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**Head and neck**

# Interventional radiotherapy (brachytherapy) for re-irradiation of recurrent head and neck malignancies: oncologic outcomes and morbidity

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SUMMARY

**Objective**. Management of recurrent head and neck cancer (HNC) is challenging. One option in previously irradiated patients is re-irradiation using interventional radiotherapy (IRT), the modern form of brachytherapy. Re-irradiation using IRT can be delivered as an exclusive strategy for salvage or through a postoperative or perioperative approach after salvage surgery. The aim of the present study is to analyse a bicentric Italian series focusing on the use of IRT as a re-irradiation modality and assess the resulting evidence concerning oncologic outcomes and morbidity.

**Methods**. This is a retrospective study performed in two referral centres in Italy: Policlinico Universitario Agostino Gemelli in Rome and Azienda Ospedaliera Universitaria in Sassari. All patients who had previously received a full course of external beam RT and have been re-irradiated using high-dose-rate IRT between December 2010 and June 2023 were included. Patients were retreated either by a combination of surgery and perioperative (either endocavitary or interstitial) IRT or by exclusive interstitial IRT.

**Results**. Thirty-four patients were included in the present series, 2 of whom underwent more than one IRT re-irradiation. Notably, no patient reported specific IRT-related toxicities. Median follow-up, excluding patients who died of HNC, was 24.5 months. Two-year local relapse-free survival was 26%, disease-specific survival 39.1%, and overall survival 36.6%.

**Conclusions**. The present series is the largest reported experience of re-irradiation by IRT for HNC in Italy. The very low rate of toxicity confirms IRT as the safest re-irradiation modality. It is noteworthy to underline that IRT is a multidisciplinary strategy based on the close cooperation between surgeons and radiation oncologists during every phase, from the recommendation of treatment and implantation in the operating theatre, to its prescription and dose painting.

KEY WORDS: head and neck cancer, interventional radiotherapy, brachytherapy, radiotherapy, re-irradiation

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## Introduction

Head and neck cancer (HNC) is the sixth most common cancer globally, and despite recent oncologic advancements, nearly 50% of patients experience a recurrence within two years of initial treatment [1]. Management of recurrent HNC is challenging. Re-irradiation represents a potential treatment option in already irradi-

ated cases: even if potentially associated to a certain degree of toxicity and limited data about its effectiveness are so far available, its indications are evolving thanks to emerging evidence and technological advancements [1]. In fact, in the last decades, brachytherapy (BT), has drastically changed and improved through dramatic technical developments, such as intensity dose modulation and image guidance, leading to a "new" proposed definition as "Interventional Radiotherapy" (IRT) in order to stress the differences with the older technique [2].

Various studies have highlighted the potential of high-dose-rate (HDR) BT (both in its old forms and as IRT) for re-irradiation in recurrent HNCs [3,4]; however, its use is still limited because of the low level of evidence, its limited access and the underdeveloped education systems [3-5]. In fact, according to the Oxford Levels of Evidence, most studies may be considered as level 4.

Re-irradiation for salvage using IRT can be delivered as an exclusive strategy or through a postoperative or perioperative approach, combined with surgery.

Our team previously described its experience, updated to July 2017 [4], and attempting to classify IRT treatments according to the underlying clinical needs, combination with surgery and implantation modality. In three of four groups described (I, II, III), namely recurrent cases, IRT was most often used to deliver re-irradiation after external beam radiotherapy (EBRT). In the present experience, we propose an update of the previous classification in order to include more clinical scenarios for the use of IRT (Tab. I).

**Table I.** Classification of IRT treatments (modified from Bussu et al., 2023 [6]), according to the underlying clinical needs, combination with surgery, and implantation modality (endocavitary *vs* interstitial).

| Group (updated classification) | Group (Bussu et al., 2019 [4]) | Clinical needs | Definition | Combination | Implantation modality | Main type of surgery used | Main clinical targets |
|---|---|---|---|---|---|---|---|
| **I. IRT boost integrated with EBRT** | **NA** | Reduce toxicity, increase effectiveness of EBRT | Integration with EBRT for dose escalation and toxicity reduction | Integrated with EBRT | Mixed | None | Oropharynx, nasopharynx, orbit |
| **II. Adjuvant IRT** | **NA** | Deliver effective adjuvant dose with reduced toxicity | Postoperative implant in case of adverse features at histopathology and focal approach could be better than EBRT | Postoperative/ perioperative | Mixed | Open surgery | Oral cavity, orbit |
| **IIIin. Perioperative/ postoperative interstitial re-irradiation** | **III** | Deliver effective dose after surgery in already irradiated cases | Perioperative (implant during surgery) or postoperative (implant after surgery in case of adverse features at histopathology) approach for a previously irradiated local recurrence | Postoperative/ perioperative | Interstitial | Open surgery with reconstruction | Neck/salivary glands/ oropharynx, orbit |
| **IIIec. Perioperative/ postoperative endocavitary re-irradiation** | **II** | Deliver effective dose after surgery in already irradiated cases | Perioperative (implant during surgery) or postoperative (implant after surgery in case of adverse features at histopathology) approach for a previously irradiated local recurrence | Postoperative/ perioperative | Endocavitary | Endoscopic resection | Nose/paranasal sinuses/ nasopharynx |
| **IV. Exclusive IRT re-irradiation** | **I** | Deliver curative dose in the re-irradiation setting | Exclusive approach for a previously irradiated local or neck recurrence | Exclusive | Interstitial | None | Oral cavity, neck, orbit |
| **V. Exclusive primary IRT** | **IV** | Preserve anatomy without compromising survival | Exclusive IRT for malignancies for which surgical reconstruction was not expected to be fully satisfactory | Exclusive | Mixed | None | Nasal vestibule, cheek, eyelid, lip |

*NA: not available; IRT: interventional radiotherapy; EBRT: external beam radiotherapy.*

In the last six years IRT has been increasingly used in midface malignancies (former group IV, current group V, Table I) and is currently being advocated as the standard treatment for primary nasal vestibule squamous cell carcinomas [6-8].

The aim of the present study is to update the previous series focusing on the use of IRT as a re-irradiation modality, and assess the resulting evidence on oncologic outcomes and morbidity.

## Materials and methods

*Patients*

This is a retrospective study performed in two referral centres in Italy: Policlinico Universitario Agostino Gemelli in Rome and Azienda Ospedaliera Universitaria in Sassari. In both institutions multidisciplinary tumour boards manage all patients with HNC in every phase, collecting demographic and clinical data in secure electronic databases. All patients re-irradiated by HDR IRT in both institutions between December 2010 and June 2023 were included. However, IRT became available in Sassari only from March 2022, through Mater Olbia Hospital which participates in the Northern Sardinia head and neck tumour board.

Three HDR IRT second or third re-irradiations were recommended and performed, after obtaining informed consent, on 2 patients.

*Clinical settings*

IRT was used in a wide range of clinical scenarios in terms of histology, primary site, IRT target, and type of implant. Therefore, we classified our re-irradiation cases according to Table I, modified from Bussu et al. [4], in the groups IIIec, IIIin, and IV:

- Group IIIec (former group II): perioperative endocavitary IRT for recurrent nasal/paranasal/nasopharyngeal malignancy. An IRT re-irradiation after salvage surgery was considered to be rational and potentially useful. Surgery was most often performed through an endoscopic approach, and the implant in these cases was performed at the end of surgical resection under endoscopic guidance (endoscopy-guided IRT, EG-IRT) [5];
- Group IIIin (former group III): perioperative interstitial IRT for neck recurrence of a malignancy previously irradiated by EBRT when a re-irradiation was considered to be rational and potentially useful after salvage surgery, also because of extracapsular spread. The plastic tubes were always placed at the end of surgical resection and before flap in-setting when reconstruction was performed [5];
- Group IV (former group I): exclusive interstitial IRT in recurrences of malignancies already irradiated by EBRT when radical resection was considered unfeasible (poor general conditions, carotid involvement, 3rd/4th extensive recurrence, heavy fibrosis in already irradiated neck, etc.).

*Treatment modalities: surgery*

In group III, we never performed surgical debulking: the aim of salvage surgery was always an R0 resection. The need for reconstruction was always preoperatively evaluated. Local, regional or free flaps were used for reconstruction when needed (Tab. II).

*Treatment modalities: IRT*

Plastic tubes were always placed in the operating room in the presence of surgeons and interventional radiation oncologists under general anaesthesia in all cases except 4 (3 patients with lower lip and one with cheek cancer) in which implants were placed under local anaesthesia because of anaesthesiology concerns. Flexible Implant 6F Tubes were inserted, spaced 0.8-1.2 cm apart, using guide metal channels previously placed with a needle, and fixed by buttons sutured to the skin. Specific additional technical tricks were used, especially in group IIIec, when needed, as previously described [5,9]. The exact configuration and number of catheters were always tailored to the target volume's extent, depth, and shape. The dose was prescribed to encompass the total clinical target volume (CTV) and spare as much of the surrounding healthy structures as possible.

The total dose of the first IRT was always 30 Gy in 12 fractions of 2.5 Gy each, twice daily for five days per week [5]. The dose of the three IRT re-treatments in group IIIec (one patient underwent 2 further IRT treatments and another one received a further IRT treatment) was defined in every single treatment plan, considering the dose to the target and the organs at risk.

All patients underwent computed tomography (CT) scan after the implant. CTV and organs at risk were contoured and catheters were reconstructed. After this, the CTV contouring was always discussed with the surgeon as a follow-up of the surgical implantation phase to ensure that the entire area of the tumour bed and the areas at risk for recurrence were fully covered by the dose prescribed. Treatment planning was implemented with manual optimisation under direct supervision of a radiation oncologist. Radiation oncologists and surgeons discussed the final dose distribution to ensure that the prescription dose covered the entire tumour bed area. Irradiation started between the 3rd and 5th day following implantation. The dose distribution to the surrounding normal tissues was defined according to the QUANTEC constraints. All patients were treated with an HDR after-loading machine containing an Ir-192 point-source.

**Table II.** Descriptive statistics of the IRT re-irradiation series (n = 34 patients). In case of patients undergoing multiple treatments (both in group IIIec), only the first IRT has been considered in the present table.

| Features | | Group IV (n = 5; 14.6%) | Group IIIec (n = 14; 41.2%) | Group IIIin (n = 15; 44.2%) | Entire series (n = 34; 100%) |
|---|---|---|---|---|---|
| **Mean age** | Years | 70 | 61.9 | 61.6 | 64.5 |
| **Sex** | Male | 2 (40%) | 10 (71.4%) | 11 (73.4%) | 23 (67.6%) |
| | Female | 3 (60%) | 4 (28.6%) | 4 (26.6%) | 11 (32.4%) |
| **Interventional radiotherapy delivery** | Endocavitary | 0 (0%) | 14 (100%) | 0 (0%) | 14 (41.2%) |
| | Interstitial | 5 (100%) | 0 (0%) | 15 (100%) | 20 (58.8%) |
| **Exclusive/perioperative** | Exclusive | 5 (100%) | 0 (0%) | 0 (0%) | 5 (14.7%) |
| | Perioperative | 0 (0%) | 14 (100%) | 15 (100%) | 29 (85.3%) |
| **Primary site** | Ethmoid | 0 (0%) | 3 (21.4%) | 0 (0%) | 3 (8.8%) |
| | Hypopharynx | 0 (0%) | 0 (0%) | 2 (13.3%) | 2 (5.9%) |
| | Larynx | 0 (0%) | 0 (0%) | 3 (20%) | 3 (8.8%) |
| | Nasal cavity | 0 (0%) | 2 (14.3%) | 0 (0%) | 2 (5.9%) |
| | Nasal vestibule | 2 (40%) | 0 (0%) | 0 (0%) | 2 (5.9%) |
| | Nasopharynx | 3 (60%) | 9 (64.3%) | 0 (0%) | 9 (26.6%) |
| | Oral cavity | 0 (0%) | 0 (0%) | 4 (26.6%) | 7 (20.6%) |
| | Oropharynx | 0 (0%) | 0 (0%) | 2 (13.3%) | 2 (5.9%) |
| | Parotid gland | 0 (0%) | 0 (0%) | 1 (6.7%) | 1 (2.9%) |
| | Skin | 0 (0%) | 0 (0%) | 1 (6.7%) | 1 (2.9%) |
| | Submandibular gland | 0 (0%) | 0 (0%) | 1 (6.7%) | 1 (2.9%) |
| | Unknown primary | 0 (0%) | 0 (0%) | 1 (6.7%) | 1 (2.9%) |
| **Histology** | Adenocarcinoma | 0 (0%) | 2 (14.3%) | 0 (0%) | 2 (5.9%) |
| | Adenoid cystic | 0 (0%) | 1 (7.1%) | 0 (0%) | 1 (2.9%) |
| | Malignant mixed tumour | 0 (0%) | 0 (0%) | 1 (6.7%) | 1 (2.9%) |
| | Melanoma | 0 (0%) | 1 (7.1%) | 0 (0%) | 1 (2.9%) |
| | Mucoepidermoid | 0 (0%) | 0 (0%) | 1 (6.7%) | 1 (2.9%) |
| | SCC | 5 (100%) | 10 (71.5%) | 13 (86.6%) | 28 (82.5%) |
| **Combined with CT** | No | 5 (100%) | 11 (78.6%) | 15 (100%) | 31 (91.2%) |
| | Yes | 0 (0%) | 3 (21.4%) | 0 (0%) | 3 (8.8%) |
| **Primary treatment** | EBRT | 2 (40%) | 9 (64.3%) | 5 (33.3%) | 16 (47.1%) |
| | Surgery + EBRT | 3 (60%) | 5 (35.7%) | 10 (66.7%) | 18 (52.9%) |
| **Interventional radiotherapy target** | Ethmoid | 0 (0%) | 3 (21.4%) | 0 (0%) | 3 (8.8%) |
| | Midface | 2 (40%) | 0 (0%) | 0 (0%) | 2 (5.9%) |
| | Nasal cavity | 0 (0%) | 2 (14.3%) | 0 (0%) | 2 (5.9%) |
| | Nasopharynx | 0 (0%) | 9 (64.3%) | 0 (0%) | 9 (26.5%) |
| | Neck | 0 (0%) | 0 (0%) | 15 (100%) | 15 (44.1%) |
| | Oral cavity | 3 (60%) | 0 (0%) | 0 (0%) | 3 (8.8%) |
| **Reconstructive procedure** | ALT | 0 (0%) | 0 (0%) | 6 (40%) | 6 (17.6%) |
| | Exclusive IRT | 5 (100%) | 0 (0%) | 0 (0%) | 5 (14.7%) |
| | Forehead | 0 (0%) | 1 (7.1%) | 0 (0%) | 1 (2.9%) |
| | Pectoralis major | 0 (0%) | 0 (0%) | 6 (40%) | 6 (17.6%) |
| | Supraclavicular flap | 0 (0%) | 0 (0%) | 1 (6.7%) | 1 (2.9%) |
| | No Reconstruction | 0% | 13 (92.9%) | 2 (13.3%) | 15 (44.1%) |
| **Surgery** | Endoscopic resection | 0 (0%) | 12 (85.7%) | 0 (0%) | 12 (35.3%) |
| | ND | 0 (0%) | 0 (0%) | 2 (13.3%) | 2 (5.9%) |
| | ND + skin | 0 (0%) | 0 (0%) | 12 (80%) | 12 (35.3%) |
| | Paranasal/midface degloving | 0 (0%) | 2 (14.3%) | 0 (0%) | 2 (5.9%) |
| | Parotidectomy + ND | 0 (0%) | 0 (0%) | 1 (6.7%) | 1 (2.9%) |
| | None | 5 (100%) | 0 (0%) | 0 (0%) | 5 (14.7%) |

*ALT: anterolateral thigh flap; ND: neck dissection; EBRT: external beam radiotherapy; SCC: squamous cell carcinoma; CT: chemotherapy; IRT: interventional radiotherapy.*

*Statistical analysis*

Head and neck surgeons and radiation oncologists performed follow-up jointly. They relied on head and neck physical exam, endoscopy, head and neck contrast-enhanced CT and, in controversial cases, MRI, PET-CT, and biopsies. The oncological endpoints included locoregional relapse-free survival (LRFS), disease-specific survival (DSS), and overall survival (OS). Survival curves were calculated using the Kaplan-Meier method from the day of IRT completion. Grade 3, 4 and 5 toxicities have been systematically recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Statistical analysis was performed using JMPin software, release 7.0.1, by the SAS Institute.

## Results

Table II reports the demographic data and clinical parameters of our series of 34 patients. Two of these patients underwent more than one IRT re-irradiation. One patient underwent 3 IRT treatments for recurrences of an intestinal-type adenocarcinoma of the ethmoid at 3 years and a second primary in the irradiated field; the second underwent 2 IRT treatments for recurrences of a nasal cavity melanoma at 3 years. Notably, none of patients in this series reported specific IRT-related toxicities.

The only recorded toxicities related to IRT in our series was a transient yet complete paralysis of the sixth cranial nerve 2 days after completion of IRT in one patient who underwent endoscopic resection and EG-IRT for a recurrent naso-ethmoidal adenoid cystic carcinoma. No interruptions of the IRT schedule for acute toxicity were recorded.

As for surgery, a partial necrosis of the skin in a myocutaneous pectoralis major flap, which healed secondarily over the underlying vital muscle at 5 weeks was recorded.

Two of 5 patients in group IV could have been placed in group V according to our previously proposed classification, since they were previously irradiated at the level of nasal vestibule primaries (one submitted to surgery and adjuvant EBRT, the other to exclusive EBRT), not technically unresectable. However, as the present study focuses on the issue of re-irradiation, we decided to assign both to group IV.

During follow-up, death occurred in 24 (70.6%) patients, of whom 21 (61.8%) for disease. Twenty-four (70.6%) patients experienced local recurrence after IRT re-irradiation and in 5 (14.7%) cases distant metastases occurred, which were not associated with local relapse and represented the cause of death in only one patient.

The median follow-up in the present series, excluding patients who died for HNC, was 24.5 months. For this reason, survival rates are shown at 30 months and 2-year survivals are reported.

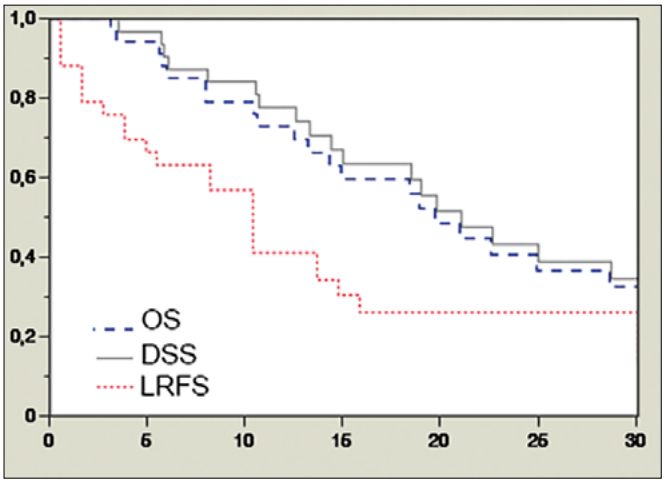



**Figure 1.** Overall (OS), disease-specific (DSS) and locoregional relapse-free (LRFS) survivals in the entire series, computed from the time of the first IRT re-irradiation.

In the entire series, at two years, LRFS was 26%, DSS 39.1%, and OS 36.6% (Fig. 1).

The survival curves look different among the 3 treatment groups (Fig. 2), but without statistical significance probably due to the relatively small sample size. Group IIIec showed the best survival rates (2-year LRFS: 32.1%, DSS: 58.7%, OS: 54.6%) and group IV the worst (2-year LRFS/DSS/OS: 0%), with group IIIin in the middle (2-year LRFS: 26.7%, DSS: 41%, OS: 38%).

## Discussion

To the best of our knowledge, the present series represents the most extensive reported experience of re-irradiation through IRT for HNC in Italy. Some published papers also reported on the use of IRT in a palliative setting [10]. However, we recommend IRT only when a curative dose can be delivered to the CTV. Therefore, we will discuss only our experience in the context of IRT re-irradiation with a curative perspective.

The survival rates are low, as expected for recurrent HNC already treated by a full course of EBRT, and are in line with the literature [11]. However, the present work confirms the main advantage of IRT compared with other re-irradiation strategies, which is the markedly lower rates of toxicity [12]. In fact, in the present series, we did not record any grade 4/5 toxicity and the only grade 3 toxicity (sixth cranial nerve palsy) was temporary and recovered completely. On the other hand, the high toxicity of EBRT re-irradiation, including grade 3 and 4 events, is its main limitation, leading to a reduction of the

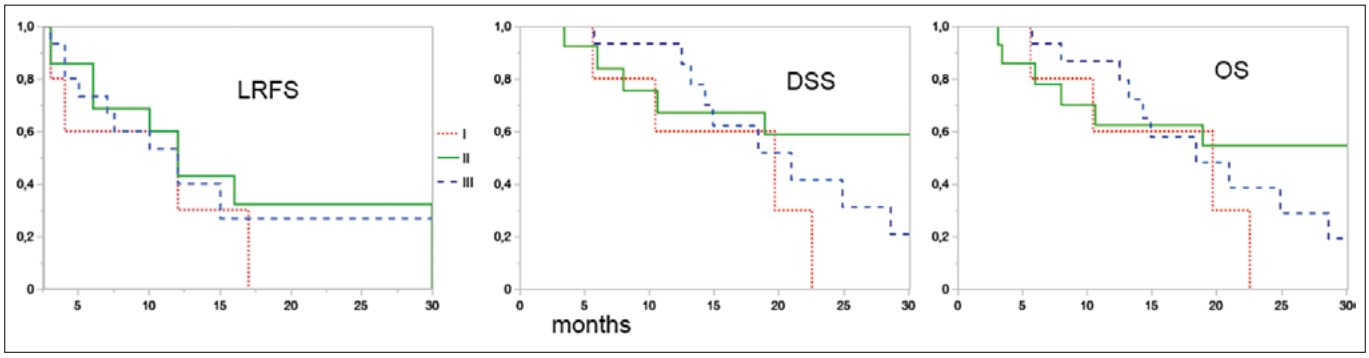



**Figure 2.** Locoregional relapse free (LRFS), disease-specific (DSS) and overall (OS) survivals in the three groups. No significant differences emerged from statistical analysis (both at Log rank and Wilcoxon tests), probably because of the small numbers, even though the curves appear consistently different in the three populations.

total dose on CTV and therefore of its effectiveness, so that many centres never perform it and deem it too risky and/or not effective enough. In fact, available reports of patients submitted to re-irradiation with EBRT show toxicity rates ≥ G3 ranging from 18.3% to 50% [13].

However, even if the recommendations concerning patient selection criteria, implant techniques, target volume definition, and HDR treatment parameters (such as time, dose, and fractionation schedules) have been generally described and standardised [14], we feel that the potential of IRT in post-irradiation recurrences [15] is not fully exploited yet. This is confirmed by a recent survey among radiation and clinical oncologists, in which BT is not even considered an option for re-irradiation of HNC even in its modern IRT form [16].

The advantages and results of IRT re-irradiation differed among the three groups considered herein, with group IV being the worst in terms of DSS. In this group, a potentially curative dose was nonetheless delivered to patients who were otherwise mostly candidates for palliation or best supportive care as radical salvage surgery was not considered feasible [17,18]. We recommend IRT in such cases if we see the perspective of curative treatment, which can be obtained only with a complete coverage of the tumour volume, and at the same time low-risk and easy catheter placement. Therefore, strictly adhering to these selection criteria, only a few otherwise untreatable patients with midface (cheek/buccal mucosa, nasal vestibule) and floor of mouth recurrences were treated with exclusive interstitial IRT. We consider our results encouraging even in this group since we offered a rational treatment option and reasonable survival with minimal or no toxicity.

Not surprisingly and consistent with the literature, the combination of surgery with IRT in the perioperative setting is associated with better DSS, both in case of endocavitary (group IIIec) as well as interstitial (group IIIin) delivery [19,20].

The group IIIin includes cases of perioperative interstitial IRT for neck recurrence of a HNC, previously irradiated with EBRT. This approach is likely the most frequent perioperative use of IRT in head and neck oncology and has been long validated in international studies with very encouraging oncological results [21]. We often associated this treatment with reconstructive procedures (87%) because the recurrences were mostly bulky and within previously irradiated necks. The pectoralis major flap remains the workhorse in this setting [22] (Fig. 3), but we also successfully used free flaps. The high rate of bulky recurrences likely accounts for the lower survival rates (DSS: 41% at 2 years) in comparison to the best literature series [12,23].

A clear limitation of IRT re-irradiation is represented by the fact that it is not always feasible because of issues in terms of implantation to obtain adequate coverage of the entire CTV, or of organs at risk. For example, it makes no sense to consider an IRT re-irradiation of an involved internal carotid axis in the neck, as previously described [12], both because surgery is not indicated as it is not expected to be R0 and because an effective dose on a clearly infiltrated carotid artery dramatically increases the risk of blowout.

On the other hand, EG-IRT [24] used in most group IIIec cases, looks like an elegant solution in paranasal and, particularly, nasopharyngeal local recurrences, at the same time increasing the effectiveness of salvage surgical endoscopic procedures as nasopharyngeal endoscopic resections (NER) [25]. After a NER, re-irradiation would be rational and potentially useful and, at the end of surgery, the endoscopic view and surgical exposure can solve most of the feasibility issues for adequate implantation of IRT tubes for re-irradiation. Therefore EG-IRT exploits the advantages of endoscopy itself (e.g., clear anatomical view, low morbidity, and preservation of anatomy and function) and combines them synergistically with the pros of IRT (e.g., extremely con-




**Figure 3.** A typical group IIIin patient. A 44-year-old male with a neck/skin recurrence (**A**) of an oropharyngeal squamous cell carcinoma treated one year before by chemoradiation. Perioperative IRT re-irradiation was planned. The recurrence was resected (**B**) through a radical neck dissection extended to the skin, but the adventitia of the internal carotid artery resulted positive at frozen sections, and then confirmed positive at final histopathology report (R1). Plastic tubes were implanted to cover the entire surgical bed and in particular the carotid axis (**C**). The large skin defect was closed with a pedicled myocutaneous pectoralis major flap (**D**). Notably the flap was folded over itself so that the distal, more at risk, skin came back to be in the most caudal part of the defect over the bulk of the muscle and a double layer of muscle fully obliterated the neck dead space giving stability to the implant for the following re-irradiation and reducing the risk of acute complications (bleeding, infection, fluid collection in the surgical cavity). A suction drain stayed in place until the completion of re-irradiation and removal of plastic tubes after 9 days, to keep the geometry of the target stable and prevent fluid collections as well. Two years after treatment the flap was vital (**E**) with no morbidity at the donor site (**F**). However, a further recurrence became evident at month 18 along the internal carotid artery and patient died for disease at 33 months after re-irradiation in spite of immuno- and chemotherapy.

formal dose, low morbidity also in case of re-irradiation) via an extremely precise placement of applicators, which is particularly beneficial in patients who were previously irradiated through external beams and who can potentially gain an additional survival advantage [26,27] (Fig. 4).

To provide a full view of the different experiences reported in the literature it is worth to add that some authors have also considered the possibility of combining HDR IRT in the re-irradiation strategy of recurrent HNCs with other therapeutic options such as systemic treatment or EBRT [28-30]. Unfortunately, we have limited and still inconclusive data on this strategy (only 3 patients treated with concomitant chemotherapy in the present series, Table II).

## Conclusions

IRT should not be considered an alternative to EBRT or surgery in all HNC, but is a valuable and useful tool in selected situations where the limited possibilities of surgery and EBRT create a clinical need which IRT may respond to. Re-irradiation is clearly one of these situations where IRT can deliver an effective dose without harming neighbouring normal tissues, with different strategies according to the target, feasibility of an R0 salvage surgery, and the patient's general conditions.

The most evident advantage of IRT compared to EBRT in re-irradiation is represented by the virtual absence of severe toxicities. However, IRT remains widely underexploited in daily clinical practice, even if it is probably the safest re-irradiation modality [5,31]. This is also because IRT is a multidisciplinary tool at the intersection between surgery and radiotherapy, and close cooperation between surgeons and radiation oncologists during every phase is mandatory, from the recommendation of treatment and implantation in the operating theatre, to the prescription and dose painting within the radiation oncologist unit. Achieving this is not easy, but it is necessary to perform high-quality IRT.

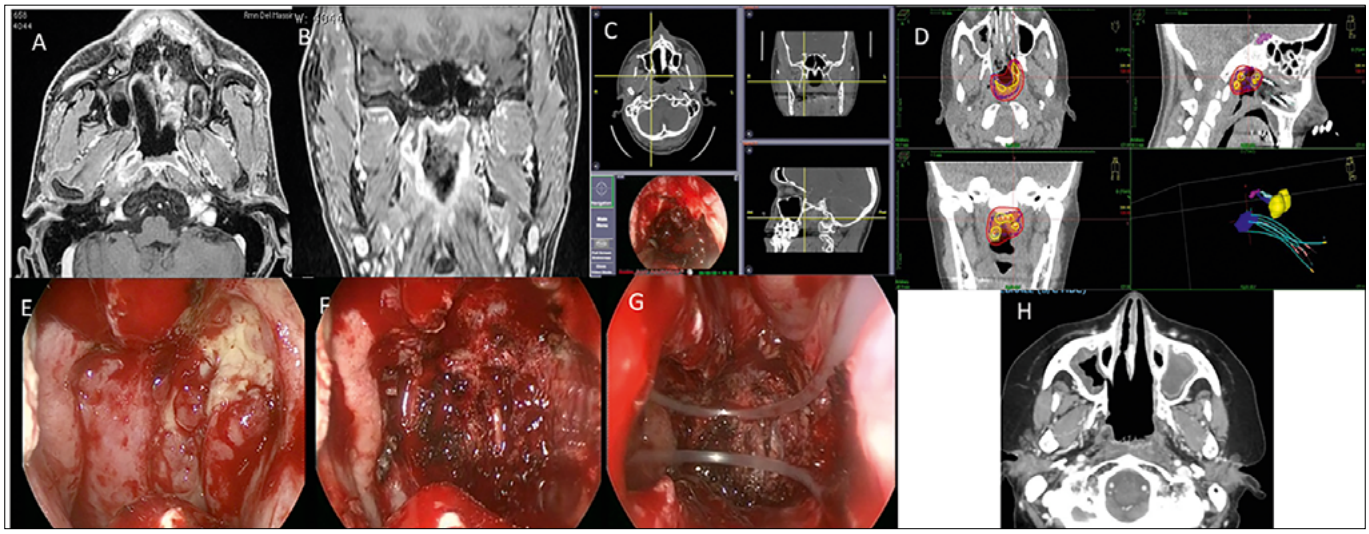



**Figure 4.** Endoscopic treatment + IRT in a case of recurrent nasopharyngeal squamous cell carcinoma. In **A** and **B**, MRI in the axial and coronal planes shows the recurrence in the left posterior-superior wall of the nasopharynx. Intraoperative endoscopic view (**E**) of the recurrence. A navigation system (**C**) was used as aid for the endoscopic resection (**F**) of the posterior-lateral pharyngeal wall (NER type III). In G the endoscopic positioning (EG-IRT) of the catheters in a loop within the posterior part of the nasopharyngeal cavity is shown. The BT planning with the dose description and organ of interest is shown in **D**. The CT scan at 6 months (**H**) demonstrated no residual/recurrent disease.

### *Conflict of interest statement*

The authors declare no conflict of interest.

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### *Author contributions*

FB, LT, JG: conceptualisation; BF, VL: methodology; AL, BF: software; GCM, GK, DR, JG: validation; RG, VL, MR: formal analysis; AT, LMDL, AD, MFC: investigation; FB, LT: resources; JG, MR, GCM: data curation; AL, RG, BF: writing – original draft preparation; FB, LT, GK: writing – review & editing; DR, VL: visualisation; FB, JG: supervision; FB: project administration.

### *Ethical consideration*

Ethical review and approval were waived for this study, due to the observational retrospective design, and in this case a mandatory ethical approval was not requested by the Italian law (GU No. 76, 31 March 2008).

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

Written informed consent was obtained from each participant/patient for study participation and data publication.

## References

1. Gordon K, Smyk D, Gulidov I, et al. An overview of head and neck tumor reirradiation: what has been achieved so far? Cancers (Basel) 2023;15:4409. https://doi.org/10.3390/cancers15174409
2. Tagliaferri L, Vavassori A, Lancellotta V, et al. Can brachytherapy be properly considered in the clinical practice? Trilogy project: the vision of the AIRO (Italian Association of Radiotherapy and Clinical Oncology) Interventional Radiotherapy study group. J Contemp Brachytherapy 2020;12:84-89. https://doi.org/10.5114/jcb.2020.92765
3. Yamazaki H, Masui K, Suzuki G, et al. Reirradiation for recurrent head and neck carcinoma using high-dose-rate brachytherapy: a multi-institutional study. Brachytherapy 2022;21:341-346. https://doi.org/10.1016/j.brachy.2021.12.011
4. Bussu F, Tagliaferri L, Mattiucci G, et al. HDR interventional radiotherapy (brachytherapy) in the treatment of primary and recurrent head and neck malignancies. Head Neck 2019;41:1667-1675. https://doi.org/10.1002/hed.25646
5. Tagliaferri L, Bussu F, Fionda B, et al. Perioperative HDR brachytherapy for reirradiation in head and neck recurrences: single-institution experience and systematic review. Tumori 2017;103:516-524. https://doi.org/10.5301/tj.5000614
6. Bussu F, Tagliaferri L, Crescio C, et al. New standards for the management of nose vestibule malignancies. Acta Otolaryngol 2023;143:215-222. https://doi.org/10.1080/0016489.2023.2179662
7. Bussu F, Tagliaferri L, Corbisiero MF, et al. Management of nasal vestibule carcinomas: recommendations by the Oncological Committee of the Italian Society of Otorhinolaryngology - Head and Neck Surgery. Acta Otorhinolaryngol Ital 2024;44:13-20. https://doi.org/10.14639/0392-100X-N2786
8. Bussu F, Tagliaferri L, Piras A, et al. Multidisciplinary approach to nose vestibule malignancies: setting new standards. Acta Otorhinolaryngol Ital 2021;41(Suppl. 1):S158-S165. https://doi.org/10.14639/0392-100X-suppl.1-41-2021-16

[9] Tagliaferri L, Bussu F, Rigante M, et al. Endoscopy-guided brachytherapy for sinonasal and nasopharyngeal recurrences. Brachytherapy 2015;14:419-425. https://doi.org/10.1016/j.brachy.2014.11.012

[10] Tselis N, Karagiannis E, Kolotas C, et al. Image-guided interstitial high-dose-rate brachytherapy in the treatment of inoperable recurrent head and neck malignancies: an effective option of reirradiation. Head Neck 2017;39:61-68. https://doi.org/10.1002/hed.24697

[11] Rodin J, Bar-Ad V, Cognetti D, et al. A systematic review of treating recurrent head and neck cancer: a reintroduction of brachytherapy with or without surgery. J Contemp Brachytherapy 2018;10:454-462. https://doi.org/10.5114/jcb.2018.79399

[12] Teudt IU, Kovàcs G, Ritter M, et al. Intensity modulated perioperative HDR brachytherapy for recurrent and/or advanced head and neck metastases. Eur Arch Otorhinolaryngol 2016;273:2707-2715. https://doi.org/10.1007/s00405-015-3794-3

[13] Mohamad I, Abu Hejleh T, Abdelqader S, et al. Re-irradiation for recurrent head and neck cancer: freedom from cancer recurrence rate. J Clin Med 2023;12:2979. https://doi.org/10.3390/jcm12082979

[14] Kovács G, Martinez-Monge R, Budrukkar A, et al. GEC-ESTRO ACROP recommendations for head & neck brachytherapy in squamous cell carcinomas: 1st update – improvement by cross sectional imaging based treatment planning and stepping source technology. Radiother Oncol 2017;122:248-254. https://doi.org/10.1016/j.radonc.2016.10.008

[15] Pellizzon AC, Salvajoli JV, Kowalski LP, et al. Salvage for cervical recurrences of head and neck cancer with dissection and interstitial high dose rate brachytherapy. Radiat Oncol 2006;1:27. https://doi.org/10.1186/1748-717x-1-27

[16] Willmann J, Appelt L, Balermpas P, et al. Re-irradiation in clinical practice: results of an international patterns of care survey within the framework of the ESTRO-EORTC E2-RADIatE platform. Radiother Oncol 2023;189:109947. https://doi.org/10.1016/j.radonc.2023.109947

[17] Strnad V, Lotter M, Kreppner S, et al. Reirradiation for recurrent head and neck cancer with salvage interstitial pulsed-dose-rate brachytherapy: long-term results. Strahlenther Onkol 2015;191:495-500. https://doi.org/10.1007/s00066-014-0809-8

[18] Kolotas C, Tselis N, Sommerlad M, et al. Reirradiation for recurrent neck metastases of head-and-neck tumors using CT-guided interstitial 192Ir HDR brachytherapy. Strahlenther Onkol 2007;183:69-75. https://doi.org/10.1007/s00066-007-1632-2

[19] Tselis N, Ratka M, Vogt HG, et al. Hypofractionated accelerated CT-guided interstitial $^{192}$Ir-HDR-Brachytherapy as re-irradiation in inoperable recurrent cervical lymphadenopathy from head and neck cancer. Radiother Oncol 2011;98:57-62. https://doi.org/10.1016/j.radonc.2010.10.025

[20] Narayana A, Cohen GN, Zaider M, et al. High-dose-rate interstitial brachytherapy in recurrent and previously irradiated head and neck cancers – preliminary results. Brachytherapy 2007;6:157-163. https://doi.org/10.1016/j.brachy.2006.12.001

[21] Martínez-Monge R, Alcalde J, Concejo C, et al. Perioperative high-dose-rate brachytherapy (PHDRB) in previously irradiated head and neck cancer: initial results of a Phase I/II reirradiation study. Brachytherapy 2006;5:32-40. https://doi.org/10.1016/j.brachy.2005.11.003

[22] Bussu F, Gallus R, Navach V, et al. Contemporary role of pectoralis major regional flaps in head and neck surgery. Acta Otorhinolaryngol Ital 2014;34:327-341.

[23] Khan N, Clemens M, Liu J, et al. The role of salvage surgery with interstitial brachytherapy for the management of regionally recurrent head and neck cancers. Cancers Head Neck 2019;4:4. https://doi.org/10.1186/s41199-019-0043-2

[24] Wan XB, Jiang R, Xie FY, et al. Endoscope-guided interstitial intensity-modulated brachytherapy and intracavitary brachytherapy as boost radiation for primary early T stage nasopharyngeal carcinoma. PLoS One 2014;9:E90048. https://doi.org/10.1371/journal.pone.0090048

[25] Castelnuovo P, Dallan I, Bignami M, et al. Nasopharyngeal endoscopic resection in the management of selected malignancies: ten-year experience. Rhinology 2010;48:84-89. https://doi.org/10.4193/Rhin09.079

[26] Senan S, Levendag PC. Brachytherapy for recurrent head and neck cancer. Hematol Oncol Clin North Am 1999;13:531-542. https://doi.org/10.1016/s0889-8588(05)70073-3

[27] Stevens KR Jr, Britsch A, Moss WT. High-dose reirradiation of head and neck cancer with curative intent. Int J Radiat Oncol Biol Phys 1994;29:687-698. https://doi.org/10.1016/0360-3016(94)90555-x

[28] Ritter M, Teudt IU, Meyer JE, et al. Second-line treatment of recurrent HNSCC: tumor debulking in combination with high-dose-rate brachytherapy and a simultaneous cetuximab-paclitaxel protocol. Radiat Oncol 2016;11:6. https://doi.org/10.1186/s13014-016-0583-0

[29] Soror T, Paul J, Melchert C, et al. Salvage high-dose-rate interventional radiotherapy (brachytherapy) combined with surgery for regionally relapsed head and neck cancers. Cancers (Basel) 2023;15:4549. https://doi.org/10.3390/cancers15184549

[30] Li J, Huang L, Wu H, et al. Re-irradiation for recurrent cervical cancer: a single institutional experience. Clin Transl Radiat Oncol 2023;43:100690. https://doi.org/10.1016/j.ctro.2023.100690

[31] Kirthi Koushik AS, Alva RC. Brachytherapy in head and neck cancers: "Are we doing it or are we done with it". Indian J Surg Oncol 2018;9:171-174. https://doi.org/10.1007/s13193-018-0735-9.