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Salvage photodynamic therapy for recurrent nasopharyngeal carcinoma

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KEYWORDS
Photodynamic therapy;
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Summary
Background: To evaluate the feasibility of photodynamic therapy (NP-PDT) in the palliative management of recurrent/persistent nasopharyngeal cancer (NFC).
Methods: Six patients with persistent/recurrent NPC underwent PDT with palliative intent. NP-PDT was delivered by three different methods depending on the localization, size and depth of the lesion: type I NP-PDT: transnasal direct illumination of postero-superior recurrence; type II NP-PDT: transnasal direct illumination of the whole nasopharynx; type III NP-PDT: transoral direct or interstitial illumination of lateral recurrence. In this case, the ENT-magnetic navigation system (MNS) was extremely useful in identifying the tumor and its distance from the ICA.
Results: Both patients treated with NP-PDT type I are free from disease at 38 and 71 months after treatment; both patients treated with NP-PDT type II experienced further local and loco-regional recurrence of disease within 16 months; one died of the disease while the second underwent a second palliative treatment, NP-PDT type I, and is currently living with the disease; of the two patients who underwent NP-PDT type III, one died as a result of regional and systemic recurrence without local recurrence while the second experienced a superficial recurrence. He underwent a second NP-PDT type III treatment and is currently free from disease at 21 months.
Conclusions: NP-PDT is a non-invasive and simple treatment modality that may have an important role in the treatment of selected cases of persistent/recurrent NPC in its early stage, not suitable for a conventional therapeutic protocol. Coupling NP-PDT with the ENT-MNS can be an effective strategy to obtain more precise light delivery within the tumor, particularly in lateral and parapharyngeal localization.

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Introduction

Nasopharyngeal cancer (NPC), a tumor of epithelial origin, represents 90% of neoplasms that develop in the nasopharynx (NP). It occurs sporadically in Western countries, but is endemic in certain parts of South-East Asia (southern China, the Indonesian archipelago) [1]. The worldwide incidence of NPC exceeds 80,000 new cases/year with 19,616 new cases each year in southern China [2]. Epidemiological data are scarce and imprecise. The incidence rate, however, shows important geographical variations and depends on many risk factors [Epstein—Barr virus, genetic and environmental factors, alimentary habits (smoked and salted food)] [3,4].

The gold standard for primary NPC treatment is radiotherapy, combined with chemotherapy in advanced stages. Despite the good responsiveness of NPC, the long-term survival (10 years) of the disease ranges between 67% and 71% for T1-2/N0-1 and between 29% and 54% for locally advanced stages (T3-4 and N2-3). These results are justified by the high local recurrence rate (63.8%) in stages III—IV and the high rate of distant metastases (approximately 50%) in the T1-2/N2-3 category [4—6].

Several options are available for the treatment of local recurrent/persistent NPC — surgery (open or endoscopic approach), external re-irradiation, or brachytherapy [7—9] alone or in combination with external re-irradiation [10] or stereotactic radiosurgery [11]. All of these options have advantages and disadvantages, poor survival outcomes and severe side effects. Only nasopharyngeal endoscopic resection seems to have made a significant contribution to the reduction of complications [12].

Photodynamic therapy (PDT) can represent a valid alternative in the treatment of selected recurrent NPC in its early stage, with either curative or palliative intent [13—15]. In the present study, we report our experiences in palliative management with PDT for six locally recurrent NPC, localized in different nasopharyngeal sites and treated using three different protocols.

In two cases, PDT has been carried out with the aid of the ENT-magnetic navigation system (MNS) to obtain maximum precision in the delivery of light and we are the first to describe the ergonomics of this technique.

The aim of the study was to define the precise indications for this type of therapy depending on the tumor site, to describe the different ways of delivering light to the tumor with great precision, and to report our preliminary results in terms of complications and local control.

Materials and methods

Between January 2005 and December 2010, six patients (five males and one female) affected by persistent/recurrent NPC underwent PDT with palliative intent at the ENT Department of Martini Hospital in Turin. All patients had previously received external beam radiotherapy on the primary site and neck, with or without concurrent chemotherapy. A bilateral neck dissection was performed on one patient 60 days after the end of chemo-radiotherapy due to cervical persistence of disease.

All locally recurrent NPC were fully investigated to confirm the stage in the primary site and the status of the cervical lymph nodes. The investigations included posterior rhinoscopy with biopsy, maxillofacial and neck MRI or CT-scan, chest X-ray, and total body PET-scan. All patients showed histologically proven local persistence/recurrence of NPC classified as rT1 and rT2a according to the 2007 (7th Edition) Union Internationale Contre le Cancer (UICC)/American Joint Committee on Cancer (AJCC) TNM system. As a rule, only cases without neck recurrence and distant metastasis were considered for PDT.

In three cases, it was not possible to offer alternative treatments because of poor general condition or severe comorbidities while in the remaining three cases, patients did not accept the conventional (surgery or re-irradiation) treatments proposed.

The treatment protocol was approved by the Ethics Committee of Martini Hospital of Turin and the patients signed a specific informed consent before the procedure.

Photodynamic therapy

All patients were subjected to slow intravenous injection ($\geq$6 min) of Temoporfin (Foscan®) at a dose of 0.15 mg/kg with activation of the drug after 96 h. In the time interval between administration of the drug and its activation (DLI), the patients were maintained at home in a darkened room (curtains drawn, light bulbs no brighter than 60 W) (not more than 200 lux).

In all cases, the illumination was performed in the operating room under general anesthesia, for optimal patient comfort and to obtain a better exposure of the lesion. For activation, a laser light of wavelength 652 nm was used, at a dose of 20 J/cm^2 and an intensity of 100 mW/cm^2 for 200 s. Photosensitizer activation was achieved with a diode laser system (Biolitech), delivering light using fiber optics with a microlens for superficial illumination or through a cylindrical/bare fiber optic inserted within the mass for interstitial illumination of the tumor. Normal laser safety precautions were required for the patient.

In the postoperative period, the patients received therapy with antibiotics, opiates and non-steroidal anti-inflammatory drugs.

Exposure to light was gradually increased to about 200 lux per day over a period of approximately 2 weeks, giving an average hospitalization of 8.3 days (min. 6 days, max. 15 days).

After discharge, the patients received regular follow-up scheduled at 15, 30, and 60 days after the procedure and then every 2 months, during which the degree of response to treatment and any complications or sequelae were evaluated. A control biopsy and a maxillofacial/neck MRI-CT-scan were performed, not earlier than 12 weeks after PDT. A complete disappearance of the lesion with negative biopsy was defined as complete response (CR), a reduction of more 50% of the volume of the lesion with positive biopsy was defined as partial response (PR), and a lack of response or progression of the disease as null response (NR).

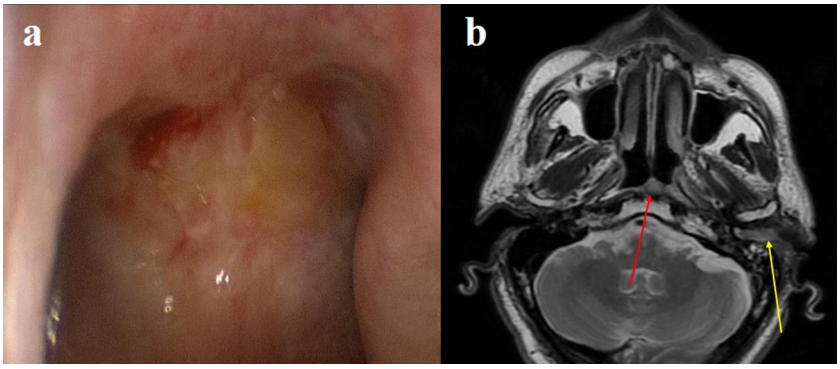

Fig. 1 (a) Small recurrence at the nasopharyngeal postero-superior wall (rT1). (b) The MRI shows the superficial nasopharyngeal recurrence (red arrow) and a second primary tumor at the external auditory canal (yellow arrow).

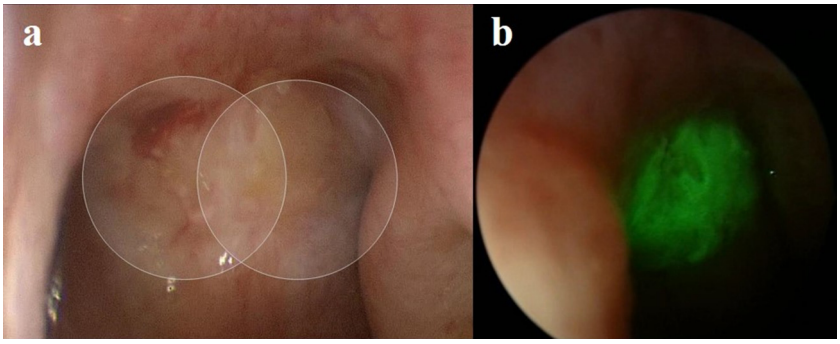

Fig. 2 Type I NP-PDT. (a) Illumination planning. (b) The green guiding light during the treatment shows a safety margin on the left side.

Type I NP-PDT: transnasal direct illumination of postero-superior recurrence

Two patients had a small-sized recurrence at the nasopharyngeal postero-superior wall (rT1). The first case was a persistence after chemo-radiotherapy interruption due to the onset of a demyelinating neuropathy. The second case was a recurrent NPC, 12 years after the previous chemo-radiotherapy, associated with a second primary tumor localized to the external auditory canal and extending to the parotid gland (Fig. 1a and b). The patient underwent an initial surgical procedure (subtotal petrosectomy, total parotidectomy, neck dissection) and then declined any further treatment other than radiotherapy on the neck and temporal region; in particular, the patient refused an endoscopic resection of recurrent NPC. In these cases, we proceeded to a superficial treatment by transnasal direct illumination through both nasal cavities. A laser fiber optic was used with a 0°, 4 mm telescope (Karl-Storz, Tuttlingen, Germany). One or multiple spots were planned to illuminate the visible lesion, depending on the diameter and morphology of the tumor (Fig. 2a and b). As in ordinary surgery, a safety margin of 0.5—1 cm, enclosing normal tissue around the tumor, was included in the treatment field (Figs. 3—7).

Results

No side effects were observed in patients during drug injection for PDT. PDT was well tolerated and in the postoperative period, all patients complained of pain, especially during swallowing. In one patient, a nasogastric tube (NGT) was necessary temporarily, due to intense dysphagia. In one patient, we observed acute skin toxicity from early exposure to light, with second-degree burns to the forearm which were treated with medical dressing.

Patients undergoing superficial or blended precision PDT (Type I or Type II NP-PDT) complained of nasopharyngeal burns of lower grade than patients treated with Van Veen's applicator (Type III NP-PDT) (Fig. 8a—c). Five out six patients (83.3%) showed a CR to treatment and only in one case was there a PR. The follow-up period ranged from 24 to 71

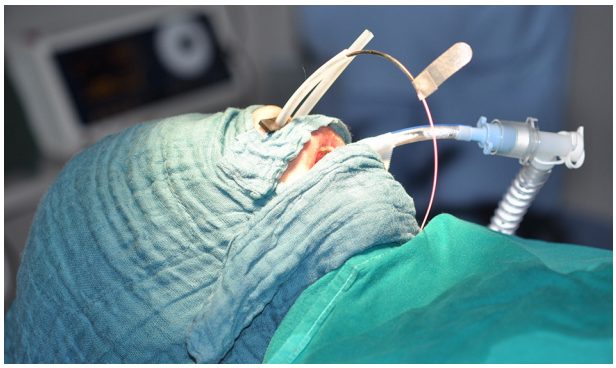

Fig. 3 Type II NP-PDT: transnasal direct illumination of the whole nasopharynx, using Van Veen's device. Single contemporary illumination.

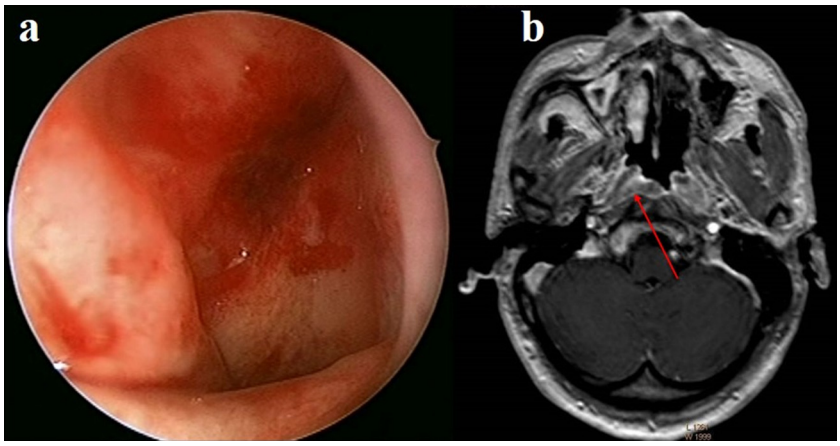

Fig. 4 (a) Recurrence at the lateral nasopharyngeal wall (rT1) in Rosenmüller's fossa. (b) The MRI shows a recurrence involving Rosenmüller's fossa toward the parapharyngeal space (red arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

months; at the time of last follow-up, three patients (50%) were free from disease, one (16.6%) was alive with disease and two (33.3%) had died from disease. No postoperative adjuvant treatment was delivered (Fig. 9).

Both patients treated with NP-PDT type I are free from disease at follow-up of 71 and 38 months, respectively. One patient developed a regional recurrence 28 months after PDT and underwent modified radical neck dissection (Table 1).

Discussion

Different strategies are available for the salvage treatment of early-stage local failures of NPC: surgery ± radiotherapy, brachytherapy alone [7—9] or in combination with external re-irradiation [10] and finally, stereotactic radiosurgery [16]. The standard treatment for advanced recurrent/persistent NPC is sequential or concomitant chemo-re-irradiation [11].

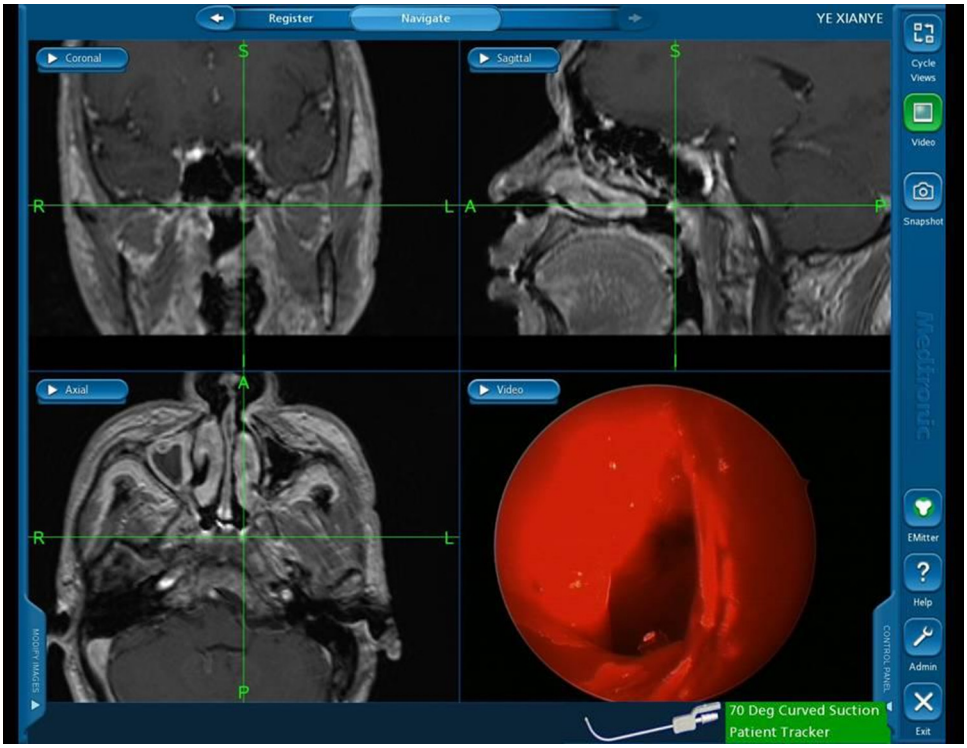

Fig. 5 Type III NP-PDT: transoral direct illumination of lateral nasopharyngeal wall. The use of ENT-MNS and transnasal endoscopy allows a double control, optical and radiological.

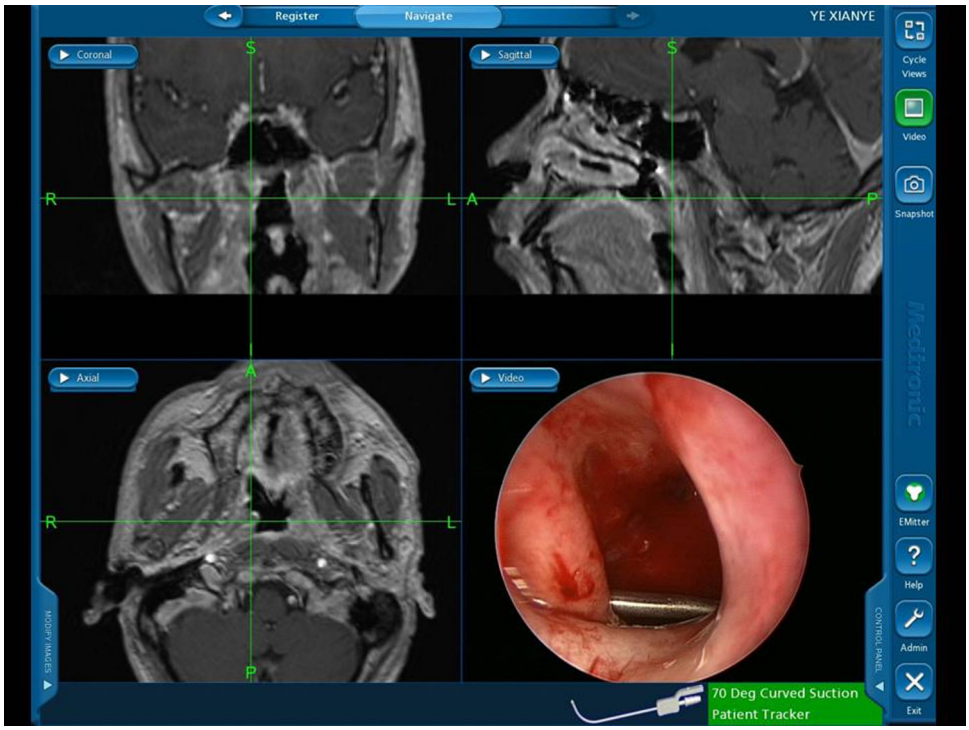

Fig. 6 Type III NP-PDT: transoral interstitial illumination of lateral nasopharyngeal wall. The use of ENT-MNS and transnasal endoscopy allows a double control, optical and radiological.

The unsatisfactory surgical exposure and the high frequency of destructive surgical complications using open approaches have prompted the development of a minimally invasive surgical method to overcome the limitations of current surgical methodologies. Endoscopic procedures have opened new and innovative surgical possibilities [12].

In a series of 17 consecutive patients with primary or recurrent NPC treated with pure endoscopic resection, Castelnuovo et al. [12] have classified three different types of nasopharyngeal endoscopic resection (NER), graded from 1 to 3 on the basis of the extent of resection, with 71% disease-free survival and a median follow-up of 41 months.

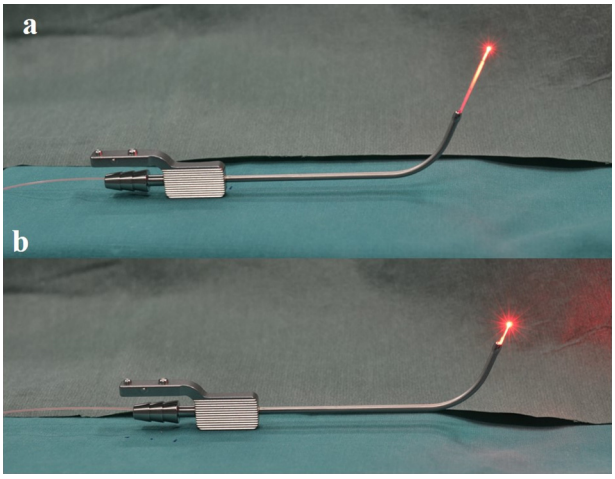

Fig. 7 Type III NP-PDT: transoral interstitial illumination of lateral nasopharyngeal wall. The previously marked bare fiber optic is inserted inside the curved suction cannula coupled to the ENT-MNS. (a) Starting position for pull-back illumination; (b) final position.

In this scenario, PDT could represent a straightforward and effective alternative treatment option. In the literature, several articles have shown that PDT is effective in destroying NPC, with good local control of tumor growth and complete responses in the majority of small recurrent or persistent disease (rT1—T2) and long-term palliation in advanced stage (rT3—T4) disease [13,15].

By analyzing the cases in this series, it can be said that three out of six cases could have been submitted to a surgical or radio-chemotherapy salvage treatment with an excellent chance of success, but this was not possible because the patients would only accept minimally invasive palliative treatment. In the remaining three cases, because of the severe comorbidity, it was not possible to suggest any conventional salvage treatment. Despite the limitations related to a palliative therapy outcome, NP-PDT has been performed using the same principles underlying the endoscopic resections, such as preoperative imaging evaluation and the maximum accuracy in directing the light, obtained by endoscopic control coupled with the ENT MNS. This is first time that the use of this technology coupled with PDT for the treatment of recurrent NPC has been described.

PDT is essentially a cancer treatment working on the surface of the tumor; its limitation is related to the fact that light needed to activate most photosensitizers cannot pass through more than about 1 cm of tissue. In order to treat deeper lesions, it is necessary to deliver the activating light inside the lesion by diffusion from cylindrical or bare fiber optics, thus obtaining interstitial PDT (IPDT). Positioning the

Table 1 Clinical characteristics of patients.

N	Gender	Age	AJCC TNM stage at diagnosis	Primary treatment	AJCC TNM stage at recurrence	Time of recurrence (mo)	Type of NP-PDT	Response to PDT	Site and time of further recurrence (mo)	Further treatment	Follow-up
1	F	56	T2N0M0	CHT-RT	rT1N0M0	6	I	CR	Regional	mRND	NED (71 mo)
2	M	54	T2N0M0	CHT-RT	rT1N0M0	144	I	CR	Regional	—	NED (38 mo)
3	M	65	T1N0M0	RT	rT1N0M0	12	II	PR	Loco-regional	NP-PDT type I	LWD (25 mo)
4	M	59	T2N0M0	CHT-RT+ neck dissection	rT2N0M0	27	II	CR	Loco-regional [12]	—	DWD (20 mo)
5	M	37	T2N2bM0	CHT-RT+ neck dissection	rT1N0M0	48	III	CR	Local [12]	NP-PDT type III	NED (21 mo)
6	M	67	T2N0M0	CHT-RT	rT2N0M0	36	III	CR	Regional + systemic [16]	—	DWD (28 mo)

CHT, chemotherapy; RT, radiotherapy; CR, complete response; PR, partial response; NP-PDT, nasopharyngeal photodynamic therapy; mRND, modified radical neck dissection; NED, no evidence of disease; DWD, died with disease; LWD, living with disease.

fibers about 1.5 cm away from each other will deliver the activating light within the tumor, providing sufficient overlap and avoiding less illuminated areas.

In view of these physical characteristics of light diffusibility, the treatment of recurrent NPC is substantially different depending on the site. Recurrence localized to the posterior wall/roof of the nasopharynx is broadly superficial, in most cases not thicker than 1 cm, with underlying bone (bony floor of the sphenoid sinus, ventral portion of the clivus, atlas) and absence of important anatomical structures. The most ergonomic option for light delivery is the direct transnasal route (NP-PDT type I), with the fiber optics carried on a 0° 4 mm telescope, normally used in endoscopic sinus surgery. The light thus reaches the treatment area perpendicularly, with maximum tissue penetration and easily reaching the underlying bone. By reducing the endoscopic white light, the bright green light of the diode laser is dominant, which allows the PDT activating light to be targeted with great precision, with intensity equal to 652 nm. If the tumor affects a large portion of the posterior wall, multiple spots can be used, passing through both nasal fossae.

When the recurrence affects the lateral nasopharyngeal wall, we are dealing with a tumor extending deeper into Rosenmüller's fossa, involving peritubaric and parapharyngeal tissue. It is therefore absolutely necessary to accurately identify important structures such as the ICA and know the distance separating the vessel from the tumor. Previous experience has shown that PDT is not indicated when the tumor directly affects the adventitia of the arterial vessel, placing it at risk of rupture [18,19]. It is clear, therefore, that superficial PDT can only treat the vegetating portion of the tumor, whereas it is impossible to treat the tumor in Rosenmüller's fossa and peritubaric tissues without using IPDT.

To overcome these technical aspects, coupling NP-PDT with the ENT-MNS seemed interesting using transoral access for treatment and transnasal access for endoscopic control (NP-PDT type II). With this solution, the distance between the lighting fiber optic tip carried on a navigated curved suction cannula and the area to be illuminated is larger, thus obtaining a spot of adequate size, a more perpendicular orientation of the light and very good control thanks to endoscopy and probe direction assessment.

The same strategy was adopted in IPDT for treatment of the deep part of the tumor; the tip of the navigated curved suction cannula was positioned in contact with the tumor at the level of Rosenmüller's fossa and the bare fiber optic for pull-back lighting was introduced into the tumor reaching the distal end. The ENT-MNS was extremely useful to accurately identify the tumor and its distance from the ICA, providing the surgeon with accurate and continuous intraoperative monitoring of treatment accuracy.

The third adopted strategy for treatment of bulky recurrences, involving more NP subsites, was NP-PDT with Van Veen's device [17] (NP-PDT type III), similar to that used for brachytherapy. This device allows an extensive superficial treatment of the NP and, compared to the two other types of treatment, results in lower selectivity, the inability to treat the deeper part of the tumor and a lengthy postoperative period, as a result of lighting of the whole NP. In our opinion, such treatment can be advantageously replaced by a more precise PDT, arising from the routine use of the navigator.

It can therefore be said that precision PDT, coupled with the above described systems, is potentially able to achieve the same effectiveness as NER only on the soft tissues of the NP and adjacent sites but is obviously limited because it is

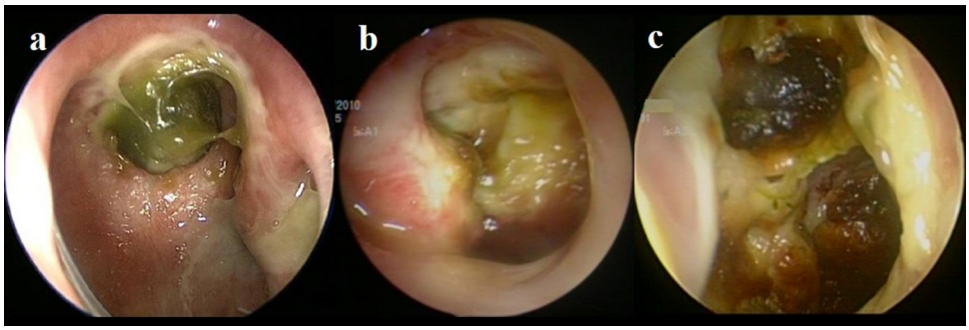

Fig. 8 Early endoscopic control after NP-PDT, showing different grades of nasopharyngeal burns. (a) Type I NP-PDT; (b) Type III NP-PDT; (c) Type II NP-PDT.

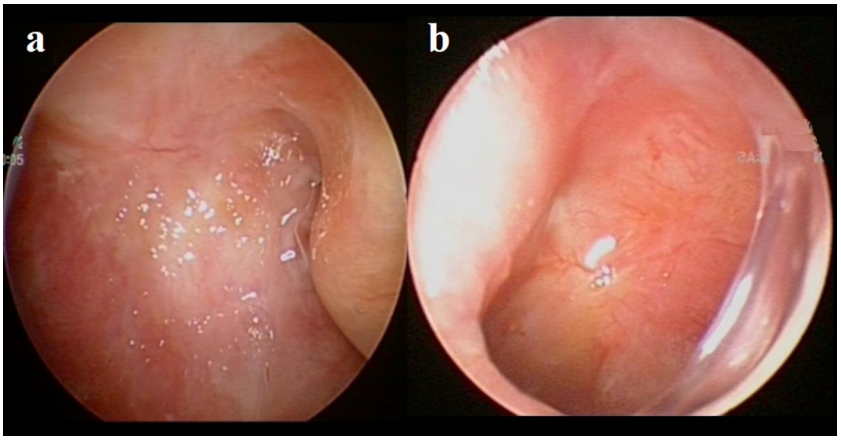

Fig. 9 Endoscopic follow-up control after NP-PDT. (a) Type I NP-PDT: no evidence of disease (NED) at 71 mo; (b) Type III NP-PDT: NED at 24 mo.

not able to resect the underlying bone tissue; this theoretically puts NP-PDT at a lower level of effectiveness compared to NER, which should therefore be considered to be the standard conventional treatment at the present time. On the other hand, NP-PDT is a simpler method, rapid and easily repeatable, especially using the ENT-MNS. In our study, NP-PDT offered to patients as palliative therapy to treat slow tumor growth has proved to be a very effective local treatment, without severe side effects, resulting in good disease-free survival (50%), and comparable with other salvage treatments.

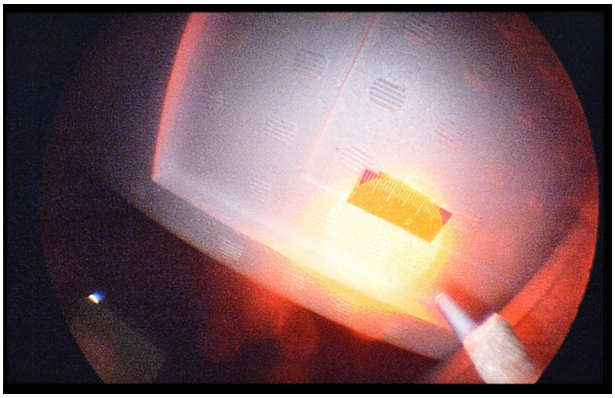

Fig. 10 Possible refinement of endoscopic control in Type III NP-PDT: the navigated curved suction cannula and fiber optic are tethered to a 70° angled telescope that allows coaxial vision with the laser light.

Another important advantage is its repeatability, as shown in this series. PDT does not have cumulative effects. In the case of a partial response, the same area could be illuminated again.

Further refinements of the technique are possible. The possibility to tether a 70° angled telescope to the curved probe coupled to the MNS is under study in order to obtain coaxial optical control of the area to be illuminated by transoral access (Fig. 10) as well as trying to illuminate the lateral nasopharyngeal wall by positioning the 70° telescope tethered to a curved suction cannula in the contralateral choana.

Conclusions

Precision NP-PDT may have a significant role in the treatment of selected persistent/recurrent NPC (rT1—T2a) not suitable for further conventional treatment. The preliminary survival outcomes appear encouraging, and are comparable with other salvage treatments. The main advantages of PDT are the lower morbidity, the repeatability, the improved preservation of surrounding tissues and negligible side effects.

Although preliminary results are encouraging and considering the good precision that comes with coupling NP-PDT and the ENT-MNS, more clinical experience in terms of the knowledge of proper light dosimetry, as is performed in radiotherapy, is still needed to fully address the role of photodynamic therapy as a salvage treatment option for persistent/recurrent nasopharyngeal carcinoma.

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Conflict of interest

There are no competing interests for this article.

Author contributions

Giovanni Succo, surgeon who performed the surgical procedures, conception and design, drafting the article, and final approval of the version to be published; Stefano Rosso, surgeon who performed the surgical procedures, conception and design; Gian Luca Fadda and Marco Fantini collected the data and organized the last follow-up; Erika Crosetti, surgeon who performed the surgical procedures, conception and design, drafting the article, and final approval of the version to be published.

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