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Intratumoral injection of radioactive holmium-166 microspheres in recurrent head and neck squamous cell carcinoma: preliminary results of first use

Robbert C. Bakker[a,b], Robert J.J. van Es[c], Antoine J.W.P. Rosenberg[b], Sebastiaan A. van Nimwegen[d], Remco Bastiaannet[a], Hugo W.A.M. de Jong[a], Johannes F.W. Nijsen[a] and Marnix G.E.H. Lam[a]

Background **Limited treatment options exist for patients with locoregional recurrences of head and neck squamous cell carcinoma (HNSCC). In the palliative setting, a single session, minimally invasive, and relatively safe therapy is desirable. This case series illustrates the feasibility of a direct intratumoral injection of radioactive holmium-166 microspheres (^{166}HoMS) in patients as a palliative treatment for recurrent HNSCC.**

Patients and methods **In this retrospective analysis, patients with already reirradiated irresectable recurrent HNSCC, for whom palliative chemotherapy was unsuccessful or impossible, were offered microbrachytherapy with ^{166}HoMS. The intratumoral injection was administered manually under ultrasound guidance. Parameters scored were technical feasibility (i.e. administration, leakage, and distribution), clinical response (response evaluation criteria in solid tumors 1.1), and complications (Common Terminology Criteria for Adverse Events 4.3).**

Results **From 2015 to 2017, three patients were treated. None of the patients experienced adverse events; however, therapeutic effects were minimal. Technical difficulties, including precipitating of microspheres and high intratumoral pressure, resulted in suboptimal distribution of the microspheres.**

Conclusion **Intratumoral injections with ^{166}HoMS are minimally invasive and relatively safe in palliation of HNSCC patients. Careful patient selection and improved administration techniques are required to provide a more effective treatment. Further investigation of this novel treatment modality should be carried out because of the absence of side effects and lack of other treatment options.** ***Nucl Med Commun*** **39:213–221 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Keywords: brachytherapy, head and neck squamous cell carcinoma, holmium-166, intratumoral treatment, palliation

[a]Department of Radiology and Nuclear Medicine, [b]Department of Oral and Maxillofacial Surgery, University Medical Center Utrecht, [c]Department of Head and Neck Surgical Oncology, UMC Utrecht Cancer Center and [d]Department of Clinical Sciences of Companion Animals, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands

Correspondence to Robbert C. Bakker, MD, MSc, Department of Radiology and Nuclear Medicine, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
Tel: +31 887 555 555; fax: +31 887 555 551; e-mail: r.c.bakker@umcutrecht.nl

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Introduction

Cancer of the head and neck accounts for ~685 000 (4.9%) of all new cancer cases worldwide and over 375 000 deaths annually. The survival of patients with head and neck squamous cell carcinoma (HNSCC) mainly depends on the stage of disease at the time of diagnosis. For advanced (stage III–IV) carcinomas, the survival rate decreases to ~35%. Over the last decades, only limited improvements in survival were achieved, which urges the need for new treatment modalities. Especially for patients with locoregional recurrences, limited options exist [1–3].

For previously irradiated, irresectable regional recurrences, only two options for palliative treatment remain: palliative reirradiation or chemotherapy. In most cases with recurrent HNSCC, palliative reirradiation can be administered only once. This reirradiation usually consists of accelerated hyper-fractionated schemes of 1.5 Gy twice daily, up to 60 Gy depending on the dose previously administered [4,5]. With new developments such as intensity-modulated radiotherapy and stereotactic body radiation therapy, new schemes of 4–6 fractions of 6 Gy reduce treatment duration in patients with a limited life expectancy [6]. Palliative chemotherapy may provide a meaningful response in some patients. However, many patients are medically unfit for a platinum compound with capecitabine/fluorouracil and/or cetuximab [7]. There are currently some developments with monoclonal antibodies and tyrosine kinase inhibitors such as

PI3K/AKT/mTOR that may prove beneficial in the near future [8]. Furthermore, brachytherapy with a high or a pulsed dose rate [9] and bleomycin-electroporation therapy [10,11] are being studied in salvage patients, but these treatment modalities require a good performance status. As a result, only best supportive care remains for patients with severe comorbidities or a poor performance status.

Radioactive holmium-166 microspheres (^{166}HoMS) and currently used in intra-arterial radioembolization of liver malignancies [12]. These microspheres emit β radiation with a maximum penetration depth of 8.7 mm and are also used off-label in veterinary patients with unresectable oral squamous cell carcinomas and other tumors [13,14]. Intratumoral injections of ^{166}HoMs in veterinary patients showed a relevant response without severe morbidity [13]. This article presents the first experience on the feasibility and safety of intratumoral injections of ^{166}HoMS in human patients with recurrent cancer in the head and neck.

Patients and methods

Patient selection

In this retrospective analysis, patients with confirmed local or regional recurrence of HNSCC with or without distant metastasis, as evidenced by recent imaging, were discussed in the multidisciplinary head and neck oncology team for regular treatment options and/or ongoing trials. If no palliative treatment options were available, and nonetheless a strong wish for treatment existed, patients were amenable for direct intratumoral injections of ^{166}HoMS, with the aim of improving the patients' quality of life. Only tumors accessible for ultrasound (US)-guided manual injections with at least more than 5 mm distance to vital anatomical structures, such as the common carotid artery, were selected. Immediately after the injection procedure, a planar scintigraphy of the thorax and abdomen, as well as a single-photon emission computed tomography (SPECT)/computed tomography (CT) of the head and neck region were performed. Patients provided informed consent after receiving detailed information. The Ethical Committee of the Universty Medical Center Utrecht approved the study.

Holmium-166 microspheres preparation

^{166}HoMS of 30 μm diameter were prepared in the Universty Medical Center Utrecht as described previously [15,16] and CE-approved (QuiremSpheres; Quirem Medical B.V., Deventer, The Netherlands). Briefly, nonradioactive ^{165}Ho complexed with acetylacetonate is incorporated into poly(L-lactic acid) by solvent evaporation to form microspheres. Subsequently, the nonradioactive ^{165}HoMS were made radioactive by neutron activation in a nuclear facility (RID Reactor, Delft University of Technology, Delft, The Netherlands) to form ^{166}HoMS. After neutron activation, ^{166}HoMS were suspended in a PBS with 2% weight per volume of polyoxyethylene–polyoxypropylene copolymer (Pluronic F-68; Sigma-Aldrich Chemie B.V., Zwijndrecht, The Netherlands). The ^{166}HoMS were suspended for 10 min on a vortex, followed by repeatedly drawing up and down with a syringe.

The amount of radioactivity present in each syringe was measured in a dose calibrator (VDC-404; Veenstra Instruments B.V., Joure, The Netherlands). Each syringe was placed in an acrylic glass cylinder to limit β-radiation exposure of personnel, especially to the hands, during dose preparation and administration. The treatment was performed with a quantity of 100–250 mg of ^{166}HoMS, divided over 2–10 syringes, with a volume of 0.2–0.5 ml. The required ^{166}Ho activity was determined on the basis of tumor volume and aimed tumor-absorbed dose according to the following equation: $D = A \times 15.87/W$, where D is the tumor-absorbed dose [in Gy (J/kg)]; A is the ^{166}Ho activity (MBq); ^{166}Ho-specific tissue dose conversion coefficient = 15.87 mJ/MBq; and W is the tumor weight (g). Assumed tumor tissue density was 1.0 g/cm^3 and β radiation was assumed to absorb completely in the treated tissue [17]. The required activity was obtained by varying the neutron activation time of the microspheres.

Treatment

Before injection, the ^{166}HoMS were resuspended in the syringe by gentle agitation. The injections were administered manually under US guidance to prevent accidental intravenous administration. On the basis of the veterinary experience and review of the available literature, the following assumptions were made. The average injection percentage of ^{166}HoMS in the veterinary experience was ~50%; therefore, the prepared activity was doubled. The injection volume ranged from ~7 to 25% of the tumor volume. Per injection, a 1 cm^3 distribution of microspheres was expected. A 1 ml syringe was used for optimal control during the injection of small volumes with a 'luerlock' tip to reduce the risk of needle dislodgement. 21 G × 2′ and 23 G × 11/4′ needles were used depending on the tumor location. The aimed absorbed dose was 70–100 Gy. Immediately after treatment, a SPECT/CT was performed. Follow-up was performed at 1, 2, and at 4 weeks combined with a PET/CT. The following parameters were scored: technical feasibility (i.e. administration, leakage, distribution), response according to the response evaluation criteria in solid tumors (RECIST 1.1) [18], and complications according to the Common Terminology Criteria for Adverse Events (CTCAE 4.3) [19].

Case series

Three consecutive patients with a locoregional recurrence of HNSCC, who presented to the University Medical Center Utrecht between November 2015 and

Table 1 Patient characteristics

	Patient 1	Patient 2	Patient 3
Sex	Male	Male	Female
Age	75	75	73
History	Appendectomy, diabetes + retinopathy, CVA, hypertension, LVH, mild AOS, HNP L5–S1, cognitive impairment, CABG + AF	Hypertension, HNP, cardiac arrest, myocardial infarction	Uterusextirpation, cataract surgery
Origin	Gingiva of the maxilla	Skin retroauricular	Oropharynx
TNM classification	cT4aN2cM0	pT3N2bM0	cT2N2bM0
Histopathology	SCC Prior resection specimen G1: well differentiated Infiltrative growth Perineural invasion	SCC Prior resection specimen G2/3: moderately/poorly Differentiated infiltrative growth Perineural invasion + vascular invasion	SCC
Surgical treatment	Subtotal maxillectomy	Amputation left ear Selective neck dissection level Ib–III + 5A Superficial parotidectomy	2010: first T2N0M0 tongue, resection, ND I–III, en FRFF-reconstruction + second pTis SCC oral floor right 2016 tracheotomy airway obstruction
Radiotherapy	Primary EBRT neck bilateral $35 \times 2 = 70$ Gy	$33 \times 2 = 66$ Gy on tumor bed + LN level II right $33 \times 1.5 = 49.5$ Gy on surgical field + LN levels Ib–V left + tract of the nervus facialis till the base of the skull	2016: third oropharynx + fourth primary tonsil carcinoma cT1N2b gross tumor volume + positive LN $30 \times 2.3 = 69$ Gy Clinical target volume $30 \times 2.2 = 66$ Gy Level Ib–V L + R $30 \times 1.7 = 51$ Gy
Chemotherapy	–	–	Six sessions of carboplatin, capecitabine, cetuximab
Recurrence location	Neck, level II left Necrotic lymph node	Neck, level II left Ulcerative lesion	Neck, multiple cutaneous metastases
Reason for therapy	Local compression and pain	Pain of localized skin area	Pain and disfiguring sight

AF, atrial fibrillation; AOS, aortic valve stenosis; CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; EBRT, external beam radiation therapy; HNP, hernia nuclei pulposi; LN, lymph node; L, left; L5–S1, lumbar 5 sacral 1 disc; LVH, left ventricle hypertrophy; myocardial infarction; ND, neck dissection; R, right; SCC, squamous cell carcinoma; TNM, tumor node metastases; VF, ventricle fibrillation.

June 2017, were treated with intratumoral ^{166}HoMS (Tables 1 and 2).

Patient 1

A 75-year-old man with a history of diabetes, hypertension, a cerebrovascular ischemic accident, coronary artery bypass grafting, and atrial fibrillation was diagnosed with a squamous cell carcinoma of the maxillary gum, staged cT4aN2cM0. A partial maxillectomy was performed, with primary bilateral radiotherapy (70 Gy) of the neck because of his poor general condition. After 1 year, the patient developed a bilateral regional recurrence. US and CT indicated neck nodes with a diameter of 27 and 44 mm on the right and left side, respectively. Because of his poor medical condition, the patient was not amendable for salvage surgery or chemotherapy. The patient refused palliative reirradiation. In consultation with the patient, the largest left sided neck node was treated because of complaints of local compression and pain.

The treatment plan was to inject 200 MBq in 100 mg of ^{166}HoMS divided over two syringes with a volume of 0.5 ml and a 21 G × 2′ needle, which would result in an average absorbed dose of 70 Gy. Syringes were filled with 396.3 MBq and 204.1 mg of ^{166}HoMS to correct for the expected injection percentage of 50%. The injection procedure was not painful (maximum grade 1) and particle-reflections could be observed on US during administration (Fig. 1). In this patient, 366.8 MBq (92.5%) of the prescribed activity could be injected, equivalent to an absorbed dose of 130 Gy. SPECT/CT imaging showed some precipitation of the microspheres, especially in the dorsocaudal part of the tumor. Estimated activity on SPECT/CT was 309.2 MBq or 84.3% of the injected activity (Fig. 2).

The patient was admitted for observation of unexpected side effects before discharge 24 h after treatment. Clinical follow-up was performed at 1 and 2 weeks and did not indicate any toxicity. His complaints of tension in his neck diminished. At 4 weeks, an fluorine-18-fluorodeoxyglucose PET was performed to evaluate the response. This showed a 37% volume increase of the nontreated right lesion and a 30% volume increase of the treated left lesion. The treated lesion showed a lower maximum standardized uptake value on the fluorine-18-fluorodeoxyglucose PET/CT of 8.7 compared with 9.5 of the nontreated lesion, respectively. Especially, the uptake of the dorsal and caudal tumor parts was lower. Two months after ^{166}HoMS treatment, the patient died of respiratory insufficiency caused by aspiration pneumonia and progressive disease.

Patient 2

A 75-year-old man with a history of hypertension, myocardial infarction, and an out of hospital cardiac arrest was referred with an irradical excision of a left-sided retroauricular cutaneous squamous cell carcinoma. At the

Table 2 Treatment characteristics

	Patient 1	Patient 2	Patient 3		
Number of injections	2	4 (only 2 performed)	10		
Amount of volume (ml)	0.5	0.5	0.2		
Amount of HoMS (mg)	100	100	250		
Planned activity (MBq)	200	30	75		
			Right	Left	Total
Total					
Injected activity (MBq)	366.7	3.3	67.0	68.6	135.6
Injection percentage (%)	92.5	9.5	90.8	91.2	91.2
Syringe 1					
Injected activity (MBq)	182.9	1.4	12.7	14.5	–
Injection percentage (%)	92.0	8.7	90.6	90.9	–
Syringe 2					
Injected activity (MBq)	183.8	1.9	12.6	13.0	–
Injection percentage (%)	93.0	10.3	91.0	92.0	–
Syringe 3					
Injected activity (MBq)	–	–	14.3	13.9	–
Injection percentage (%)	–	–	92.8	93.2	–
Syringe 4					
Injected activity (MBq)	–	–	14.0	13.1	–
Injection percentage (%)	–	–	88.1	91.4	–
Syringe 5					
Injected activity (MBq)	–	–	13.5	14.3	–
Injection percentage (%)	–	–	92.2	90.1	–
Leakage					
Injected activity (MBq)	–	–	3.2	14.7	17.9
Injection percentage (%)	–	–	4.7	21.4	13.2
Administered (MBq)	366.7	3.3	63.8	53.9	117.7
Tumor volume (cm^3)	44.6	4	6.1	5.6	–
Absorbed dose (Gy)	130	–	165	153	–
SPECT/CT					
Injected activity (MBq)	309.2	–	16.9	9.6	26.7
Injection percentage (%)	84.3	–	26.5	17.8	22.7
Follow-up					
Side effects CTCAE 4.03	Pain: grade I	Pain: grade I	Pain: grade I		
Efficacy RECIST 1.1	Stable disease at 1 month ^{18}F-FDG-PET CT Decreased uptake in the caudal part of the lesion	–	Stable disease at 2 weeks		
Efficacy subjective	–	Less skin tension	Less pain and friction		
Observations/remarks	Precipitating of microspheres in necrotic/liquid filled lymph node	Solid malignancy, inability to inject	External leakage ulcerative lesion		
Survival	2 months	6 days	44 days		
Cause of death	Progressive disease→aspiration pneumonia→respiratory insufficiency	Progressive disease→respiratory insufficiency	Progressive disease→respiratory insufficiency		

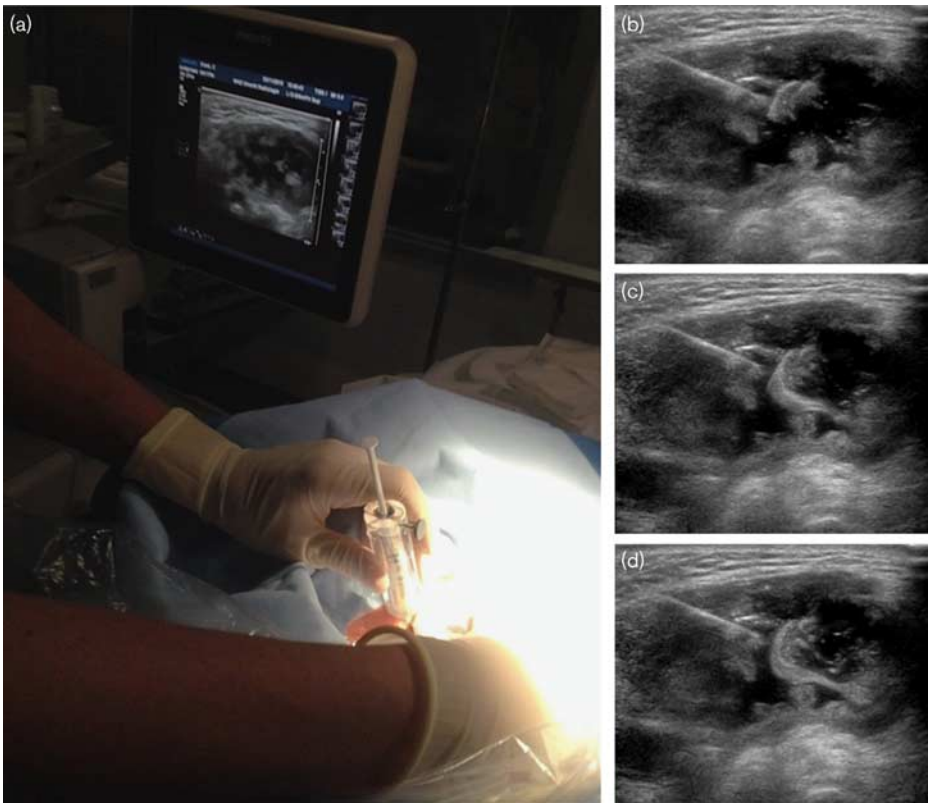
CTCAE, Common Terminology Criteria for Adverse Events; CT, computed tomography; ^{18}F-FDG, fluorine-18-fluorodeoxyglucose; HoMS, holmium microspheres; RECIST, response evaluation criteria in solid tumors; SPECT, single-photon emission computed tomography.

initial consultation, a 3×3 cm skin defect with nodules in the parotid gland was found. After surgical resection, which included a left ear amputation, selective neck dissection, and a superficial parotidectomy, the tumor was staged as pT3N2b with extracapsular extension. Subsequently, the patient received 49.5 Gy on the entire surgical field and neck with a simultaneous integrated boost technique: 66 Gy on the tumor bed and lymph nodes in level II. After 8 months, the patient presented with a regional recurrence in the left neck with carotid encasement up to the base of the skull, involvement of the vagal nerve, and tumor infiltration in the skin.

At clinical examination, a massive tumor, infiltrating and ulcerating the skin, was observed. The patient's main complaint was localized pain of the skin just below the mandible, poorly responding to oral morphine. In consultation with the patient, it was decided, despite the poor prognosis, to treat only this superficial area of the recurrence, avoiding the risk of traumatizing the carotid artery, and with the aim to palliate symptoms.

Four syringes with an activity of 13.5–16.5 MBq in 0.3 ml were prepared, which would result in an absorbed dose of 100 Gy for 4 cm^3. However, during the first two injections, an unexplained obstruction of the syringe occurred almost immediately. As a result, the injection procedure was terminated. Post-treatment measurements showed that only 3.3 MBq (9.5%) of the ^{166}HoMS was injected. The injection procedure was minimally uncomfortable (i.e. pain: maximum grade 1). Unfortunately, the patient was unable to undergo the SPECT/CT imaging because of pre-existing dyspnea. The patient was discharged, but readmitted 2 days later, because of progressive dyspnea. No adverse effects of the ^{166}HoMS injections were noted and a subjective decline in skin tension and pain was experienced, but no objective response was observed. The clinical condition declined rapidly, and the patient died of respiratory insufficiency 6 days after the treatment.

Fig. 1



(a) Setup of the ultrasound-guided injection with the syringe with holmium-166 microspheres shielded with acrylic glass. (b–d) Ultrasound images of an injection in a large necrotic fluid-filled lymph node metastasis, clearly visible flow of microspheres inside the tumor.

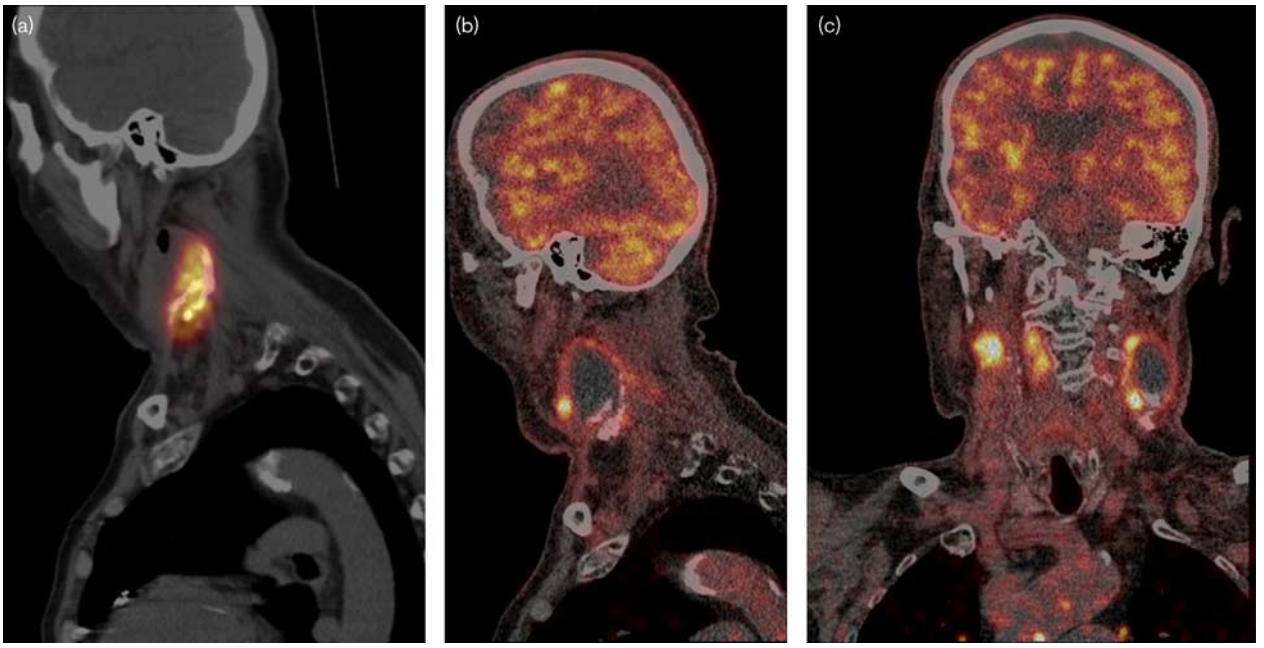
Patient 3

A 73-year-old woman with a history of alcohol and tobacco abuse was referred with a cT2N0M0 tongue carcinoma. A partial glossectomy, resection of the oral floor, a level I–III neck dissection, and reconstruction with a free radial forearm flap were performed. Simultaneously, a synchronous primary pTis of the floor of the mouth was resected. Six years later, she presented with a third primary T2N2bM0 oropharyngeal carcinoma with a synchronous primary contralateral cT1N2b tonsillar fossa carcinoma. Both tumors were treated with radiotherapy: 69 Gy on both gross tumor volumes and the positive lymph nodes. Level Ib–V left and right received 51 Gy. After 6 months, cutaneous metastases developed on both sides of the neck, causing dyspnea. Additional staging indicated multiple pulmonary nodules suspicious for metastatic disease. The patient received a tracheostomy and palliative carboplatin/capecitabine/cetuximab weekly, which showed a substantial response initially. However, after six cycles of systemic therapy, growth of the cutaneous metastases progressed. The patient's complaints were friction, pain, and the disfiguring sight of the cutaneous metastases.

It was planned to treat multiple nodules; however, in the 3 weeks between consent and treatment, the metastases progressed rapidly (Fig. 4). Therefore, only two large lateral lesions were treated with five injections of 0.2 ml, with an average of 25 mg and 15 MBq ^{166}HoMS, respectively. Of the total prescribed activity of 148.7 MBq, 91.2% was injected. Because of the superficial lesions, some backflow of microspheres was observed with needle retraction. In addition, some leakage of 166HoMS was observed during the injection of the ulcerative tumor on the left side. The cumulative leakage was 3.2 MBq (4.5%) on the right side and 14.7 MBq (21.5%) on the left side, resulting in a total administered activity of 117.7 MBq (79.2%) (Fig. 3).

After the procedure, the patient was discharged. No discomfort was experienced during or after the treatment. The progression of her complaints of friction and the disfiguring sight was halted. Tumor inspection after 1 week showed marked central necrosis of both injected tumors. This remained visible at 2 weeks (Fig. 4). This was interpreted as treatment effect. The right lesion measured 28 × 24 mm before treatment and 30 × 23 mm after 2 weeks, and the left lesion 24 × 15 and 25 × 14 mm, respectively. The tumor edge seemed still partially vital 2 weeks after treatment. Progressive dyspnea and growth

Fig. 2



Patient 1 with a large necrotic lymph node metastasis with clearly visible precipitation of the holmium-166 microspheres. (a) Single-photon emission computed tomography immediately after injection in the supine position. (b, c) Sagittal and coronal slices of fluorine-18-fluorodeoxyglucose PET 1 month after injection.

of nontarget lesions resulted in severe discomfort. The patient asked for and received euthanasia 6 weeks later.

Discussion

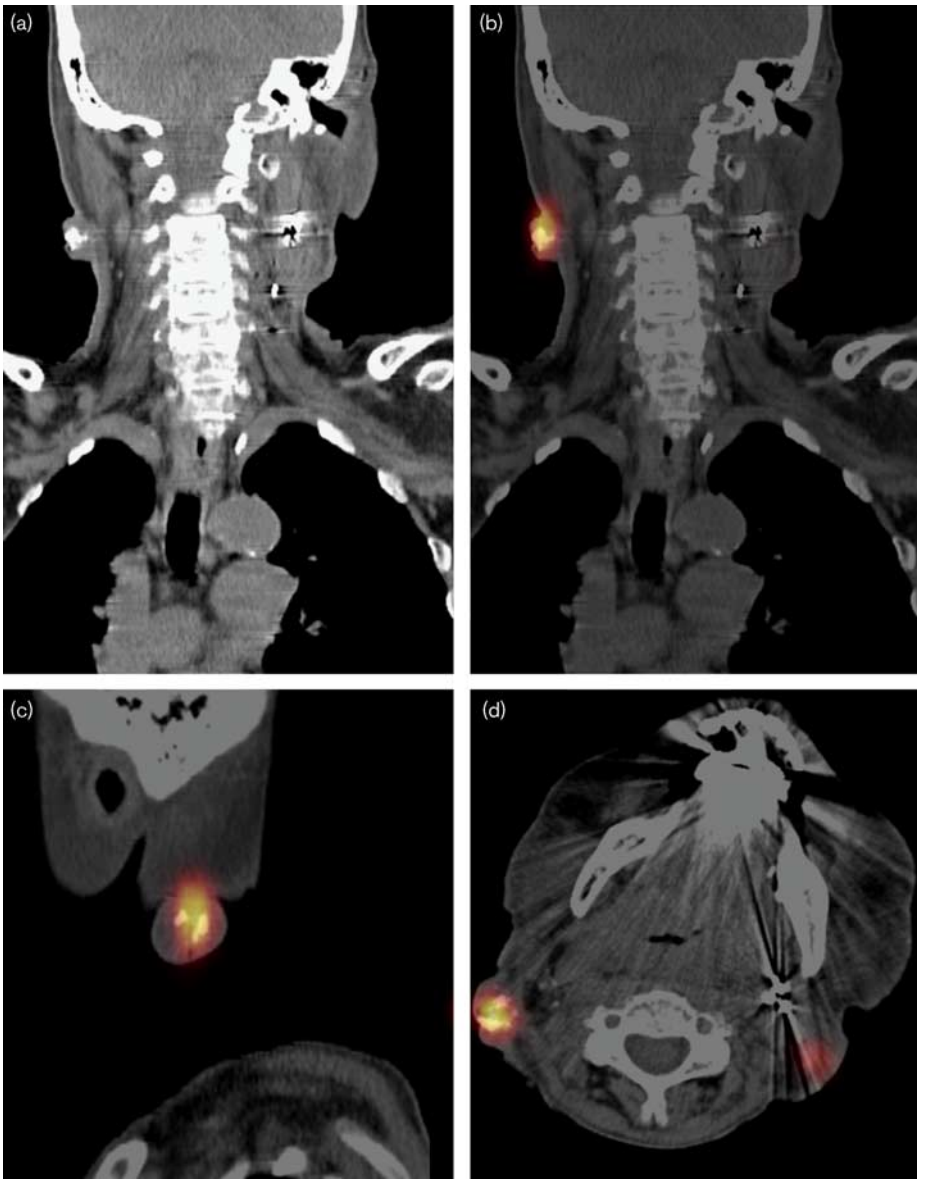
In this case series, the first experience with a direct intratumoral free-hand injection of ^{166}HoMS in patients with recurrent HNSCC for whom no other palliative retreatment options were available was described. The preparation of syringes with the desired activity and amount of ^{166}HoMS was accurate, and the resuspension before injection consisted of some gentle agitation of the syringe. The injection procedure went smoothly in patients 1 and 3, with some leakage in superficial and ulcerative lesions. This leakage was easily absorbed in a compress and did not result in contamination of personnel or equipment.

In the palliative setting, a single-session, minimally invasive, and relatively safe treatment is desirable. Intratumoral injections with ^{166}HoMS are minimally invasive and seem to be safe. Only slight discomfort during needle insertion was experienced. No discomfort related to radiation was experienced during follow-up. In addition, no systemic side effects were observed, or expected, as post-treatment imaging did not show activity outside the tumor.

There were some subjective improvements in tension and pain in the tumor region of all patients; however, objective efficacy (i.e. reduction in the size of the targeted metastasis) was not observed. The tissue penetration of the β radiation of ^{166}Ho is limited and 90% of the dose is absorbed in the first 3 mm [20]. Subsequently, the efficacy is probably strongly related to an appropriate dose distribution. The microspheres distribution therefore needs to be homogeneous for antitumor efficacy and the absorbed radiation dose should sufficiently cover all areas of vital and proliferating tumor tissue. In contrast, however, post-treatment SPECT/CT imaging showed a nonhomogenous distribution of ^{166}HoMS after the injections (Fig. 2). This could explain tumor progression in patient 1, albeit decreased metabolic activity on PET/CT dorsocaudally in the tumor, consistent with the area of higher microsphere density on SPECT/CT. In patient 3, the absorbed dose was high enough and the distribution seemed sufficient for inhibition of tumor growth, although size reduction of targeted metastases was not observed.

An accurate selection of patients for ^{166}HoMS treatment seems important. Treatment of a large, cyst-like lymph node metastasis with central necrosis resulted in precipitation of microspheres inside the tumor of patient 1. In patient 2, the injection of ^{166}HoMS proved difficult because of obstruction of the syringes. It was initially hypothesized that precipitation and agglomeration of ^{166}HoMS could have resulted in obstruction of (smaller) needles. However, in patient 2 also the larger 21 G needles seemed obstructed/occluded. With the multisizer

Fig. 3

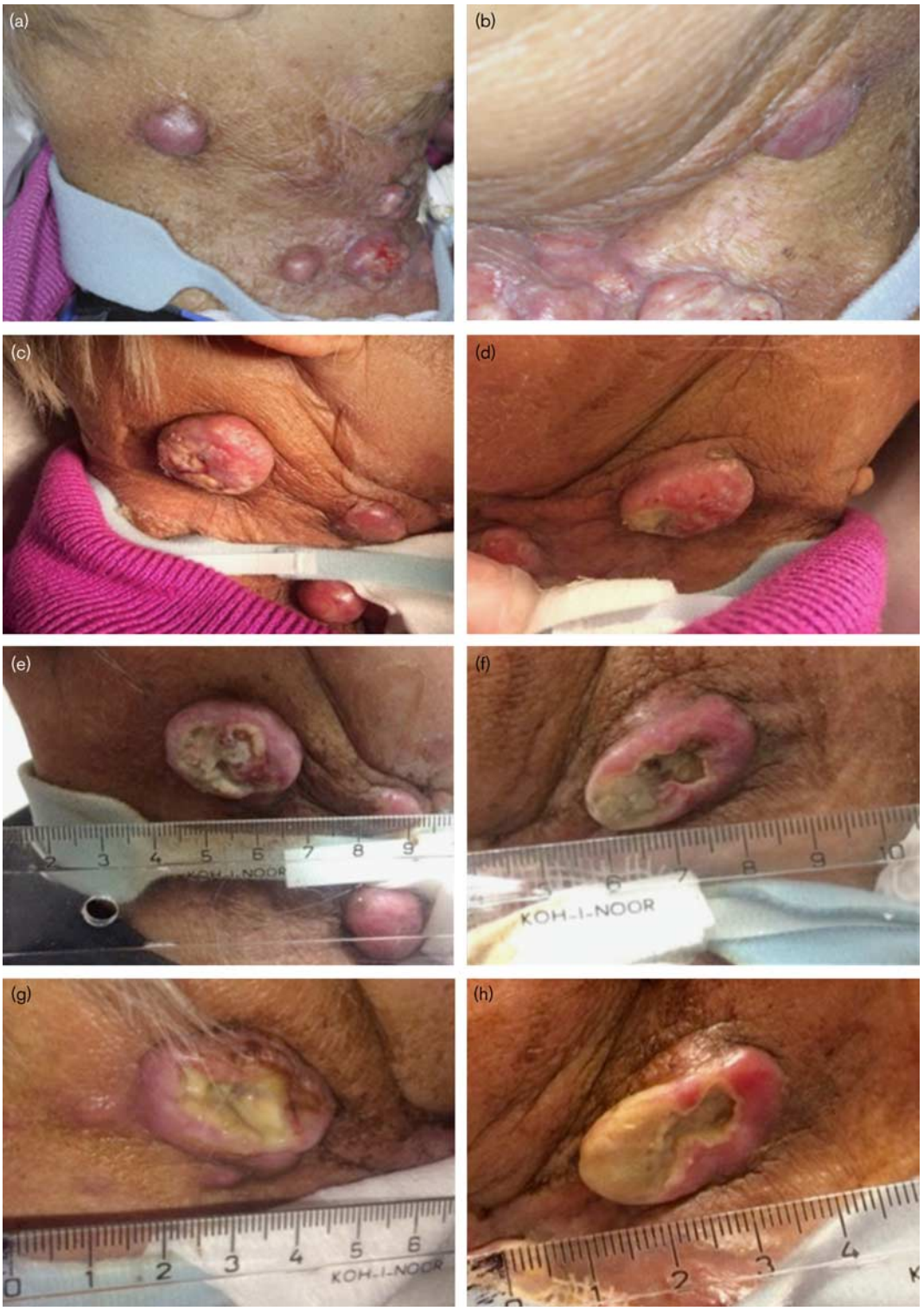


Patient 3, (a) clearly visible accumulations of holmium-166 microspheres as white dots on computed tomography. (b–d) Single-photon emission computed tomography reconstructions in coronal, sagittal, and axial directions.

(Multisizer 3; Beckman Coulter Life Sciences, Indianapolis, Indiana, USA) (data not shown) and under a microscope, no agglomerations of ^{166}HoMS were detected in the suspension. Therefore, difficulty in injecting the ^{166}HoMS suspension was probably caused by a high intratumoral pressure in the firm consistency of the tumor in patient 2. As an increased pressure force can result in needle dislodgement, the injection position was sometimes changed in case of high resistance in the veterinary experience [13]. In patient 3, with soft cutaneous metastases without large ulceration, the injection procedure was feasible. However, in the case of a skin ulcer, some precaution is necessary to prevent a potential spill of activity through the skin defect.

On the basis of the current experience, the absence of significant side effects, and lack of other treatment options, an intratumoral injection with ^{166}HoMS deserves further investigation. Therefore, the following considerations are suggested to improve the efficacy of future ^{166}HoMS treatments. Patients with relatively small, soft, and superficial tumors seem more amenable for ^{166}HoMS treatment in comparison with patients with large necrotic or indurated tumors. In addition, the focus should be directed toward the vital tumor edge, and

Fig. 4



Patient 3, (a, b) tumor 3 weeks before treatment, (c, d) tumor 2 days after treatment, (e, f) tumor 8 days after treatment, (g, h) tumor 15 days after treatment.

peritumoral injections of the tumor bed should be considered. Furthermore, the main advantage of ^{166}Ho over other high-energy β-emitting radionuclides for local treatment is its visibility on SPECT, CT, and MRI. This should be used for imaging of the ^{166}HoMS distribution and dosimetry [21–23]. The distribution of ^{166}HoMS must be a priority in future studies, and the effect of injection volume, the amount of microspheres, and injection locations should be investigated. When image-guided feedback is used, the dose distribution can be improved and treatment efficacy will likely improve. In addition, the aid of robotic administration systems [24] could allow for quicker and more accurate needle placement.

Conclusion

Intratumoral injections with ^{166}HoMS seem to be feasible as a single-session, minimally invasive, and relatively safe treatment in the palliative setting for heavily comorbid HNSCC patients. Improving patient selection, administration techniques, and use of real-time high-resolution imaging is necessary to optimize the dose distribution. Considering the suggested improvements and the absence of side effects, this palliative microbrachy treatment may be of additional value in a specific group of HNSCC patients.

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Conflicts of interest

J.F.W. Nijsen is co-founder and scientific director of Quirem Medical B.V., and has a minority share in the company Quirem Medical B.V. Furthermore, Nijsen is inventor on the patents related to the ^{166}Ho-PLLA-microspheres, which are assigned to University Medical Center Utrecht Holding B.V. (patent numbers: O2012060707 A1 and US 2005/0201940 A1). The Department of Radiology and Nuclear Medicine of the Universty Medical Center Utrecht receives royalties from Quirem Medical B.V. M.G.E.H. Lam is consultant for Sirtex, BTG, Mirada and Bayer Healthcare. For the remaining authors there are no conflicts of interest.

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