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CLINICAL PRACTICE GUIDELINE

International guidelines for intratumoral and intranodal injection of NBTXR3 nanoparticles in head and neck cancers

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Abstract

Background: An international multidisciplinary panel of experts aimed to provide consensus guidelines describing the optimal intratumoral and intranodal injection of NBTXR3 hafnium oxide nanoparticles in head and neck squamous

cell carcinoma (HNSCC) of the oral cavity, oropharynx, and cervical lymph nodes and to review data concerning safety, feasibility, and procedural aspects of administration.

Methods: The Delphi method was used to determine consensus. A 4-member steering committee and a 10-member monitoring committee wrote and revised the guidelines, divided into eight sections. An independent 3-member reading committee reviewed the recommendations.

Results: After two rounds of voting, strong consensus was obtained on all recommendations. Intratumoral and intranodal injection was deemed feasible. NBTXR3 volume calculation, choice of patients, preparation and injection procedure, potential side effects, post injection, and post treatment follow-up were described in detail.

Conclusions: Best practices for the injection of NBTXR3 were defined, thus enabling international standardization of intratumoral nanoparticle injection.

KEYWORDS

head, nanoparticle, neck, NBTXR3, radiotherapy

1 | INTRODUCTION

NBTXR3 (Hensify) is a sterile aqueous suspension of functionalized metal oxide nanoparticles. The nanoparticles are composed of a core of Hafnium oxide functionalized with phosphate groups on the surface, which constitutes a coating of homogeneous negative charge. NBTXR3 is a tumor agnostic radioenhancer. NBTXR3 has both a physical mode of action and triggers an adaptive immune response based on pre-clincal studies. The interaction between radiotherapy (RT) and NBTXR3 enhances the production of free radicals, which leads to an increase in DNA damage inside tumor cells.[1] NBTXR3 activated by RT leads to increased cell destruction compared to RT alone, allowing a greater release of tumor-associated antigens, promoting the development of the antitumor immune response. Pre-clinical studies and one clinical randomized trial have demonstrated the antitumor effect of NBTXR3 activated by RT over RT alone.[2] In head and neck squamous cell carcinoma (HNSCC), feasibility and promising results have been demonstrated in a phase 1 study,[3] and a phase 3 clinical trial is ongoing. Nevertheless, the quality of the injection is a fundamental element in the efficacy of this novel therapeutic modality. Therefore, a detailed description of the injection techniques is necessary to standardize the procedure among injectors.

The Delphi method allows the establishment of clinical consensus guidelines based on good practices,[4,5] using recommendations from experts. Advantages of the method include the capacity to establish a consensus or compromise based on the level of agreement and the transparency and rigor in the development of recommendations allowing a high level of agreement. The objective of this project was to describe the intratumoral (IT) and intranodal (IN) injection technique for NBTXR3 and to evaluate the level of consensus by using the Delphi method to foster the optimal reproducibility, efficacy, and safety in HNSCC.

2 | MATERIALS AND METHODS

A multidisciplinary steering committee (two head and neck surgical oncologists, one radiation oncologist, one interventional radiologist) was created. The objective of this committee was to draft the proposals and recommendations dealing with the calculation of the volume of the product, product preparation, IT and IN injection, potential adverse events, and patient follow-up. A document containing nine sections was drafted. A monitoring committee was created with the objective of reviewing the proposals and recommendations made by the steering committee using the Delphi method with two rounds of voting. The monitoring committee was composed of a multidisciplinary and international panel of experts including three head and neck surgical oncologists, three radiation oncologists, and four medical oncologists, all of whom were participants in NBTXR3 clinical trials. Each expert scored each of the nine sections of the document of proposals ranging from 1 (*total disagreement*) to 9 (*total agreement*) during two rounds of voting using a secure

TABLE 1 First round voting scoring.

Proposal score		Median value of vote	Distribution of responses	Eligibility for second round
Appropriate	Strong agreement	≥7	All votes between 7 and 9	No, recommendation accepted
	Relative agreement	≥7	All votes between 5 and 9	Yes
Inappropriate	Strong agreement	≤3	All votes between 1 and 3	No, recommendation rejected
	Relative agreement	≤3.5	All votes between 1 and 5	Yes
Uncertain	Indecision		All votes between 4 and 6.5	Yes
	Absence of consensus	≥7	At least one vote <5	Yes
		≤3.5	At least one vote >5	Yes

TABLE 2 Second round voting scoring.

Proposal score		Median value of vote	Distribution of responses
Appropriate	Strong agreement	≥7	7–9
	Relative agreement	≥7	5–9
Inappropriate	Strong agreement	≤3	1–3
	Relative agreement	≤3.5	1–5

online voting platform. The voting platform also ensured each expert could vote only once. After the first round, strong positive and negative agreements emerged (Table 1). Each expert was required to provide feedback on the reasons for any score less than or equal to 3, while feedback for proposals scored greater than 3 was optional. Each recommendation eligible for a second round of voting was reviewed by the steering committee and all commentary was considered. After the second round, a global consensus was reached (Table 2). If necessary, each expert was contacted after revision to obtain a high level of consensus for all recommendations. A three-member reading committee composed of one head and neck surgical oncologist, one radiation oncologist, and one medical oncologist was created. The reading committee did not have experience with NBTXR3 clinical trials and was asked to provide feedback on the consensus guidelines.

3 | RESULTS

3.1 | First round of voting

Following the first round of voting (week of April 26, 2021) none of the recommendations were rejected. The experts were in strong agreement (no need for second round of voting) on the recommendations regarding storage, preparation and handling of syringes, and the contra-indications to IN injection. The recommendations with the lowest level of agreement (average score less than 7) were those regarding the indication for injection in patients in the palliative setting, the possibility of injection in patients in the palliative setting, the possibility of injection under local versus general anesthesia, the modalities for NBTXR3 volume calculation, the best diagnostic test to measure lesions to be injected, the procedure for injecting the lymph node, and the possibility of injecting the larynx, hypopharynx, and/or nasopharynx. Following the first round of scoring, the steering committee modified the recommendations eligible for a second round of voting with major modifications of the recommendations with the least agreement.

3.2 | Second round of voting

Following the second round of voting (week of June 14, 2021) none of the recommendations were judged inappropriate. Twenty-five recommendations, corresponding to most of the recommendations, were accepted with strong agreement (median score of 9 and no average scores under 7). A recommendation concerning the planning of RT was accepted with relative agreement, with some considering the recommendation too strict. The text was modified to address this feedback. Four proposals did not reach agreement, regarding the calculation of NBTXR3 volume, the treatment of metastatic patients, the procedure for injection in the lymph node, and the evaluation of response post-RT. For each of these recommendations a single expert had given a score of less than 5. The steering committee modified the text and sent it

directly to the dissenting expert for review. Following these modifications, all experts accepted the recommendation and modified their scoring to strong agreement. The monitoring committee also proposed and validated the figures unanimously.

3.3 | Reading committee

The reading committee reviewed the guidelines between September and November 2021. The committee provided a favorable review and requested clarification of certain subjects which had not come up during the two rounds of voting by the monitoring committee: size of syringes for IN injection, limitations on the use of epinephrine, need for conducting a post injection visualization scan, and degree of minimal vascular contact constituting a contraindication for IT injection.

4 | DISCUSSION

Use of standardized methodology for IT/IN injection will support practice harmonization for a new local intervention in cancer. Tailored therapies require harmonization to reduce variation in IT/IN administration of products, avoiding a one size fits all approach. Such harmonization will enable a reduction in treatment heterogeneity leading to an improvement of patient outcomes.

The final consensus recommendations clarified concerns on a variety of subjects ranging from patient selection and follow-up to the number of syringes to prepare and the planning of puncture points for injection. While the guidelines are too long to be published in their entirety, the complete document is provided in Data S1, Supporting Information. The most important sections are summarized below.

5 | GUIDELINES

5.1 | Eligibility for NBTXR3 injection

5.1.1 | Which patients can receive NBTXR3?

Patients fulfilling the following four criteria may be injected: (i) planned for RT; (ii) absence of history of RT in the target field; (iii) histology of squamous cell carcinoma (SCC); (iv) presence of a target lesion. The target lesion(s) can be the primary tumor and/or one or several cervical lymph nodes (Figure 1).

Carcinomas of unknown primary, consisting of SCC located in one or several cervical lymph node(s) in the absence of an identified primary tumor, are eligible for IN injection. Patients with recurrent cancer without a history of RT who fulfill all the above-mentioned criteria are eligible. Patients with a history of RT requiring re-irradiation are subjects of an ongoing phase I clinical

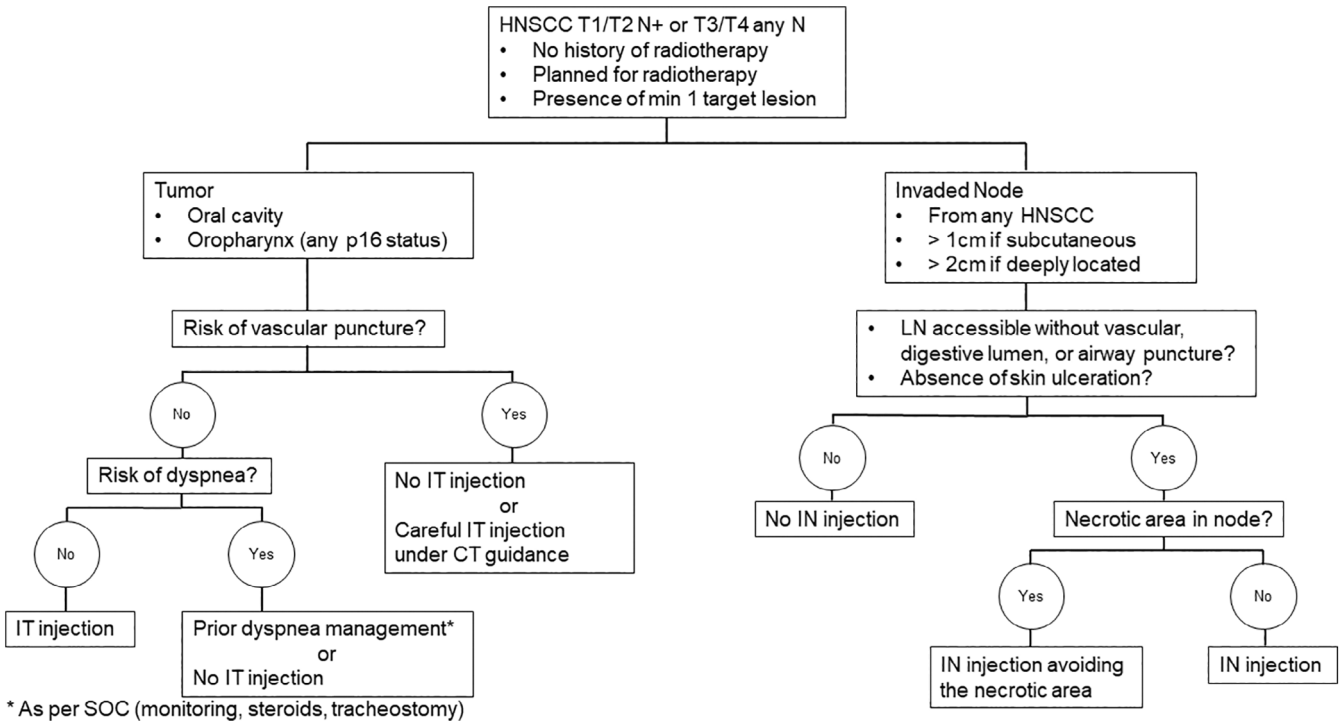

FIGURE 1 Eligibility for NBTXR3 intratumoral (IT) and intranodal (IN) injections. SOC, standard of care.

trial, but minimal safety data for re-irradiation is not yet available. Pre-cancerous lesions are not eligible.

In case of dissociated adjuvant treatment, with surgery performed on the tumor only or on lymph nodes only, the remaining target(s) may be injected.

5.1.2 | Which anatomical regions are fit for NBTXR3 injection?

Regarding the location of the primary tumor, NBTXR3 has been tested in oral cavity and oropharyngeal cancers with acceptable safety outcomes (NCT01946867).[3]

Any cervical lymph node is an injectable target insofar as it can be imaged and is accessible using ultrasound (US) or computed tomography (CT) guidance without transfixing any vital structures such as the carotid or vertebral arteries or their main branches, or the esophagus, trachea, or major nerves. The target must be at least 1 cm in the shortest dimension when subcutaneous and 2 cm when deeply located.[6]

To date in HNSCC, NBTXR3 injections into the larynx, hypopharynx, or nasopharynx have not yet been tested and are therefore not detailed in these present guidelines. However, metastatic lymph nodes of a larynx, hypopharynx, or nasopharynx cancer may be injected if clinically needed, as described above.

Other regions, such as nasal cavity, paranasal sinus, skin, or salivary gland cancers, either have not been evaluated or are currently being investigated in phase I/II clinical trials and should only be injected under the auspices of a clinical trial.

5.1.3 | What are the tumor characteristics that may preclude the IT injection?

IT injections should not be performed if there is a risk of vascular puncture or of airway obstruction. Clinical and imaging (ultrasound, CT, or magnetic resonance imaging [MRI]) evaluation of the carotid is necessary. The risk of vascular puncture must be assessed on pre-treatment imaging using either CT, MRI or US with evaluation of tumor vascular encasement, uncontrolled hemorrhage, and anatomical location of carotid artery including proximity with the tumor or planned needle path.

A history of prior embolization of tumor arterial feeders that was used to control hemorrhage does not exclude the patient from the IT treatment. The risk of dyspnea is defined by the presence of a pre-existing dyspnea or of a significant airway obstruction identified by clinical examination. Such situations require pre-treatment management by tracheotomy or the organization of a close monitored surveillance, as it would in the absence of IT injection.

In some cases the IT injection may not be feasible for technical reasons of accessibility, such as the presence of trismus persistent under general anesthesia. In these rare clinical cases, the use of image-guided injection by a transcutaneous approach may be discussed. The presence of a large liquidated and necrotic region will modify the IT injection plan, as explained below. Bleeding diathesis and use of anticoagulation drugs are not contraindications to the injection but require increased care and surveillance during and after injection. Tumor-induced skin ulceration raises the risk of NBTXR3 leakage, but the patient may still be injected if an accurate clinical evaluation is reassuring for integrity of the tumor surface.

5.1.4 | What are the involved lymph node characteristics that may preclude IN injection?

Targeted lymph nodes must be visible and accessible under US or CT guidance with a needle path avoiding airways, digestive lumen, or large vessels. Injection into lymph nodes that are abutting or encasing major vessels (e.g., the common, internal, external carotid arteries and their main branches, jugular veins, ...) should be considered carefully before patient selection with regards to the possible risks of vascular puncture or inadvertent intravascular leak from the tumor at the time of injection of NBTXR3 (Figure 1). Furthermore, targeting such lymph nodes encasing or abutting large vessels must be discussed to evaluate the risk of radiation-induced vascular rupture.[7] Ulcerated malignant lymph nodes extending through the skin surface must be evaluated carefully avoiding any risk of further rupture, leak of NBTXR3, or septic complication. Malignant lymph nodes with disrupted capsule depicted at imaging are not contraindicated for NBTXR3 injection, given careful evaluation of NBTXR3 spatial repartition which must be evaluated at subsequent CT imaging before irradiation. The coagulation profile and platelet count must allow for percutaneous puncture.

Although injecting the necrotic portion of a lymph node does not carry a specific risk, the necrotic portion should be avoided for the sake of efficacy, as the injection should target areas with viable cancer cells. Consequently, the anechoic region on grey scale imaging must be avoided as these areas are usually suspicious for necrosis. Contrast-enhanced ultrasound can be used if available for a more accurate determination of viable and necrotic areas.[8]

5.2 | Procedure of NBTXR3 intratumoral or intranodal injection

5.2.1 | What is the recommended dose of NBTXR3 and how is it calculated?

The NBTXR3 injection volume is calculated as a percentage of the total tumor volume (TV) measured on the diagnostic MRI or CT scan, as determined by the physician. For tumors in the oropharynx or oral cavity, the preferred imaging is contrast enhanced MRI. To obtain the most accurate and real volume determination across different centers for patients with HNSCC, it is recommended to estimate the tumor volume in mL (cm^3) by contouring the tumor on a diagnostic MRI or contrast enhanced CT scan.

The volume (dose) of NBTXR3 (54.2 g/L) to be administered is 33% of the pretreatment TV (primary tumor and/or lymph node). Separate syringes are prepared for IT or IN injection of each targeted tumor and the volumes are calculated as follows:

Total volume of NBTXR3 to be injected IT = Primary TV × 0.33 = _ _ _ _ _ _ mL.

Total volume of NBTXR3 to be injected IN = Target lymph node TV × 0.33 = _ _ _ _ _ _ mL.

5.2.2 | Patient preparation

Clinical experience to date shows that NBTXR3 injection is well tolerated.[9] The use of prophylactic corticosteroids (prednisone 30 mg orally at 12 and 2 h before NBTXR3 administration) prior to NBTXR3 injection is required and can control the severity of acute immune-related adverse effects. General anesthesia is recommended for injection, following the standard practice of the medical center. In case of an accessible lesion in a patient considered at high risk for general anesthesia, local anesthesia can be considered. All such patients should have an intravenous catheter in place before the injection, and physicians must have immediate access to a suction device and intensive care equipment.

5.2.3 | How is NBTXR3 injection in the primary tumor performed?

Basic principles and definition

The objective of the IT injection is to disperse the product as evenly as possible within the tumor. While a completely even dispersion of NBTXR3 within the lesion may not be achieved, the mechanism of action will still increase the effective dose of RT near the particles. IT injection is performed at room temperature by an expert physician in head and neck anatomy (surgeon, radiologist), with minimal external pressure, as slowly as possible. IT injection should be planned based on close analysis and pre-procedural measurements on the pretreatment imaging (MRI preferred). Puncture points are defined by the points of entrance of the needle. Target areas are defined by subdivisions of the tumor volume. To avoid the risk of tumor seeding, puncture points should be strictly IT. To date, safety has been assessed with strictly intratumoral injections, and peritumoral injections are therefore not recommended. More studies are required to assess the safety and efficacy outcomes after peritumoral injection and RT.

Syringes and injection planning

NBTXR3 is provided by the pharmacy in pre-filled syringes as mentioned in section 6 of Data S1. We recommend the use of 25 gauge (25G) needles. In case of stiff tumor, if the 25G needle is too flexible, larger needle sizes up to 22G may be used. Standard length needles are recommended for anterior tumors, whereas longer needles such as spinal needles may be preferred for posterior tumors.

We define target areas as spheres with a diameter of 1.5 cm within the tumor volume (Figure 2). The physician should define the number and the position of these target areas based on the baseline tumor volume and the tumor size, shape, and topography on the MRI. The total volume of NBTXR3 provided by the pharmacy should be divided by the number of target areas, to determine the volume to be injected within each target area. The number of puncture points is also determined by the tumor characteristics (e.g., location, shape, exposure of the different parts for large tumors). It is acceptable that a single puncture is used to access two or more adjacent target areas if feasible, especially in case of superficial and deep target areas in the same direction. To avoid the leakage within the surrounding tissues, puncture points should be more than 0.5 cm from the tumor margin. In the rare case of tumors presenting with a large liquid necrotic region, target areas will be limited to the surrounding viable solid cancer tissue.

Injection

The tumor is exposed according to its location, using a mouth-opening stent or an endoscope. Several IT injection techniques are acceptable if they achieve NBTXR3 dispersion within the tumor. One option is to reach the center of the target areas, to immobilize the needle, and to slowly inject the calculated volume. Another option is to inject the same volume while moving slowly from the deepest limit of the target area to its superficial limit. To reach the deepest target areas, marks can be performed on the needle to ensure the positioning at the appropriate

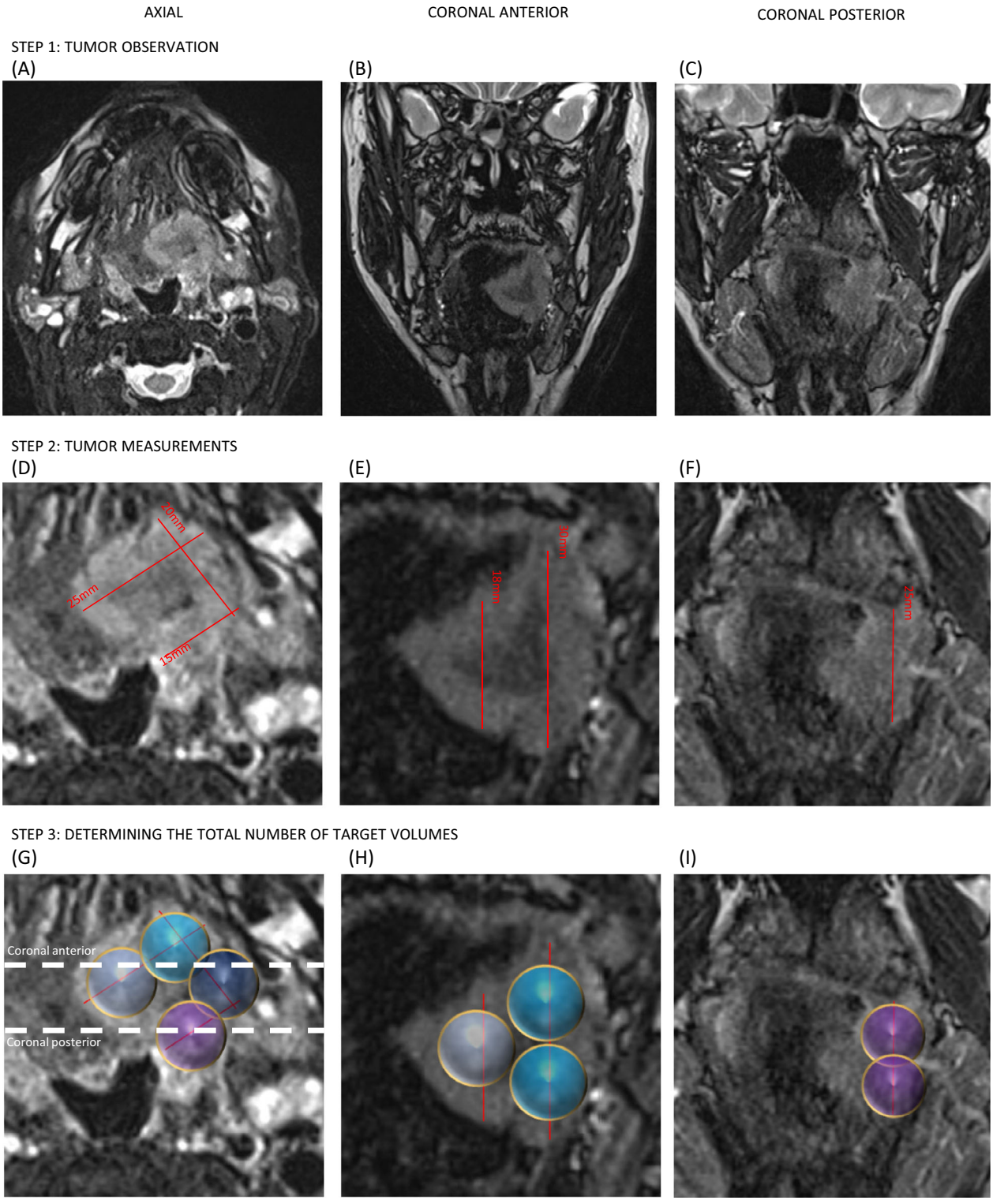

FIGURE 2 Example of IT planning using pre-injection MRI. (A, D, G) Axial; (B, E, H) coronal anterior; (C, F, I) coronal posterior. Dashed lines in (G) show the correspondence between axial and coronal images. (A–C) Step 1, tumor observation. (D–F) Step 2, tumor measurements. (G–I) Step 3, determining the total number of target volumes represented here by the spheres. Spheres of the same color represent similar location on the axial plan. Here, one light blue, two intermediate blue, two dark blue (not shown in coronal) and two purples volumes are planned, for a total of seven target volumes. [Color figure can be viewed at wileyonlinelibrary.com]

depth. While injecting, external pressure should be limited as much as possible to avoid any disruption of the tumor margins. All of the planned NBTXR3 volume must be injected. More detailed procedures for lesions accessible or not accessible through direct mouth opening are available in Data S1.

5.2.4 | How is NBTXR3 injection in the lymph nodes performed?

IN injection is to be performed by a trained physician and is recommended to be performed at the same time as IT injection where possible, particularly if the patient is under general anesthesia.[10]

IN injection of NBTXR3 requires real-time image guidance for safe access and accurate needle tip positioning prior to the injection of NBTXR3, as well as to evaluate the tumor injectability due to local tissue changes such as IN areas of necrosis as previously explained (Figure 3). Image guidance essentially involves real-time guidance of the needle from the level of the skin to the targeted area in the lymph node, assessment of the needle's location before injection of NBTXR3, and potentially assessment of product delivery. US guidance is considered a safe, reliable, and effective procedure in skilled hands for injection into most superficially located lymph nodes. US guidance is highly preferred whenever NBTXR3 injection is performed because it is readily available, allows real-time monitoring and access in any angle, and does not irradiate the patient as compared to CT. Only very deep lymph nodes may require a CT-guided procedure. US can be used to identify a safe needle path from the level of the skin to the target, avoiding vascular structures and proceeding through a single puncture of the lymph node to minimize the risk of tumor seeding and the risk of NBTXR3 leaks induced by multiple punctures of the capsule. If the anatomic location or large lymph node size requires the use of several needles, it is advisable to place all the needles before starting the injection, and then to inject the needles sequentially, with imaging-based re-confirmation of each needle position before each injection(s). After injection, the mandrils are placed back in the needles and left in place ideally at least 5 min before withdrawing the needles, to avoid as much as possible back flow of NBTXR3 through puncture tract(s). This time may be decreased for patient comfort or unstable needle position but a minimum of 1 min is highly recommended.

Local anesthesia is needed for lymph node injection. Skin analgesia at the site of puncture can be administered using topical xylocaine (4%) or other local anesthetic agents. When needed, injectable xylocaine can be used to avoid pain during puncture of deeply located lymph nodes. Systemic analgesic treatments should be planned and are recommended to be initiated at least 30 min before undertaking the injection procedure.

22G needles are a good compromise between rigidity, visibility, and small caliber. Luer lock syringes should be used to avoid spillage of NBTXR3 due to accidental disconnection of the needle and syringe during IN injections.

NBTXR3 will be injected as slowly as possible under minimal external pressure. Ideally NBTXR3 is injected into the entire lymph node volume through multiple positionings within the lymph node through a single puncture of the lymph node capsule. This technique can apply multiple depots and cover as much as possible of the targeted lymph node volume while minimizing disruption of the node capsule.[7] This technique of injection can be described as a

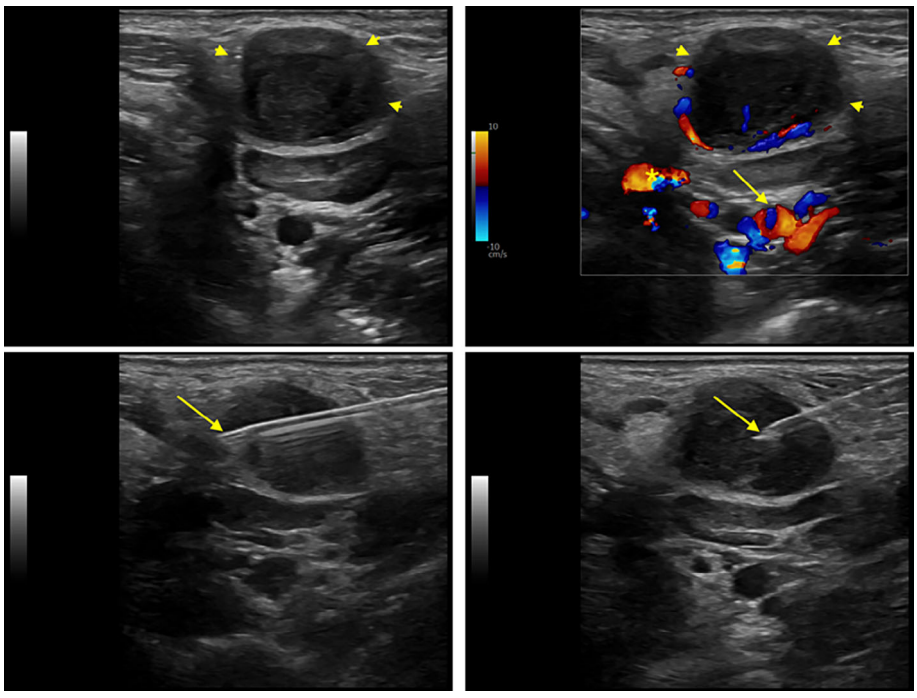

FIGURE 3 Ultrasound-guided intranodal injection. Top left: Grey scale ultrasound of a jugular lymph node with the needle (arrow heads). Top right: Color Doppler mode clearly displaying the carotid bifurcation (arrow) and the jugular vein (*). Bottom left: Needle has been inserted in an axis that avoids inadvertent puncture of any vessels. Tip of the needle (arrow) has been inserted to the deep part of the lymph node for a first location of injection in the deep and central part of the lymph node. Bottom right: Needle tip (arrow) has been withdrawn to the center of the lymph node for a second location of injection in the deep and central part of the lymph node. [Color figure can be viewed at wileyonlinelibrary.com]

"radial technique." A single puncture of the targeted lesion is also a countermeasure to minimize any risk of tumor seeding along the needle track,[11] and avoidance of a large needle caliber will further reduce this risk. While a single puncture is optimal, in the case of a very large lymph node, two or more punctures may need to be performed.

5.2.5 | Adverse events

Does NBTXR3 IT injection increase the risk of tracheotomy?

In the HNSCC phase I study, safety evaluation has not identified an increased risk of tracheostomy after IT injection.[3] However, there was one case of emergency tracheostomy in one patient with known COPD (chronic obstructive pulmonary disease) and a large tumor in the base of tongue. For large tumors that obstruct the upper airways, the injected volume may further decrease the potential upper airway space, especially during the first 24 h before liquid suspension absorption, potentially increasing the need for tracheostomy. Therefore, post-injection monitoring should be planned for larger obstructive tumors. Altogether, the consensus is that risk of increased dyspnea may occur in some situations where there is pre-existing airway obstruction.

How are diffusion and leakage of NBTXR3 assessed?

Diffusion is defined by the presence of NBTXR3 outside of the target zone, in the surrounding healthy tissues. CT is always required to determine IT dispersion (coverage of the tumor volume). NBTXR3 appears as a hyperdense depot in the injected tissues on the post-treatment CT-scan. Possible diffusion outside of the tumor or lymph node at the time of injection can be prevented by careful choice of the target, slow injection under conditions of low pressure and, for IN injection, real-time imaging of the placement of the needle tip before and during injection of NBTXR3. Of note, MRI and US cannot evaluate the spatial location of NBTXR3, and CT scan should be considered.

Leakage is defined by the loss of NBTXR3 due to a leak through the surface of the mucosa or skin surface. It is easily visualized by the presence of the white suspension on the surface of the tumor, mucosa, or skin. If leakage is observed on the surface of the tumor when starting the IT injection, the injection should be paused, and the leaking product should be aspirated. IT injection can then be resumed avoiding the most superficial parts of the tumor and redistributing the remaining volume into the deeper target areas to limit further loss of the product. Diffusion and leakage may lead to uneven dispersion of NBTXR3 in the target(s). At present, there is no data to suggest that RT dose planning should be modified by the observation of the lack of NBTXR3 is one or more areas of the target(s).

Does NBTXR3 persist within the tumor?

In the phase I trial, local (IT) nanoparticle dispersion and NBTXR3 diffusion or leakage were evaluated by CT scan on Day 2 post injection and during week 7, at the end of RT.[3] These evaluations showed appropriate dispersion of NBTXR3 in the tumors, as well as persistence of NBTXR3 throughout the RT treatment. NBTXR3 will remain in the former tumor bed and has been observed up to 20 months post-RT (Figure 4). No adverse consequences related to this long-term persistence were detected in the phase I study. Blood and urine quantification of hafnium

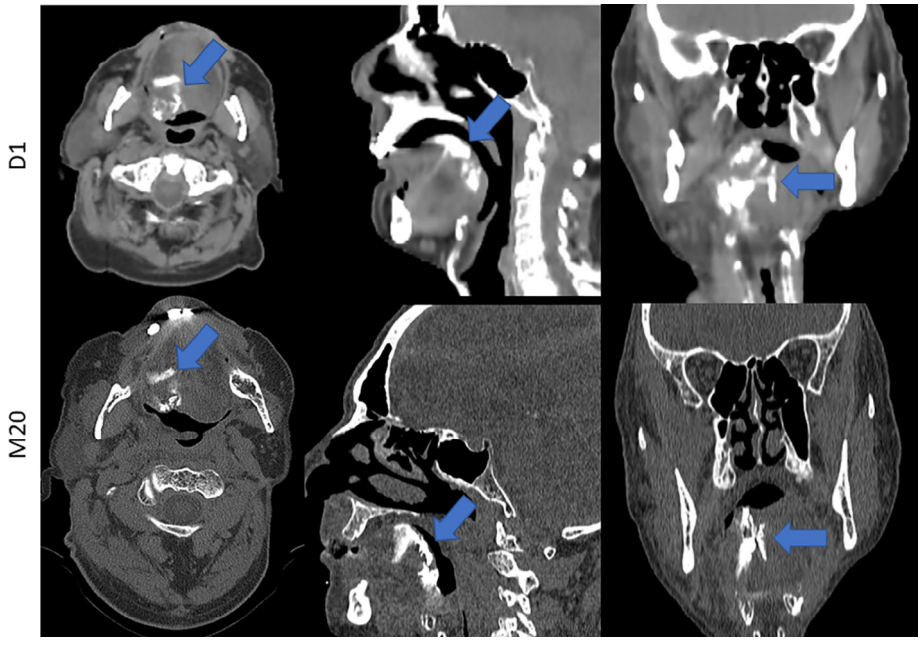

FIGURE 4 CT scans post NBTXR3 intratumoral injection. CT-scan showing the same patient as in Figure 2, 24 h after injections (D1, top row) and 20 months after injection (M20, bottom row), in axial, sagittal and coronal plans from left to right. Blue arrow showing the nanoparticles. [Color figure can be viewed at wileyonlinelibrary.com]
[Color figure can be viewed at wileyonlinelibrary.com]

were performed pre- and post-injection. No NBTXR3 was detected in the urine after injection in any patient. The persistence of NBTXR3 in the tumor/lymph node bed should be expected on follow-up CT scans and PET-CT. To date, there is no specific recommendation on the CT acquisition and reconstruction parameters as NBTXR3 has been readily visualized on CT scans obtained per the usual standard of care.

6 | CONCLUSIONS

Using a robust methodology, we drafted a comprehensive set of consensus guidelines governing the IT and IN injection of NBTXR3. A more detailed version of these guidelines is provided in Data S1. This article aims to harmonize the process of injection and can be used as a basis for the IT and IN injection technique. This harmonization will be particularly important as part of an ongoing randomized phase III trial, in which patients ineligible for cisplatin will receive radiotherapy and NBTXR3 with or without cetuximab (NCT04892173). Ongoing trials with NBTXR3 address other questions such as RT planning or dose modifications, utility in metastatic patients, and combinations with immunotherapy or chemotherapy. Modifications in injection techniques and assessment of product delivery will be modified to meet the emerging needs of these studies.

AUTHOR CONTRIBUTIONS

XL, TdB, JR, and CH: Study design; steering committee; article writing. OIV: Study design; article writing. TYS, CS, ZP, VM, ZTN, FH, JT, ZG, TGH, and CLT: Monitoring committee. SSY, PB, and RLF: Reading committee.

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Nanobiotix participated in the logistical organization and in the development of these guidelines.

CONFLICT OF INTEREST STATEMENT

OIV is an employee of Nanobiotix.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Marill J, Mohamed Anesary N, Paris S. DNA damage enhancement by radiotherapy-activated hafnium oxide nanoparticles improves cGAS-STING pathway activation in human colorectal cancer cells. *Radiother Oncol*. 2019;141:262-266.
2. Zhang P, Darmon A, Marill J, Mohamed Anesary N, Paris S. Radiotherapy-activated hafnium oxide nanoparticles produce abscopal effect in a mouse colorectal cancer model. *Int J Nanomedicine*. 2020;15:3843-3850.
3. Hoffmann C, Calugaru V, Borcoman E, et al. Phase I dose-escalation study of NBTXR3 activated by intensity-modulated radiation therapy in elderly patients with locally advanced squamous cell carcinoma of the oral cavity or oropharynx. *Eur J Cancer*. 2021;146:135-144.
4. Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ (Clin Res Ed)*. 1995;311(7001):376-380.
5. Dalkey N. An experimental study of group opinion: the Delphi method. *Futures*. 1969;1(5):408-426.
6. Tselikas L, Champiat S, Sheth RA, et al. Interventional radiology for local immunotherapy in oncology. *Clin Cancer Res*. 2021;27:2698-2705.
7. Marabelle A, Andtbacka R, Harrington K, et al. Starting the fight in the tumor: expert recommendations for the development of human intratumoral immunotherapy (HIT-IT). *Ann Oncol*. 2018;29(11):2163-2174.
8. Prud'homme C, Deschamps F, Allorant A, et al. Image-guided tumour biopsies in a prospective molecular triage study (MOSCATO-01): What are the real risks? *Eur J Cancer*. 2018;103:108-119.
9. Bonvalot S, Rutkowski PL, Thariat J, et al. NBTXR3, a first-in-class radioenhancer hafnium oxide nanoparticle, plus radiotherapy versus radiotherapy alone in patients with locally advanced soft-tissue sarcoma (Act.In.Sarc): a multicentre, phase 2-3, randomised, controlled trial. *Lancet Oncol*. 2019;20(8):1148-1159.
10. Ginat DT, Juloori A, Vivar OI, Farber LA, Gooi Z, Rosenberg AJ. Imaging features of intratumoral injection of NBTXR3 for head and neck squamous cell carcinoma lymph node metastases. *Diagnostics*. 2022;12(9):2156.
11. Ito Y, Tomoda C, Uruno T, et al. Needle tract implantation of papillary thyroid carcinoma after fine-needle aspiration biopsy. *World J Surg*. 2005;29(12):1544-1549.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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