumor, the type of radiation, and tissue range and dose rate of the particles. In this respect, dosimetry is key to accurately determine the tumor-absorbed dose and relate this to the biological effects of the therapeutic radionuclides and specific tumor characteristics (e.g. size, perfusion, immunological status). In patients, (pre-treatment) dosimetry can also play a key role in optimal selection and planning of RNT for individual patients. However, in order to apply this correctly, more knowledge on the dose-biological effect relationship is essential, and this will therefore be studied in detail in UNRANU.

For objective 2 and 3, we aim to improve the accessibility of RNT. Currently, RNT applications are mostly limited to academic hospitals to a selected group of patients with a specific oncological indication. This is a drawback compared to more general treatment modalities such as external beam radiation therapy (EBRT) or chemotherapy. There are several reasons for the limited accessibility. First, many clinicians and patients are not fully aware of the potential of RNT, which challenges rapid developments and clinical implementation. Second, not all therapeutic radionuclides can be regularly supplied at sufficient amounts or quality. In UNRANU we aim to improve all aspects involved in making RNT accessible to larger cohorts of cancer patients, from target production to its application in the clinic (figure 1).

Work packages

UNRANU is divided in 5 Work Packages (WP), which will focus on a selection of 6 different clinically relevant radionuclides: lutetium-177 (^{177}Lu), terbium-161 (^{161}Tb), holmium-166 (^{166}Ho), yttrium-90 (^{90}Y), actinium-225 (^{225}Ac) and lead-212 (^{212}Pb). These radionuclides have been selected as representative for a panel of radionuclides with varying characteristics such as half-life, dose rate, energy disposition. The first 4 radionuclides are beta-emitters and the last 2 radionuclides are alpha-emitters (see table 1 for

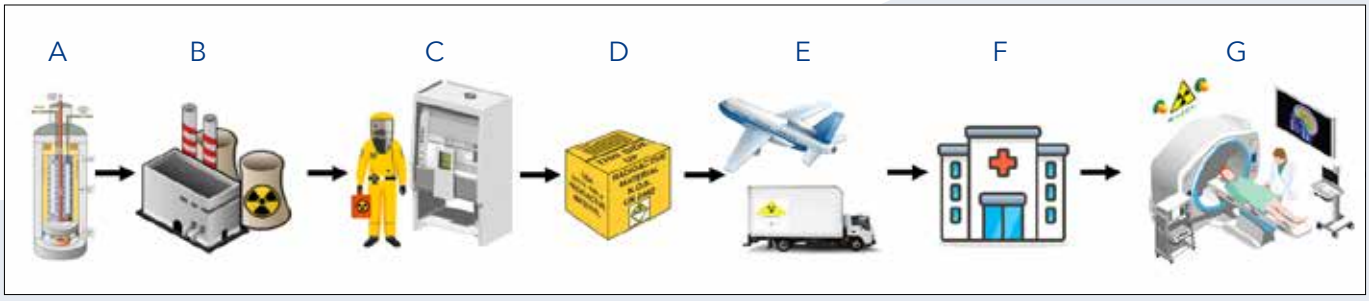

Figure 1. Nuclear industry value chain. Examples of companies/institutes that are partners in this proposal: A) enriching target material (URENCO), B) neutron activation to produce medical isotopes (NRG, Pallas, RTM, AlfaRIM, TerThera), C) Handling & production: Shielding, production laboratory (Von Gahlen, Fieldlab NRG, Quirem Medical), D) Packaging, E) Transport, F) Hospitals (Radboudumc, Erasmus MC), G) Imaging apparatus (MILabs, VSL, Siemens).

characteristics). ^{177}Lu and ^{161}Tb have comparable, but not the same physical characteristics, i.e., ^{161}Tb also emits Auger electrons. ^{177}Lu is frequency used in clinical practice, while ^{161}Tb application is under development, but it could potentially serve as replacement of ^{177}Lu when this radionuclide would become scarce. ^{177}Lu and ^{161}Tb have a relative long half-life of approximately 1 week, while ^{166}Ho and ^{90}Y have a much shorter half-life of a few days. In addition, ^{166}Ho and ^{90}Y have different physical characteristics, including a longer range. Both ^{166}Ho and ^{90}Y are being used in clinical practice, but it is unknown whether they can be exchanged, since they have different dose-rate. Besides the use of beta-emitters, alpha-emitters are used in the clinic, of which ^{225}Ac has shown great results. ^{225}Ac has a long half-life of 10 days and decays via several daughter radionuclides emitting four alpha particles in total. ^{212}Pb is an alpha-emitter with a half-life of 2 days, emitting one alpha particle.

In WP1, we will improve the availability and specific activity of therapeutic radionuclides, by developing new or improving existing production routes. In WP2-4, we will determine the radiobiological effects of radionuclides with different physical properties on tumor cell survival in monolayer settings (WP2) and 3D tumor structures (WP3), and unravel the radiobiological and immunological effects in animal models (WP4). In figure 2 an overview of the models used is given, illustrating their characteristics in relation to the complexity, relevance and multiplexing capacity. Finally, we will transfer the obtained knowledge to society and commercial and care industry in WP5 Program management, communication and utilization.

Expected outcome

At the end of the project, we expect to have a more detailed fundamental understanding of the biological effects of therapeutic radionuclides,

Table 1. Overview of the different radionuclides used in UNRANU and their physical properties.

Radionuclide	Main type of therapeutic dec	Half-life	Energy (E_{max})	Penetration in soft tissue
Lutetium-177	β- particles	6.7 days	0.497 MeV	Maximum 1.7 mm
Terbium-161	β- particles Auger electrons	6.9 days	0.593 MeV	<2 mm (β-) <1 µm (Auger)
Holmium-166	β- particles	27 hours	1.855 MeV	Maximum 8.7 mm
Yttrium-90	β- particles	64 hours	2.280 MeV	Maximum 1.1 cm
Actinium-225	Four Alpha particles	10.0 days	5.935 MeV	<10 µm
Lead-212	One Alpha particle	10.6 hours	6.207 MeV	<10 µm

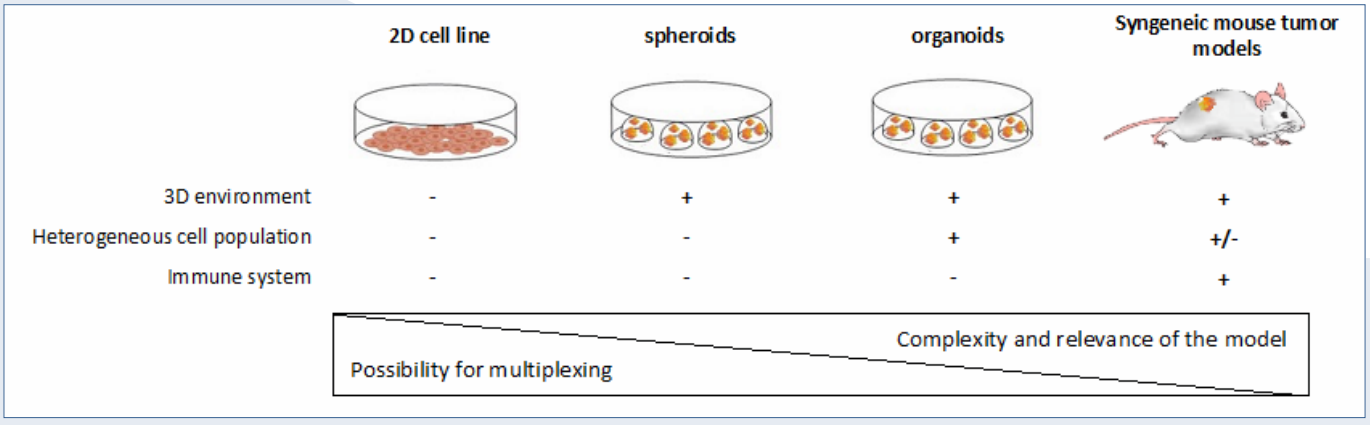

Figure 2. Overview of the models used in WP 2, 3 and 4 illustrating their characteristics in relation to the complexity, relevance and multiplexing capacity.

which will result in better informed decisions which radionuclides are most effective to treat a certain type of tumors. Furthermore, we will have contributed to a more reliable and sustainable supply of therapeutic radionuclides leading to better accessibility and therefore eventually the project is expected to have high societal impact not only in the Netherlands but worldwide.

Disclosure
J.F.W. Nijsen is co-founder of Quirem Medical which has been acquired by Terumo Europe NV in July 2020. Nijsen has a scientific advisory role and is entitled to certain milestone payments from Terumo which are related to Quirem's financial, operational and regulatory performance in the future. Furthermore, Nijsen is inventor on the patents related to radioactive microspheres that are assigned to University Medical Center Utrecht Holding BV, Quirem Medical or BASF Corp. The activities of J.F.W. Nijsen within Quirem Medical are approved and supported by the Board of Directors of the Radboudumc.

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References

1. Derlin, T., [Neuroendocrine tumor therapy (NETTER-1) trial: (177)Lu-DOTA-TATE for neuroendocrine tumors]. Radiologe. 2017. 57:343-5
2. Hofman, M.S., et al., [(177)Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol. 2018.;19:825-33
3. Kennedy A, Brown DB, Feilchenfeldt J et al. Safety of selective internal radiation therapy (SIRT) with yttrium-90 microspheres combined with systemic anticancer agents: expert consensus. J Gastrointest Oncol. 2017;8:1079-99
4. Prince JF, van den Bosch MAAJ, Nijssen JFW et al., Efficacy of radioembolization with holmium-166 microspheres in salvage patients with liver metastases: a phase 2 study. J Nucl Med. 2018;59:582-8

2021 guideline on radiation exposure after radionuclide therapies: implementation in clinical practice in three different hospitals in The Netherlands. Aiming for more uniformity

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Abstract

Introduction

National guidelines on radionuclide therapies have long been based on a 2005 report (*Aanbevelingen 'Het werken met therapeutische doses radionucliden'*), mainly based on iodine-131 ([^{131}I]NaI) therapies. As new therapies were introduced, mainly lutetium-177 ([^{177}Lu]Lu) based - with less radiation burden for the environment – and with the implementation of the 2013 basic safety standards directive in European legislation, an update was necessary. In the meantime, dose rate levels for discharge after [^{177}Lu]Lu were used in the way they were used for [^{131}I]NaI (20 µSv/h at 1m). Guidelines were revised and implemented by the FMS in 2021, in hopes to reach more uniformity between hospitals as well. We investigated this pursued uniformity by the new guideline and provide insights into its implementation.

Methods

Three different hospitals participated: an academic center (UMC Utrecht), a peripheral center (St. Antonius Nieuwegein) and a cancer center (AVL Amsterdam). Each hospital provided their institutional guidelines for comparison. An online meeting was held to seek more information on differences and similarities and to discuss the rationales behind the institutional considerations made. Data collection was focused on the two most used radionuclide therapies today: [^{177}Lu]Lu-PSMA and [^{131}I]NaI.

Results

Some general practical uniformities could easily be adjusted (e.g. the general measure to flush the toilet twice was unanimously considered not useful, and the restrictions on dish washing and intimacy after [^{131}I]NaI therapy could be adapted). A radiation alert pop-up or symbol in the hospital patient file was considered very practical as were travel information letters. For [^{177}Lu]Lu-PSMA, all centers treated patients in a 6 hours admission scheme, and discharged patients without measuring dose rate levels, having patients adhere to instructions and restrictions for three days (i.e. 60 years and older). Most differences were encountered for [^{131}I]NaI therapies, especially dose rate level at discharge (20 µSv/h versus 40 µSv/h at 1 meter versus no measurement at all), and the duration of admission, restrictions after discharge and durations of those restrictions.

Conclusion

The implementation of the FMS guideline in each hospital has been different, based on different assumptions and considerations. For [^{177}Lu]Lu-PSMA the implementation was more uniform than for [^{131}I]NaI. Radionuclide therapies are increasing and becoming more patient tailored. For patients a more uniform approach could be helpful, to prevent confusion between patient information leaflets from different institutions and to prevent 'healthcare shopping' between hospitals. We intend to initiate this discussion and pursue uniformity on a national level in the future.

Introduction

Radionuclide therapies are increasing, both in frequency and in variety of different therapies, encompassing different isotopes. As patients contain radioactivity after treatment, it is important to have them adhere to restrictions for a certain period after each therapy cycle to reduce radiation burden to their environment. National guidelines on radionuclide therapies have long been based on a 2005 report (1), which was mainly based on and applied to iodine-131 ([^{131}I]NaI) therapies. Based on this report, dose rate levels after therapy dictated whether a patient had to be admitted and when to be discharged, 20 µSv/h at 1 meter being the dose rate limit. Based on the actual dose rate level measured at discharge, the duration of restrictions was determined. Meanwhile, new therapies were introduced, mainly lutetium-177 ([^{177}Lu]Lu) based. [^{177}Lu]Lu has less radiation burden due to less gamma abundancy with lower gamma energy (113 and 208 keV versus 364 keV), and a shorter half-life (6.6 versus 8.0 days) (figure 1). As no guidelines on the use of [^{177}Lu]Lu existed, most hospitals implemented the same dose rate limits and contact restrictions. In the meantime, changes in European legislation (implementation of the 2013 basic safety standards directive - Council Directive 2013/59/Euratom) and thus national legislation were implemented: the Nuclear Energy Act (Kernenergiewet; KEW) was adjusted, *and the 'Besluit basisveiligheidsnormen stralingsbescherming (Bbs)'* (2) replaced the *'Besluit stralingsbescherming'*. Therefore an update of the 2005 guideline was necessary. The report was thoroughly revised and an extensive literature review was performed by a committee existing of representatives of the Nederlandse Vereniging voor Nucleaire Geneeskunde (NVNG), Nederlandse Vereniging voor Klinische Fysica (NVKF) and Nederlandse Vereniging voor Stralingshygiëne (NVS) in collaboration with the Autoriteit Nucleaire Veiligheid en Stralingsbescherming (ANVS). This was a huge effort and took several years (3). The new guideline focusses on the moment of discharge from hospital and whether instructions and restrictions - for the patient to adhere to after discharge - are necessary. Of note, radiation exposure to health care professionals and to the environment (e.g. waste water) are not included. The guideline was implemented by the Federatie Medisch Specialisten (FMS) in 2021 (4), in hopes to reach more uniformity between hospitals as well. ANVS formal acceptance is still awaited. We investigated this pursued uniformity by the FMS guideline and provide insights into the implementation of this new guideline in three different centers.

Methods

A nuclear medicine physician and a radiation protection expert/medical physics expert of the three different hospitals participated: an academic hospital (UMC Utrecht - UMCU), a peripheral hospital (St. Antonius Nieuwegein) and a cancer center (Antoni van Leeuwenhoek - AVL). Institutional implementation of the guideline was shared for comparison. An online meeting (13th March 2023) was held to seek more information on differences and similarities and to discuss the rationales behind the institutional considerations made. Data collection on the implementation of the new guideline was focused on [^{177}Lu]Lu-PSMA and [^{131}I]NaI, as [^{177}Lu]Lu-PSMA is one of the most recently implemented therapies that was not included in the original 2005 guideline, and as [^{131}I]NaI is one of the oldest but still most often used therapies in nuclear medicine departments. As the guideline comments on radiation exposure after therapy, *per therapy* - which can be 5 or 6 cycles of [^{177}Lu]Lu-PSMA, but only 1 capsule for [^{131}I]NaI therapy - radiation exposure was compared *per cycle*.

General comments on the FMS guideline

Some important comments on the FMS guideline need to be made:
In 2020, the concept version of the FMS guideline (5) was shared among clinical physicists and radiation experts and some nuclear medicine physicians to comment on. In this concept version, some considerations were explained and discussed, that cannot be found in the final version of the guideline.

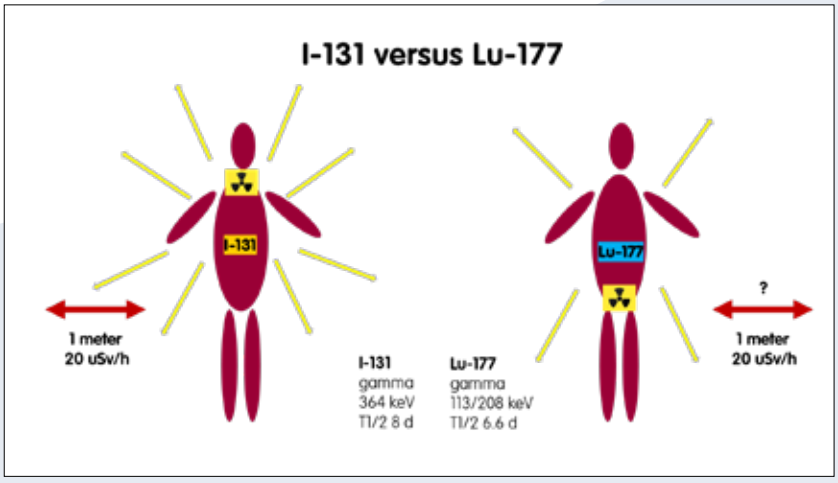

Figure 1. Radiation protection measures

Some important changes were made between the concept version and the final version: e.g. in the concept version, a dose rate limit for discharge after [^{131}I]NaI therapies for malignant thyroid disease was set at 40 µSv/h at 1 meter (20 µSv/h for benign [^{131}I]NaI), which was discarded in the final guideline. Also the duration of hospital admission for [^{177}Lu]Lu-PSMA therapy was changed from 8 to 6 hours and the duration of restrictions was changed from one week to three days.
The FMS guideline is based on dose constraints that apply to persons in direct relation to the patient ('care givers') and to the general population. Based on differences in radiation sensitivity, dose constraints are set on: 1 mSv *per therapy* for children, 3 mSv *per therapy* for adults < 60 years, and 15 mSv *per therapy* for adults > 60 years; for the general population, a dose constraint of 0.3 mSv per 'event' is advised.
The FMS guideline comments on radiation exposure *per therapy*, whereas radiation exposure *per cycle* is more convenient. This is important given the fact that especially for prostate cancer, the number of cycles can differ a lot; some patients starting [^{177}Lu]Lu-PSMA therapy may already have had 6 cycles of radium-223 ([^{223}Ra]$RaCl_2$, Xofigo,®Bayer), and still receive up to 6 cycles [^{177}Lu]Lu-PSMA, whereas others will only receive 1 or 2 cycles of [^{177}Lu]Lu-PSMA due to toxicity or non-response.
Restrictions as described in the FMS guideline for [^{177}Lu]Lu-PSMA and [^{131}I]NaI are quite similar, mainly differing in duration of adherence (table 1).
The FMS guideline refers to a *'Rekentool'* to calculate radiation exposure for the environment after each cycle. Different activities administered and different clinical scenarios can be adjusted. Of note, all *'Blootstellingsscenarios'* were used as were described in the RIVM report by Kloosterman (6).

The FMS guideline refers to a *'Rekentool'* of the 'Nederlandse Commissie voor Stralingsdosimetrie (NCS)' to determine whether a radiation travel information letter is necessary to supply when a patient is traveling after radionuclide therapy (7). Importantly, this tool does not account for biological decay (e.g. excretion). As most of administered radioactivity is excreted within the first 24 hours, this tool largely overestimates the remaining radioactivity in the patient. With care and knowledge of the individual patient, the tool can be used for this purpose.

Instructions and restrictions (table 1) were discussed. The general advise to flush the toilet twice after radionuclide therapies was unanimously considered not useful, as the little amount of radioactive urine that could potentially remain in the toilet would not cause any radiation burden, also considering the duration of toilet stay.

Missing items in the FMS guideline

Restrictions not mentioned in the FMS guideline included limitations on sharing of dishes (commonly recommended after [^{131}I]NaI) and intimacy (asked frequently by patients, but no guidance is provided and thus restrictions are often applied). All centers agreed that the stay in a hotel/ hostel during the restricted period after each cycle was not allowed.
Patients that are treated with [^{177}Lu]Lu-PSMA are, in contrast to most patients receiving [^{131}I]NaI therapy, frequently more heavily metastasized, have no other therapy options, and have a worse prognosis. Due to the local prostate cancer or previous prostate directed therapies, patients often have problems with micturition like hematuria, incontinence and/ or nephrostomies. As most radioactivity is excreted in the urine (after 4 hours, 50% of administered activity is excreted mainly in urine (8), urine incontinence is a contra-indication for therapy if not specifically taken care of by the patient. In AVL, at the start of [^{177}Lu]Lu-therapies, a bladder catheter (catheter-a-demure, CAD) was inserted to prevent contamination. However, as this resulted in even more problems (leakage, pain, possible urine retention after removal) this was discarded. When already in situ, a CAD or NSK (bladder catheter or nephrostomy catheter) is no contra-indication, if the patient is self-sufficient (UMCU/AVL). St. Antonius hospital did not encounter such cases yet.

[^{177}Lu]Lu-PSMA

[^{177}Lu]Lu-PSMA was clinically implemented in UMCU already in 2016, in AVL in 2021; in St. Antonius hospital so far only study patients were treated. All three centers eventually treated patients in a 6 hours admission (9), and discharged patients without measuring dose rate levels (table 2).
In the AVL (conform FMS guideline), the duration of contact instructions and restrictions was 3 days for all care givers including children, as dose constraints were not exceeded. UMCU used a longer duration of restrictions (UMCU institutional guidelines): 3 days for care givers > 60 years old, versus 7 days for children and adults < 60 years old, as these restrictions were already shorter than used before. Restriction on using public transport and flying was 3 days (AVL) and a radiation information letter was supplied until 3 weeks after therapy; in UMCU these restrictions were 7 days, and a travel information letter was provided on request.
For patients treated with [^{177}Lu]Lu-PSMA, frequent visits to other health care professionals can be necessary; the need to report radionuclide therapy was 3 days in the UMCU (conform FMS guideline) whereas in the AVL a longer duration of 14 days was implemented, because of the possible radioactive waste material.

Table 1. Instructions and restrictions according to the FMS guideline.

	[^{177}Lu]Lu PSMA	[^{131}I]NaI benign	[^{131}I]NaI malignant
The patient needs to take care of good toilet hygiene:	**3d**	**3d**	**7d**
-If possible, use a separate toilet.			
-When using the toilet: in a sedentary position.			
-Flush the toilet twice.			
-Wash hands after using the toilet.			
-In case of contamination (urine, other body fluids): clean them yourself.			
-House mates and guests need to take care of toilet hygiene:			
-Wash hands after using the toilet.			
-Use disposable gloves when cleaning the toilet.			
At least the following should be mentioned, to adhere to after therapy administration (distance):	**3d**	**7d**	**7d**
The patient needs to stay away from house mates:			
-Sleeping together is not allowed			
-Keeping a distance (social activities)			
The patient needs to prevent situations in which keeping a distance of more than 1 meter for more than 1 hour is not be possible:			
-Visiting sport competitions/ restaurants/ theaters etc.			
-Using public transport/ taxi etc.			
-Office hours/ work/ school etc.			
Instruct the patient about a travel information letter	***rekentool**	***rekentool**	***rekentool**
Instruct the patient to report the radionuclide therapy when visiting a health care professional.	**3d**	**3d**	**7d**
In case of death after therapy, restrictions may be required; the radiation protection expert should be contacted if death occurs within a certain period of time after therapy.	**13d**	**45d**	**58d**
Before therapy, have the patient empty his/her bladder; after therapy, have the patient void at the toilet of the Nuclear Medicine department before leaving the hospital.	**NA**	**Y**	**NA**

d: days; FMS: Federatie Medisch Specialisten; NA not applicable; Y: yes. * The FMS guideline refers to a *'Rekentool'* of the 'Nederlandse Commissie voor Stralingsdosimetrie (NCS)' to determine whether a radiation travel information letter is necessary when a patient is traveling after radionuclide therapy (7).

[^{131}I]NaI for malignant thyroid diseases (1.1-7.4 GBq)

All centers performed [^{131}I]NaI therapy for thyroid cancer (table 2). The FMS guideline discarded the need to measure dose rate levels, whereas the concept guideline set the dose rate level for discharge at 40 µSv/h. In the final guideline, a 24 hours admission is mentioned.

In St. Antonius hospital, radiation exposure per category (child, adult care giver and general population) was calculated based on a general scenario, using the FMS '*rekentool*'. Based on these assumptions, two options were possible: a 48 hours hospital admission (standard), or, if predefined criteria were met, a 24 hours admission plus a 24 hours isolation period at home was possible. These criteria were:
1. No children < 18 years at home;
2. Sleeping separately at, at least 3 meter is possible; 3. A separate toilet is

Table 2. Instructions and restrictions according to three different hospitals.

	[^{177}Lu]Lu-PSMA	[^{131}I]NaI benign	[^{131}I]NaI malignant
Administered dose (GBq)			
AVL	*7.4*	*NA*	*1.1-7.4*
St. Antonius Ziekenhuis	*6.8 (study)*	*≤ 2.0*	*1.1-7.4*
UMCU	*7.4*	*≤ 1.0*	*1.1-7.4*
Hospital admission	**6h**	**NN**	**24h**
AVL	*6h*	*dose rate dependent*	*≥ 24h, dose rate dependent*
St. Antonius Ziekenhuis	*6h*	*- <0.4 GBq: no - ≥0.4 GBq: 48h or 48h isolation at home**	*- 48h or - 24h + 24h isolation at home**
UMCU	*6h*	*dose rate dependent (max 3d)*	*≥ 24h, dose rate dependent (max 5d)*
Dose rate level at discharge (µSv/h at 1m)	**NA**	**NA**	**NA**
AVL	*NA*	*<20*	*<40*
St. Antonius Ziekenhuis	*NA*	*N/A*	*N/A*
UMCU	*NA*	*<20*	*<20*
Instruct the patient to adhere to good toilet hygiene	**3d**	**3d**	**7d**
AVL	*3d*	*3d*	*7d*
St. Antonius Ziekenhuis	*3d*	*- ≤1.0: 7d - >1.0: 14d*	*7d*
UMCU	*3d (>60y) 7d (<60y)*	*dose rate dependent (20/ 10/ 5)*	*dose rate dependent (20/ 10/ 5)*
Instruct the patients to keep a distance	**3d**	**7d**	**7d**
AVL	*3d*	*7d*	*7d*
St. Antonius Ziekenhuis	*3d*	*- ≤1.0 GBq: 7d - >1.0 GBq: 14d*	*7d*
UMCU	*- 3d (>60y) - 7d (<60y)*	*dose rate dependent (20/10/5 µSv/h)*	*dose rate dependent (20/10/5 µSv/h)*
Instruct the patient to ask for a travel information letter	**rekentool#**	**rekentool#**	**rekentool#**
AVL	*3 weeks*	*3 weeks*	*3 weeks*
St. Antonius Ziekenhuis	*NS*	*3 months*	*3 months*
UMCU	*NS*	*on patient request*	*on patient request*
Instruct the patient to report the radionuclide therapy when visiting a health care professional	**3d**	**3d**	**7d**
AVL	*14d*	*14d*	*14d*
St. Antonius Ziekenhuis	*NS*	*7d*	*7d*
UMCU	*3d*	*7d*	*7d*
Before therapy, have the patient empty his/her bladder; after therapy, have the patient void at the toilet of the Nuclear Medicine department before leaving the hospital	**NA**	**Y**	**NA**
AVL	*NA*	*Y*	*NA*
St. Antonius Ziekenhuis	*NA*	*Y*	*NA*
UMCU	*NA*	*Y*	*NA*

In bold the duration as described in FMS guideline. AVL: Antoni van Leeuwenhoek; d: days; FMS: Federatie Medisch Specialisten; NA not applicable; NN not necessarily; Y: yes; UMCU: UMC Utrecht. *Only if predefined criteria are met. # The FMS guideline refers to a '*Rekentool*' of the 'Nederlandse Commissie voor Stralingsdosimetrie (NCS)' to determine whether a radiation travel information letter is necessary when a patient is traveling after radionuclide therapy (7).

available, which has to be cleaned by the patient him/herself; 4. The patient is totally self-dependent; 5. The patient has to be able to go to and from the hospital by himself (not using public transport); 6. The patient and his/her environment are totally aware of all risks of not sticking to the instructions and restrictions; 7. The patient agrees with the shorter admission duration. In all other cases, a 48 hours admission is necessary. Restrictions were 7 days after therapy for all patients, including restrictions to children nearby (more strict).
In AVL, radiation exposure per category (child, adult caretaker, and general population) was calculated based on a general scenario, using the FMS '*rekentool*'; some slight differences were seen. AVL used an admission of at least 24 hours, and a dose rate level for discharge of 40 µSv/h, as was used in the concept guideline. Based on some of the patients treated in AVL, an admission of only 24 hours is not considered enough to guarantee dose constraints for the environment. Some patients had a high iodine uptake and/or had several cycles of treatment (NB the standard calculations account for just one cycle); using a dose rate level of 40 µSv/h in a worst-case scenario was still considered safe. In specific cases, less strict limits could be used. Restrictions were 7 days for all patients, including children nearby.

In UMCU, radiation exposure per category (child, adult care giver < 60 years old, adult care giver > 60 years old and general population) was calculated based on a general scenario, using the FMS '*rekentool*'. Exposures per category were calculated for three different dose rates at discharge: 20, 10 and 5 µSv/h, based on which the duration of instructions and restrictions was adjusted. Of note, dose rate levels were measured on a daily base, and discharge was possible when dose rates decreased to below 20 µSv/h at 1 meter (according to the 2005 guideline).
AVL used the instructions and restrictions as mentioned in the FMS guideline (table 1). UMCU used previously developed institutional instructions and restrictions. St. Antonius hospital used the contact instructions and restrictions as mentioned in the FMS guideline, specifically adding a restriction on intimacy. St. Antonius hospital in addition implemented a complete list with items considered relevant during the duration of restrictions (like attending a library or cinema).
The restriction on using public transport and flying was 7 days (all centers). The need for the previous iodine treatment to be reported by the patient when visiting a healthcare professional differed slightly (table 2).

[^{131}I]NaI for benign thyroid diseases (≤ 2 GBq)

St. Antonius hospital and UMCU use [^{131}I]NaI for the treatment of benign thyroid diseases, using maximum doses of 2 GBq. In AVL no treatments for benign thyroid diseases were performed since 2018; the guideline was implemented anyway. The FMS guideline discarded the need to measure dose rate levels, whereas the concept guideline set the dose rate level for discharge at 20 µSv/h.
In St. Antonius hospital, a flow chart was designed, based on administered dose (< 400 MBq/ 400-1000 MBq / > 1000 MBq); a dose < 400 MBq was given on an outpatient base plus 7 days restrictions. For the higher doses, the previously mentioned criteria were used to determine whether strict isolation at home was possible for a 48 hours duration; if not possible, admission for 48 hours was necessary. This was followed by a period of contact restriction of 7 days (400-1000 MBq), or 14 days (> 1000 MBq).
In UMCU, radiation exposure per category (child, adult care giver < 60 years old, adult care giver > 60 years old and general population) was calculated based on a general scenario, using the FMS '*rekentool*'. Exposure per category was calculated for three different dose rates at discharge: 20, 10 and 5 µSv/h, based on which the duration of instructions and restrictions was adjusted. Of note, dose rate levels were measured on a daily base, and discharge was possible when dose rates decreased to below 20 µSv/h at 1 meter (according to the 2005 guideline and according to the concept FMS guideline).
In AVL, although no therapies for benign thyroid diseases are performed since 2018, radiation exposure per category (child, adult care giver, and general population) was calculated based on a general scenario, using the FMS '*rekentool*'. Dose rate levels were measured on a daily base, and discharge was possible when dose rates decreased to below 20 µSv/h at 1 meter (according to the 2005 guideline and according to the concept FMS guideline).

Discussion

The implementation of the FMS guideline in each hospital was different, based on different assumptions, prior experiences, considerations and choices. As [^{177}Lu]Lu-based therapies were not included in the original 2005 report, hospitals that implemented this therapy developed their own guidelines. Uniform use of dose rate limits for discharge of 20 µSv/h at 1 meter made implementation in the clinic relatively straightforward, even though this was more strict than absolutely necessary for [^{177}Lu]Lu due to less gamma radiation. This also fitted with the ALARA-principle to try to keep exposure as low as reasonably achievable. As most patients prefer to sleep in their own bed at home, the 6 hours admission period is very practical and allows room for more therapies per week per hospital (10). Differences in implementation of the new guideline between hospitals for [^{177}Lu]Lu-PSMA therapies were small.

Since the incidence of prostate cancer and indications for therapy are still increasing, the implementation of [^{177}Lu]Lu-PSMA therapy in different hospitals will be growing. The FMS guideline will help to standardize hospital protocols.
For [^{131}I]NaI therapies, the FMS guideline is less strict when compared to the former dose rate level for discharge (20 µSv/h at 1 meter). The results of the standardized scenarios in the FMS '*rekentool*' showed that a less strict regime did not lead to exposures of care givers or the general population that exceeded the applicable dose constraints. In the past, discussions could be encountered when patients > 60 years old could not be discharged because of measured dose rate levels of e.g. 22 µSv/h at 1 meter even though they lived alone or with a housemate of > 60 years old, not causing any radiation protection problem. The FMS guideline allows for elderly patients to be discharged with dose rate levels over 20 µSv/h at 1 meter and aims at a new balance in risk based assessment of discharge and outpatient treatment. Concerning the duration of hospital admission, differences between hospitals were seen for [^{131}I]NaI therapies, all based on clear considerations; radiation burden to the environment can be decreased by increasing duration of hospital admission. However, on a national base, this could be more expensive and most patients prefer their own bed. Of note, the '*ANVS handelingsperspectief bij overlijden*' (11) was implemented only after the implementation of the FMS guideline and gives more specific guidance on the topic of death after radionuclide therapies; considerations on a per case base can be made.
The dose rate level of 20 µSv/h at 1 meter for discharge used to be a standard condition in hospital radiation licenses. Violation of this, or any, condition is an offence. Hospitals try their best to adhere to license conditions and inspection is regularly performed. Thus, although guidelines have changed, not all hospitals feel free to change their protocols. It should be noted that the ANVS is aware of this problem. However, at the moment it seems that the new FMS guideline perhaps increased differences between hospitals. This can be confusing for patients and patient associations. Ideally, a new guideline would lead to more uniformity also in patient information leaflets and thus prevent healthcare shopping between centers in the Netherlands.

Conclusion

The implementation of the new FMS guideline in each hospital has been very different, based on different assumptions, prior experiences, considerations and choices. For [^{177}Lu]Lu-PSMA the implementation was more uniform than for [^{131}I]NaI. Radionuclide therapies are increasing and becoming more patient tailored. For patients, a more uniform approach could be helpful, to prevent confusion between patient information leaflets from different institutions and to prevent 'healthcare shopping' between hospitals. We intend to initiate this discussion and pursue uniformity on a national level in the future.

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References

1. Aanbevelingen voor Het werken met therapeutische doses radionucliden, 2004 Min VROM, Min SZW, NVNG, VROM 5049 / 02-05
2. Besluit basisveiligheidsnormen stralingsbescherming. nr. IENM/ BSK-2017/135624; Staatsblad nr. 404, 2017
3. Veltman NC, Rijnsdorp S, Rook DW, Van der Goot T, Dickerscheid DBM et al. Het werken met therapeutische dosis radionucliden – potentie;e blootstelling voor derden: a game changer. Richtlijnbespreking, Tijdsch Nucl Geneesk. 2021;3:2718-23
4. Werken met therapeutische doses radionucliden. FMS richtlijn. https://richtlijnendatabase.nl/richtlijn/therapeutische_doses_radionucliden.html
5. Werken met therapeutische doses radionucliden Conceptrichtlijn ten behoeve van commentaarfase 6 november 2020 NVNG NVKF NVS ANVS
6. Kloosterman A et al.: Nucleair-geneeskundige therapieën: potentiële blootstelling voor derden. Dosisberekeningen als basisinformatie voor de herziening van maatregelen en leefregels. RIVM-briefrapport 2020-0113A
7. https://radiationdosimetry.org/files/documents/0000048/315-indicatienoodzaakvliegbriefdiverseisotopen.xlsx
8. Kurth J, Krause BJ, Schwarzenböck SM, Stegger L, Schafers M et al. : External radiation exposure, excretion, and effective half-life in 177Lu-PSMA-targeted therapies. EJNMMI Research 2018;8:32
9. Van Golen LW, Rulof A, Van Kalmthout LWM, Lam MGEH, Leijen CATM et al. Dose rate Lu177psma Dose rate levels in patients undergoing [177Lu]Lu-PSMA-617 therapy. Tijdsch Nucl Geneesk. 2021;3:2711-7
10. Van Golen LW, Braat AJAT, De Keizer B, Leijen CATM, Lam MGEH. Radionuclide therapieën in Nederland: zijn we klaar er klaar voor? Tijdsch Nucl Geneesk. 2021;2:2663-71
11. Handelingsperspectief uitvaartbedrijven ANVS. https://www.autoriteitnvs.nl/ documenten/publicatie/2022/07/19/handelingsperspectief-uitvaartcentra

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Cursus- en congresagenda

2023

SASNM 2023 - 20th Biennial Congress of the South African Society of Nuclear Medicine
24 - 27 August 2023, Gqeberha (formerly Port Elizabeth), South Africa, https://sasnmcongress.com

EANM 2023 - 36th European Association of Nuclear Medicine Congress
9 - 13 September 2023, Vienna, Austria, https://www.eanm.org/congresses-events/future-congress/

ICDINM 2023 - International Conference on Diagnostic Imaging and Nuclear Medicine
11 - 12 September 2023, Amsterdam, Netherlands, https://waset.org/diagnostic-imaging-and-nuclear-medicine-conference-in-september-2023-in-amsterdam

ICNMMI 2023 - International Conference on Nuclear Medicine and Medical Imaging
18 - 19 September 2023, Lisbon, Portugal, https://waset.org/nuclear-medicine-and-medical-imaging-conference-in-september-2023-in-lisbon

Alkmaar Cardiac PET/CT Workshop - From basic to advanced knowledge in Cardiac PET
21 - 22 September 2023, Noordwest Academy Alkmaar, https://www.petctworkshop.nl/program-2023

AI & Informatics in Nuclear Medicine Symposium
9 - 11 October 2023, University Medical Center Groningen, https://www.nvng.nl/system/files/bestanden/documenten/save_the_date_ainm_2023_v2.pdf

ALASBIMN 2023 - XXIX Congreso de la Asociación Latinoamericana de Sociedades de Biología y Medicina Nuclear
15 - 18 November 2023, Buenos Aires, Argentina, https://alasbimnbuenosaires2023.com

ICANM 2023 - International Conference on Advances in Nuclear Medicine
27 - 28 November 2023, Paris, France, https://waset.org/advances-in-nuclear-medicine-conference-in-november-2023-in-paris

RSNA 2023 - Radiological Society of North America, Annual Meeting
26 - 30 November 2023, McCormick Place, Chicago, USA, https://www.rsna.org/annual-meeting/future-and-past-meetings

NVNG 2023 - Lustrumcongres n.a.v. 55 jaar NVNG
15 december, Noordwijk, https://www.nvng.nl/nieuws/save-date-lustrum-nvng-15-december-2023

2024

ECR 2024 - European Society of Radiology Congress
28 February - 3 March 2024, Vienna, Austria, https://www.myesr.org/congress

EMIM 2024 - 19th European Molecular Imaging Meeting
12 - 15 March 2024, Porto, Portugal, https://e-smi.eu/meetings/emim/2024-porto/

SNMMI 2024 - Annual Meeting Society of Nuclear Medicine and Molecular Imaging
8 - 11 June, 2024, Toronto, Canada, https://www.snmmi.org/MeetingsEvents/EventDetail.aspx?EventID=114208