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HEAD AND NECK

Re-irradiation with curative intent in patients with squamous cell carcinoma of the head and neck: a national survey of usual practice on behalf of the Italian Association of Radiation Oncology (AIRO)

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Abstract

Objective To report the results of a national survey investigating the pattern of practiceof curative re-irradiation (ReRT) for recurrent squamous cell carcinoma of the head andneck.

Methods In March 2016, a 22-item, 4-section questionnaire was sent to all Italian Radiation Oncology centers. Sections were focused on assessing the expertise level of each center and collecting specific information on reRT prescription modalities in the adjuvant and definitive settings.

Results Overall, 77 centers completed the survey. The majority (50/77, 64.9%) of participating radiation oncologists were senior consultants (> 10 years of experience). Of the responding centers, 63 (81.8%) performed curative ReRT, while 14 (18.1%) did not, mainly (5/14, 35.7%) due to the avoidance of severe toxicity. The use of adjuvant ReRT was reported by less than half of the interviewed radiation oncologists (36/77, 46.7%). In case of unresectable local recurrence, definitive ReRT was claimed to be adopted in 55/77 (71.4%) for non-nasopharyngeal and 47/77 (61%) for nasopharyngeal cancer. The preferred treatment technique was Intensity Modulated Radiation Therapy (IMRT) followed by Stereotactic Body Radiation Therapy (SBRT). When IMRT was applied, the most common (19/55 responders, 34.5%) selection of treatment volume consisted of the Gross Tumor Volume (GTV) + 0.5 cm margin to account for microscopic disease.

Conclusion Despite the absence of definitive evidence-based recommendations, apossible consideration for ReRT in case of unresectable recurrent head and neckcancer was reported by over 80% of radiation oncologists taking part in the nationalsurvey.

Keywords Radiation therapy · Head and Neck Cancer · Re-irradiation · Clinical practice guidelines · Squamous cell carcinoma

Introduction

Patients with non-metastatic squamous cell carcinoma of the head and neck (SCCHN) are treated with curative intent using surgery and/or radiation therapy +/− chemotherapy. However, many patients develop recurrent disease, with a predominance of locoregional failure [1]. The recurrence rate is particularly high, up to 50%, in patients with locally advanced disease at the time of diagnosis (AJCC stages III, IVA and IVB). In about 90% of cases, the recurrence occurs within the first two years after the end of the primary treatment. The prognosis of patients with recurrent SCCHN remains poor, with a median overall survival of less than 1 year [2]. Additionally, due to smoking and alcohol habits, long survivors have a higher risk of second primary tumors in the head and neck region [3].

The local tumor regrowth in recurrent SCCHN can cause significant morbidity: pain, bleeding, respiratory distress, dysphagia, speech impairment and severe self-image alterations are some of the symptoms that patients can experience. Therefore, in the presence of a local recurrence/second

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primary tumor, the main goal of the head and neck multidisciplinary team is to guide the therapeutic choice by carefully balancing the actual possibility of disease control and the burden of the treatment itself on the patient's quality of life. Surgery is considered the treatment of choice [4] and can achieve long-term disease control in 25–45% of patients. However, several factors make the surgical option available only in a minority of cases (about 20%). The non-indication of surgery could be related to the non-resectability of the tumor, the high risk of surgical morbidity, the patient's comorbidity and general conditions, and sometimes patient's refusal. In addition, it is not uncommon that patients treated with salvage surgery who have histological high-risk features such as positive margins and extra-capsular extension, necessitate a post-operative radiation treatment. If surgery is not indicated or feasible, the only therapeutic alternative with potentially curative intent is re-irradiation.

Historically, re-irradiation of recurrent and second primary SCCHN within a previous irradiated field has been discouraged due to concerns over excessive normal tissues damage [5].

However, over the last 20 years re-radiation has been progressively recognized as a possible therapeutic approach in selected patients with SCCHN. In fact, modern radiotherapy techniques such as Intensity Modulated Radiation Therapy (IMRT) and Stereotactic Body Radiation Therapy (SBRT) offered potentially superior local control rates with fewer side effects compared with conventional 2D or 3D techniques [6–8].

Post-operative re-irradiation, as well, could be considered as a therapeutic option in high-risk patients [9].

A uniform technical approach to re-irradiation as a treatment of recurrent and second primary SCCHN would be desirable in order to achieve the best outcome in terms of tumor control and toxicity. However, the general low incidence of the disease combined with the fact that these patients are managed in multiple radiation centers and that several schedules and techniques can be used could hamper this uniformity. We therefore conducted a survey that aimed to investigate the true spread of SCCHN curative re-irradiation in the national scenario of the Italian radiotherapy centers and the current re-irradiation strategies.

Materials and methods

In this paper, we describe the results of the survey that was carried out between March and May 2016. The survey is based on the assumption that the feasibility of the re-treatment has already been defined through a dosimetric reconstruction of the primary radiotherapy plan and that therefore a curative re-irradiation was deemed "technically" conceivable. Data on re-irradiation were collected using an online questionnaire that was sent to all Italian Radiation Oncology centers. The items of the questionnaire were defined over a multi-step process by a panel of experts of the Head and Neck and Re-irradiation working groups of the Italian Association of Radiation Oncology (AIRO). The final version of the questionnaire approved by the panel consisted of 22 multiple-choice items divided in 4 main sections. The first section collected general information regarding the radiotherapy centers characteristics and expertise and the responders' years of practice. The second and third sections were focused on the radiation technical characteristics of adjuvant re-irradiation and definitive re-irradiation (with the exclusion of nasopharyngeal tumors), respectively: dose schedule, planning volumes and radiotherapy technique. The last section exclusively pertained the re-irradiation of recurrent tumors of the nasopharynx, given the peculiar radiotherapy schedule and volumes used in this specific anatomical site. Participants were finally asked to provide a contact for each Institution interested in future research and cooperation on the topic of SCCHN re-irradiation.

The survey was prepared on SurveyMonkey's online interface (http://www.SurveyMonkey.com). Together with an introduction letter, personalized email invitations with direct links to the survey were sent to all members of AIRO. There were three skip logic questions in which more detailed follow-up questions were skipped if the respondent previously indicated that a question did not pertain to their practice.

All data management and statistical analyses were performed using SPSS version 17.0. Frequencies were automatically performed by SurveyMonkey but repeated for validation purposes in SPSS. Associations between categorical variables (i.e., to test if re-irradiation was done more likely in centers that reported to treat at least 50 SCCHN patients/year) were assessed by a Pearson's Chi-square test.

Results

Between March and May 2016, 77 Italian Radiation Oncology centers filled the questionnaire.

Clinical setting and experience

Respondents worked in a variety of clinical settings, with the majority of them working in public hospitals (66.2%) or in public–private partnership centers (22.1%). The remaining respondents worked in either university hospitals (9.1%) or private centers (2.6%).

The large majority of respondents had at least 5 years of experience (83.1%), with 78.1% of them with more than 10 years of practice as a radiation oncologist. Among the remaining respondents, 11.7% reported less than 5 years of experience and 5.2% were residents in Radiation Oncology.

Table 1 Radiotherapy centers' expertise

Type of treatment	# Patients/year	# Centers
All SCCHN treatment	< 20	4 (5.2%)
	20–50	28 (36.3%)
	50–100	29 (37.7%)
	> 100	16 (20.8%)
Curative re-irradiation	< 5	36 (57.1%)
	5–10	24 (38.1%)
	10–20	3 (4.8%)
	> 20	0 (0.0%)

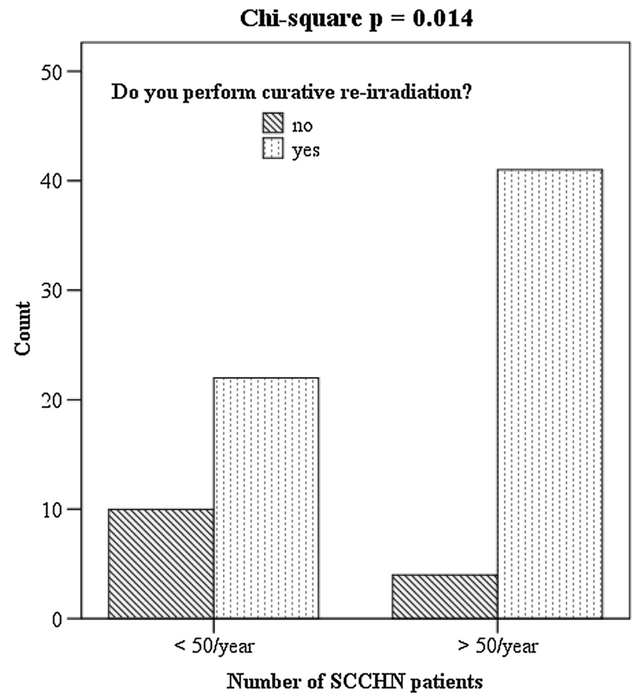

Fig. 1 Curative re-irradiation based on the center's expertise in treating SCCHN

Roughly, half of the centers treated at least 50 SCCHN patients per year, while only 5.2% treated less than 20 patients per year, as shown in Table 1. On question 4, respondents were asked if curative re-irradiation was practiced in their center. Of the 77 respondents, only 14 (18.2%) answered negatively. Those respondents were then asked to grade five possible reasons behind the choice to not re-irradiate, from the strongest to the weakest. For five centers, the main reason was the high risk of severe toxicity, for four centers it was the lack of adequate radiation technologies, for three centers it was either the lack of personnel expertise or the shortage of guidelines, while only two institutions reported that the primary reason was that re-irradiation was generally not approved by the multidisciplinary team of their center. Centers with higher expertise in treating SCCHN (> 50 SCCHN patients per year) more frequently performed re-irradiation (Pearson's Chi-square test $p = 0.014$, Fig. 1). None of the 63 centers that practiced re-irradiation reported a number of treatments > 20/year. On the contrary, the majority of them (57.1%) referred less than five cases of re-irradiation/year (Table 1).

Adjuvant re-irradiation

The use of adjuvant re-irradiation after surgery was reported by less than half of the radiation oncologists (36 participants, 46.7%). The dose schedule more frequently used was standard fractionation (2 Gy/die) up to a total dose of 60–66 Gy (44.4%, 16 centers) or 50–60 Gy (41.7%, 15 centers). Only five centers (13.9%) prescribed altered fractionations (hyperfractionation or hypofractionation) in various schedules. The treatment volume was represented by the tumor bed + 0.5–1 cm of margin plus or minus the first nodal station of drainage in 8 (22.2%) and 20 (55.6%) cases, respectively. Only two centers (5.6%) included in the treatment volume also the prophylactic irradiation of the neck.

IMRT was the technique adopted by the majority of responders (32 participants, 88.8%), while 1 (2.8%) and 3 (8.3%) centers used either brachytherapy or 3D conformal radiotherapy, respectively (Fig. 2). Overall, rotational IMRT was the preferred treatment modality for 16/36 radiotherapy units (44.4%), followed by static IMRT in 9 (25%) and tomotherapy in 7 (19.4%) cases, respectively.

Definitive re-irradiation

Sections 3 and 4 were designed to address the pattern of practice of re-irradiation for the unresectable loco-regional head and neck recurrences. The majority of radiation oncologists declared to consider the adoption of re-irradiation for non-nasopharyngeal tumors (55 participants, 71.4%) and for the nasopharyngeal cancer (47 participants, 61%). The preferred RT technique for the treatment of non-nasopharyngeal tumors was IMRT in 42/55 centers (76.3%) followed by SBRT in 9/55 centers (16.3%). The preferred RT technique for the treatment of nasopharyngeal tumors was IMRT in 36/47 centers (76.5%) followed by SBRT in 11/47 centers (23.5%) (Fig. 2). None of the participants reported to perform re-irradiation by 3D conformal radiotherapy. Among the centers that did not use SBRT the dose schedule more frequently prescribed was a daily dose per fraction of 2 Gy up to a total dose of 60–66 Gy. Altered fractionations in various schedules (hyperfractionation or hypofractionation) were the choice of roughly a quarter of respondents. In almost all the non-SBRT cases, the treatment volume was the gross tumor volume (GTV) + margin (variable, between 0.3 and 2 cm). Only one center included in the treatment volume also the prophylactic irradiation of the neck, while six

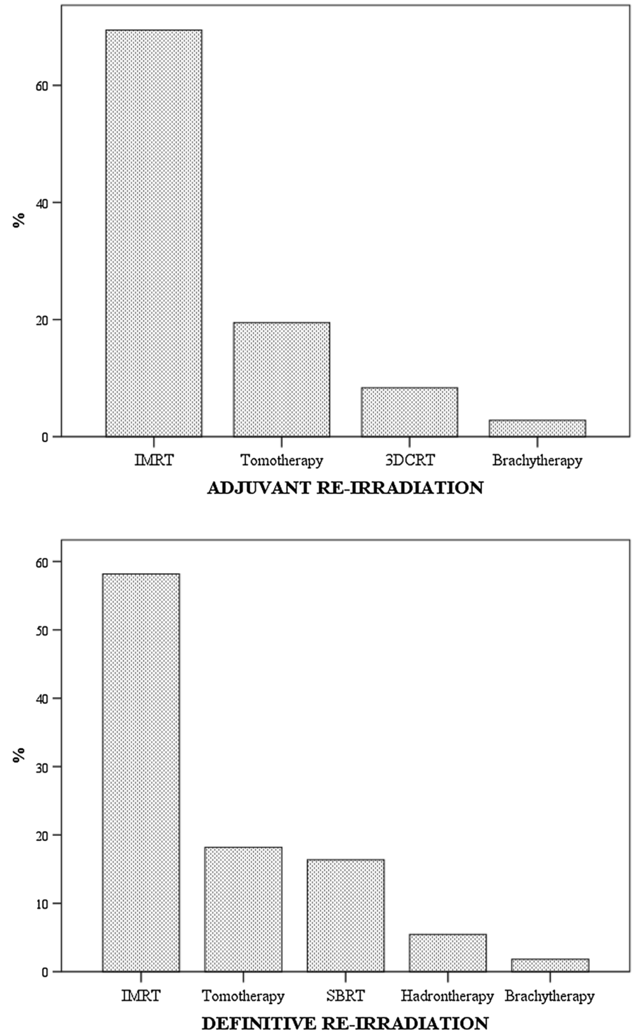

Fig. 2 Re-irradiation techniques

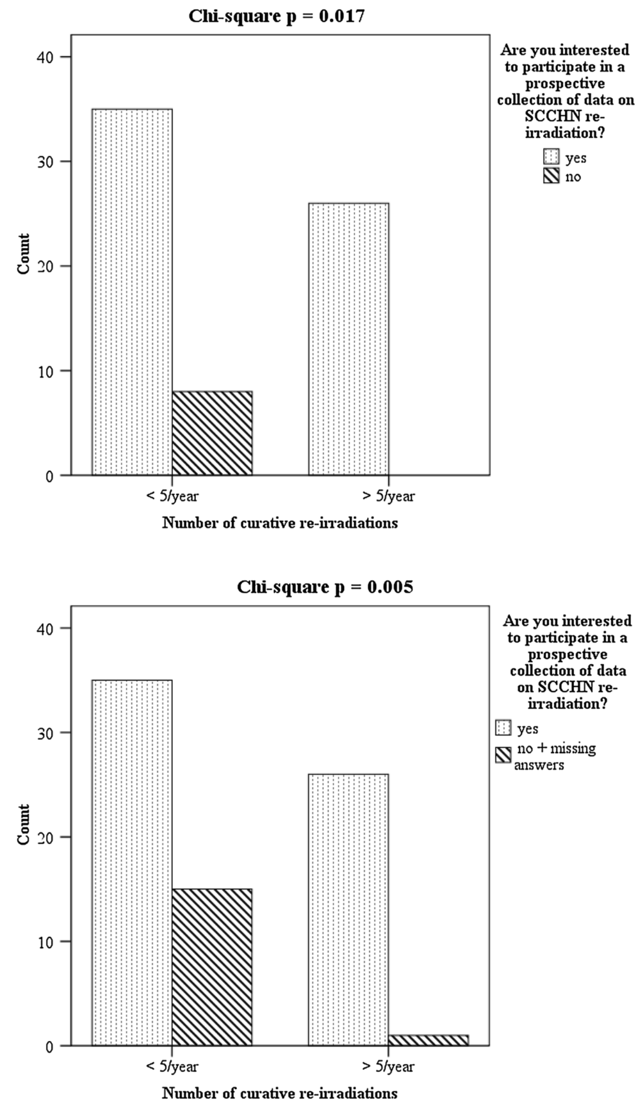

Fig. 3 Center's interest in a prospective data collection based on the center's expertise in re-irradiation

centers reported to irradiate only the GTV without margin. The preferred SBRT dose schedule was 30 Gy in 6 fractions. In almost half of the SBRT treatments, the irradiated volume was the GTV without margin.

Prospective data collection

The final item of the questionnaire asked all the respondents if their center was interested to participate in a prospective collection of data on SCCHN re-irradiation. The question had eight missing answers. Among the 69 centers that responded, 61 (88.4%) answered positively. All the eight centers that were not interested in a prospective data collection were among those with none or little experience (0–5 re-irradiation/year) in SCCHN re-irradiation (Pearson's Chi-square test $p = 0.017$). Considering the missing data as a negative answer (not interested), the significance increases to $p = 0.005$ (Fig. 3).

Discussion

The treatment of locally advanced SCCHN is based on a combined modality approach, including radiation therapy. For radio-recurrent patients, curative options should be evaluated by a multidisciplinary team at a high volume head and neck cancer center and re-irradiation should be considered. As organ preservation surgical strategies have become more successful, the role of salvage surgery has become more prominent for these patients [4, 10, 11]. Numerous publications demonstrated the safety and efficacy of re-irradiation and long-term survival rates have been reported. However, evidences of the role of re-irradiation come mainly from retrospective and phase II trials [6, 8, 12–21]. Only few experiences of re-irradiation with modern techniques have been reported among Italian institutions [22–25].

According to NCCN guidelines, reirradiation may be proposed both as exclusive and post-operative treatment but no definitive indications on factors to consider for appropriate patient selection are indicated. Reirradiation is a potentially curative treatment option for some patients with unresectable disease; however, concerns for increased risk of severe or life-threatening treatment-related toxicity and tumor radioresistance pose a challenge. In clinical practice, the choice to re-irradiate mainly depends on the radiation oncologists' attitude and the institutional policy.

The main goal of the survey here reported was to record the true rate of re-irradiation treatments in the Italian radiotherapy centers and the most frequently used re-irradiation strategies. As suggested by both international guidelines on head and neck cancer treatment and literature reviews, re-irradiation on the head and neck region should be performed only in high-volume centers with expertise in this field [26]. As expected, the present survey shows that the centers in which re-irradiation was more frequently practiced were those with a higher patient inflow. Nonetheless, the majority of the centers reported a rate of re-irradiation < 5 patients/year, suggesting that indication to re-irradiation remains limited to selected cases.

Overall, some consideration can be gleaned through these data:

- In order to maximize the "curative" potential of re-irradiation, the most crucial issue is patients' selection (age, PS, absence of toxicity from previous RT, possibility to deliver high radiation dose….).
- In absence of high-level evidence data, a decisional support for daily practice can be provided by nomograms [27–29] available in the literature.
- The feasibility of high-dose re-irradiation could therefore be defined on an individual basis, provided that a cost-benefit discussion is thoroughly shared between both the multidisciplinary team and the patient.
- If surgery is not indicated/feasible, the standard of care of unresectable, recurrent/metastatic SSCHN is palliative chemotherapy. Vermorken et al. showed that the addition of Cetuximab to cisplatin-5 FU doublet was beneficial in prolonging overall survival (10.1 months vs 7.4 months, hazard ratio for death, 0.80; 95% CI 0.64–0.99; $p=0.04$). The study was not powered to assess whether a different outcome could be shown between patients suffering from loco-regional recurrence only or metastatic and recurrent disease. Indeed, no significant difference was found between the 2 groups of each cohort of 118 and 104 subjects treated with the experimental regimen ($p=0.06$). The potential synergistic benefit of curative intent re-irradiation for properly selected patients with unresectable disease should be outlined also in the frame of more effective systemic therapies, as already shown in phase 2 trials with cetuximab [13, 16]. Currently, phase 1 studies exploring the addition of checkpoint inhibitors to re-irradiation are under way.

The setting of re-irradiation more frequently used was definitive re-irradiation for both non-nasopharynx and nasopharynx recurrences. The practice of adjuvant re-irradiation was instead less common. In 2008, the results of a phase III trial on post-operative re-irradiation have been published [30]. Even if disease-free survival and loco-regional control were both significantly superior in the re-irradiation arm, there was no difference in overall survival (but the trial was not powered to show a difference in OS) and the rate of grade 3–4 toxicity was markedly higher. Acute toxicity reported was mucositis/pharyngitis in all cases (G3–4 in 28% of patients), with four patients experiencing marked deterioration of their general condition. The main G3–4 late toxicities were sclerosis, trismus and osteoradionecrosis, with a higher numerical incidence at two years after randomization in the re-irradiation arm compared with the observation arm (39% and 10%, respectively; $p = 0.6$).

The large radiation volumes required to cover the post-operative bed, add further concerns to the practice of re-irradiation in this setting of patients.

As expected, the techniques used in the definitive setting were highly conformed (IMRT, helical tomotherapy or SBRT) and none of the centers used 3D conformal radiotherapy. Even in the adjuvant setting, where the larger treatment volumes can minimize the gain offered by new technologies in sparing normal tissues, the rate of 3D conformal re-irradiation was extremely low (< 10%). This supports the awareness that every slight advantage in terms of volume coverage and normal tissue-sparing should be taken into account when planning a re-irradiation treatment.

Non-SBRT dose schedules were extremely variable, reflecting the wide spectrum of possibilities reported in literature. Even if standard fractionation was chosen more frequently, many centers used either hyperfractionation or non-SBRT hypofractionation. As well, SBRT dose per fraction ranged between 5 and 8 Gy and SBRT total dose ranged between 18 and 40 Gy. Similar results were found regarding the target volume delineation and GTV to CTV margins. These circumstances corroborate the need of common guidelines for both non-SBRT and SBRT re-irradiation: a series of patients treated with the same protocol and dose schedule can be easily pooled together and derived analysis on the treatment safety and efficacy can be considered more reliable.

As already mentioned, re-irradiation should be reserved for high-volume head and neck cancer centers. Alternatively, it could be useful to collect re-irradiation cases on a shared national database or register, giving smaller centers the opportunity to be supported by colleagues with more expertise. Indeed, the large majority of the centers of the survey were interested to participate in a prospective collection of data on SCCHN re-irradiation, suggesting that this option can be considered in our country.

Conclusion

This survey provides an overview on current pattern of practice of re-irradiation in locally recurrent SCCHN; despite the absence of definitive recommendations, the possibility to consideration re-irradiation in the management of unresectable disease was reported by the majority of radiation oncologists taking part in the survey. Adjuvant re-irradiation is prescribed less frequently even in the IMRT era, notwithstanding prospective randomized data [30] showing a potential benefit of 3DCRT after salvage surgery for patients with high-risk features (positive margins and extra-capsular extension). The low-volume of patients treated on an annual basis may underline the need of shared national recommendations for proper patients' selection.

Future efforts should be undertaken to reduce technical heterogeneity among Italian centers and a centralized, prospective reporting of re-irradiation treatments should be warranted.

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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