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Original research article

Simultaneous Integrated Boost Radiotherapy in Unresectable Stage IV (M0) Head and Neck Squamous Cell Cancer Patients: Daily Clinical Practice

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ABSTRACT

Aim: To evaluate clinical outcome in locally-advanced stage IV (M0) head and neck cancer patients treated using intensity-modulated radiotherapy (IMRT) with simultaneous integrated boost (SIB) in daily clinical practice.
Background: Despite SIB-IMRT has been reported as a feasible and effective advanced head and neck cancer treatment, there are few data about its concurrent use with systemic therapies.
Material and Methods: We reviewed 41 staged IV (M0) head and neck cancer patients treated in two radiotherapy units in the city of Messina (Italy) during the last six years, using intensity modulated techniques-SIB. 22/41 patients had concomitant chemotherapy or cetuximab. Acute and late toxicities, objective response (OR) rate, local control (LC) and overall survival (OS) have been evaluated.
Results: 37/41 patients received the planned doses of radiotherapy, 2 patients died during the therapy. The major acute regional toxicities were skin reaction and mucositis. A case of mandibular osteoradionecrosis was recorded. At completion of treatment, OR was evaluated in 38 patients: 32/38 patients (84.2%) had complete (55.3%) and partial (28.9%) response. The 1- and 5-year LC rates were 73.4% and 69.73%, respectively. The 1-, 3-, and 5-year OS rates were 85.93%, 51.49% and 44.14%, respectively. No statistically significant differences in outcomes have been observed in patients treated with radiotherapy alone vs. irradiation concomitant to chemo/biotherapy. The median OS was 45 months.
Conclusion: SIB-IMRT is safeand can be used with concomitant chemotherapy/biotherapy in real-life daily clinical practice. SIB-IMRT alone is a valid alternative in patients unfit for systemic therapies.

1. Introduction

According to current guidelines, advanced head and neck squamous cell carcinoma (HNSCC) requires, as standard therapy, concurrent radio-chemotherapy (CCRT)[1–4] or combined Cetuximab and irradiation in patients who cannot receive platinum-based chemotherapy.[5] CCRT is associated with potential life-threatening toxicities and poorer tolerability profiles with respect to standard-fractionated radiotherapy alone.[6,7] In clinical practice, delays in the irradiation protocol and reductions in radiation doses or chemotherapy courses occur, which indicate that certain results obtained in clinical trials can only be partially transferred to the daily practice.[8] Thus, CCRT cannot be adopted as standard treatment for all patients with advanced-stage disease.[9] New delivery techniques, such as intensity-modulated radiotherapy (IMRT), have been adopted in radiation community in order to decrease radiation toxicities.[10] Indeed, today IMRT is the actual "elevated standard" therapy used in most of radiation therapy centers operating in developed countries. IMRT technique allows to prescribe different doses to different volumes; this permits to deliver, during

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the same irradiation session, higher daily doses to the tumor volume and to nodal positive volume with respect to the clinical target volume (CTV), where lower doses are necessary to control subclinical and submicroscopic disease. This is the so-called simultaneous integrated boost (SIB).[11] The SIB-IMRT technique has been reported as feasible and effective in the treatment of advanced HNSCC,[12] but there are few data about its concurrent use with systemic therapies, such as chemotherapy and Cetuximab. In hospitals where there is a multidisciplinary team devoted to treat oncologic patients, some therapeutic approaches are proposed in a "standard fashion", even if there are not large prospective studies on both feasibility and efficacy. Delivering radiation treatments, the optimal result occurs when tumor control is obtained without exceeding complications.[13] IMRT, with or without SIB, has demonstrated to decrease late toxicity (xerostomia) in parotid glands without impairing clinical results with respect to conformal techniques.[14] With these premises, the "standard" use of SIB-IMRT alone or with systemic therapies is not out of guidelines.[1] However, it seems important to define the real feasibility of this therapeutic approach in daily clinical practice; this prompted us to retrieve the data of locally advanced, stage IV (M0), HNSCC patients treated in two radiation departments operating in the city of Messina, Sicily, to verify the clinical outcome in this setting. Results of safety data, objective response (OR), local control (LC), and overall survival (OS) are reported.

2. Materials and methods

Stage IV (M0) HNSCC patients treated with SIB-IMRT through a step-and-shoot modality or SIB-volumetric modulated arc therapy (VMAT) alone or concurrently delivered with systemic chemo/or bio/therapy[15,16] were evaluated. A minimum follow-up of 5 months was considered necessary to include a patient in the study. All patients had a histological confirmed advanced and surgically unresectable stage IV (M0) HNSCC as determined by the American Joint Committee on Cancer (AJCC) TNM staging system.[17] Patients with unknown primary site tumor, nasopharynx cancer and paranasal sinus primitives were excluded as well as patients with previous or active concurrent malignancy. The reviewed data include: medical history and physical examination, complete blood count and blood tests, CT, MRI and 18F-FDG CT/PET; weekly evaluation of toxicities, graded according to the common toxicity criteria (CTC) version 2.0, with at least bi-weekly laboratory tests; follow-up controls.

We systematically defined a Gross Tumor Volume (GTVp) including the primitive tumor, the Gross Nodal Volumes (GNV) including pathological nodes, a Clinical Target Volume including areas at high-risk of subclinical disease (CTV1); a Clinical Target Volume covering sites at low-risk of subclinical-submicroscopic disease (CTV2) and a Planning Target Volume (PTV) was obtained with a 3 mm isotropic expansion of all target volumes, sparing both the skin and bones.

We paid particular attention to contour as Organs at Risk (OAR) the oral cavity and the other mucosal structures (hard and soft palate, oropharyngeal mucosa) and the constrictor muscles. Clinical volumes were drawn on both PET and MRI images co-registered with the simulation CT. PET was utilized to aid to contour both active primitive tumor and positive nodes; MRI was used to detect the presence of neurovascular, interstitial and/or muscle invasion.

Preventive supportive therapy including oraladministration of corticosteroids and antimycotics and topic applications of Vitamin E, Hyaluronic acid and Chlorhexidine was administered to all patients.

All patients were assessed for toxicity and objective response (OR).

The OR was evaluated 4–6 weeks after the end of therapy using CT and/or MRI, endoscopic evaluation and/or biopsy to investigate residual disease. We received the approval from the internal institutional review board. Informed consent was obtained prior to treatment. All the procedures were performed in accordance with the Helsinki Declaration of 1975.

2.1. Statistical analysis

Primary end points of this study were to assess the OR, acute toxicities and late sequelae. Secondary end points were the LC and OS.

Estimates of LC and OS were calculated using the Kaplan-Meier method,[18] and the log-rank test was used to compare survival curves. Univariate Cox proportional hazards models were used to investigate the association between treatments' factors LC and OS. All statistical tests were two-tailed and a p value < 0.05 was considered statistically significant. All data were analyzed using the SPSS 24.0 software package (IBM Corporation, Armonk, NY).

3. Results

From April 2012 to December 2018, 205 HNSCC patients were treated at our two Centers (Operative Units of Radiotherapy – University of Messina and Papardo Hospital). Among these patients we retrieved the clinical records of 41 patients with stage IV (M0) tumors not suitable of surgical approach due to disease extension. The primary tumor sites were: oral cavity in 15 patients (36.5%), oropharynx in 11 (26.8%), larynx in 12 (29.2%) and hypopharynx in 3 (7%). There were 32 males and 9 females. Median age was 69.5 years (range 46–93). Fourteen tumors were poor differentiated, and there were twenty-four patients with T4 stage. Thirty-three had nodal involvement (3 N1, 30 N2a-c). A Stage IV (M0) was assigned in all 41 cases. Table 1 shows both patients' and tumors' characteristics. In eight patients Cisplatin 100 mg/m^2 day 1−22 was planned: 6 of them completed the chemotherapy planned. In seven patients Cisplatin 40 mg/m^2 weekly was planned, one of them completed the concurrent treatment planned, three received 4 administrations, two were able to tolerate 3 courses and one patient had 1 administration. Seven patients had concurrent bio-radiotherapy with Cetuximab which started one week before radiotherapy as

Table 1
Baseline demographic and clinical characteristics of the study population (n = 41).

Sex	
Male	32
Female	9
Age (years)	
Median	74
Range	55−93
Tumor Site	
Hypopharynx	3
Oral cavity	15
Oropharynx	11
Larynx	12
Tumor Grading	
G1	5
G2	22
G3	14
Tumor Stage	
T2	6
T3	11
T4	24
Nodal Stage	
N0	4
N1	3
N2a-c	30
N3	4

Table 2
Courses of chemo- or biotherapy.

Number of cycles	1	2	3	4	5	6	7	Total cycles
Concurrent Chemotherapy (CDDP 1–22)	2[a]	6[a]						14[b]
Concurrent Chemotherapy (CDDP weekly)	1[a]		2[a]	3[a]		1[a]		25[b]
Concurrent Cetuximab			3[a]	3[a]			1[a]	28[b]

[a] Number of patients who received chemo- or biotherapy.
[b] Total number of chemo- or biotherapy delivered in 22 patients.

Table 3
Organs at risk and dose-constraints.

Organ	0.1cc < (Gy)	Maximum Dose (Gy)	Mean Dose < (Gy)	Priority
Spinal cord	45	46		High
Brain stem	54	60		High
Optical chiasm	54	60		High
Optical nerve/s	54	60		High
Brachial plexus	60–66			
Eyes			35	High
Glottis	30	40	25–30%	High
Oral cavity (outside PTV)	1cc <30 Gy-36Gy			Medium
"Body"	80	81		Medium
Temporal lobe/s	1cc <60	65		Medium
Parotid/s	V30 < 50–60%	V40 < 33% (contr.)	26	Medium
Internal ear/s		52.5	50	Medium
Pituitary gland	40	50		Low
Temporomandibular J	70			Low
Len/s		<4–6		Low
Larynx (supraglottic)		66		Low
Larynx (whole)		50	40–45	Low
Mandible	V55 < 20%	70		Low
Constrictor muscles			50	
Oesophagus	1cc <45–55			
Thyroid gland	V45 < 50%			

loading dose of 400 mg/m^2, followed by weekly administration of 250 mg/m^2 for a planned 6 courses schedule.[5] Full doses of Cetuximab, 7 courses, were administered in 1/7 patients, 3/7 had 4 cycles and 3/7 had 3 cycles. 19/41 patients were submitted to radiotherapy alone because they were unfit for systemic therapy due to age, comorbidity or because they refused chemo/biotherapy. Table 2 resumes both chemotherapy and Cetuximab courses administered in our patients. All patients were immobilized with a personalized thermoplastic mask. 36 patients underwent a simulation with a planning PET/CT.[19] Images were acquired with 1.5–3 mm slices. Volumes were drawn on each CT slice. MRI scans, performed according to our internal protocol,[20–23] were co-registered in 8 cases to better define the targets. Four target volumes were defined: GTV, CTV1 and CTV2. According to the primary tumor site, for each patient the OARs were contoured. Treatment planning was elaborated using Pinnacle system 9.0 and Oncentra Masterplan version 4.3. The treatment goal was to respect the dose-constraints as shown in Table 3. Planned doses in 30 daily fractions/5 days per week were: 66 Gy (2.2 Gy/die 5dd/week) to the GTV. Planned doses in 30 daily fractions/5 days per week were: 66 Gy (2.2 Gy/die 5dd/week) to the GTV.[4] All patients were treated using two Elekta Synergy TM (Elekta Oncology Systems Ltd, Crawley, UK) linear accelerators, one equipped with cone beam CT (CBCT) for image guided radiotherapy (IGRT) and one which allows positioning verification using an electronic portal imaging device. All treatments were delivered with SIB-IMRT/VMAT techniques.

37/41 patients completed the planned radiation treatment. A total of 39 chemotherapy courses were administered concurrent with irradiation. Overall, there were 28 administrations of Cetuximab. Table 2 shows in detail the delivered courses of chemotherapy and Cetuximab.

Irradiation was interrupted in 2 patients (at 55 Gy and 50.6 Gy, respectively): the first because progression of the disease occurred during the treatment and the other because of unacceptable decline of performance status due to toxicities. Two patients died during the course of radiotherapy due to heart failure. One patient died a month after the end of radiotherapy for cerebrovascular injury. There were no direct treatment related deaths.

Table 4
Cumulative acute toxicities in 41 patients. The table reports the number of patients and (%) that experienced acute toxicities.

	G1	G2	G3	G4
Skin	4 (9.75)	3 (7.31)	4 (9.75)	
Neutropenia		3 (7.31)	1 (2.43)	1 (2.43)
Mucositis	5 (12.19)	3 (7.31)	8 (19.51)	
Oral candidiasis		4 (9.75)	4 (9.75)	
Dysphagia	11 (26.83)	7 (17.07)	2 (4.87)	
Xerostomia		2 (4.87)		
Dysphonia		3 (7.31)		
Stomatitis	1 (2.43)	1 (2.43)		
Dysgeusia		2 (4.87)		
Edema		3 (7.31)		
Nausea/Vomiting	3 (7.31)	1 (2.43)	2 (4.87)	
Anemia		2 (4.87)	2 (4.87)	
Piastrinopenia		2 (4.87)		
Peripheral Neuropathy	1 (2.43)	1 (2.43)		

All patients showed skin toxicity and mucositis, which did not exceed grade 3. Grade 3 and 4 neutropenia was observed in 2 patients. Grade 3 thrombocytopenia occurred in 1 patient (Table 4). Late toxicity was evaluated using RTOG/EORTC scale (Table 5): 3 patients had mucositis (G2–3), 3 patients had xerostomia (G2–3) and one patient developed mandibular osteo-radionecrosis. Persistent dysphagia was observed in 8 patients as assessed by the FEES (fiberoptic endoscopic evaluation of swallowing).

The OR assessment has been performed on 38 patients because 2 patients died during the treatment and one patient died before the first clinical response evaluation. We observed a complete response (CR) in 21/38 patients (55.3%); a partial response (PR) in 11/38 patients (28.9%); a stable disease (SD) in 5 patients (13.2%) and pro-

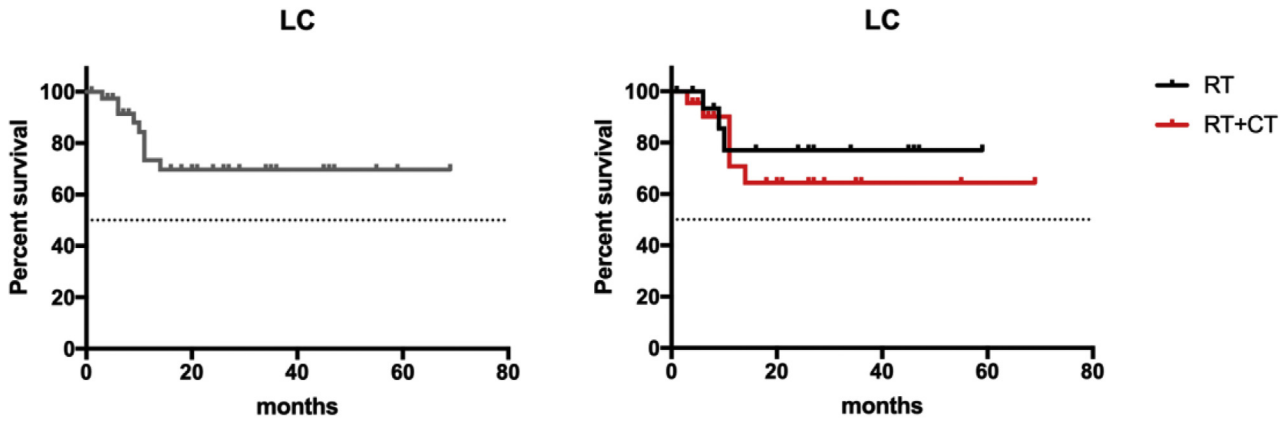

Fig. 1. Local Control (LC) for the entire sample (n = 41) and for patients who underwent RT-alone. (n = 19) or RT + CT (n = 22).

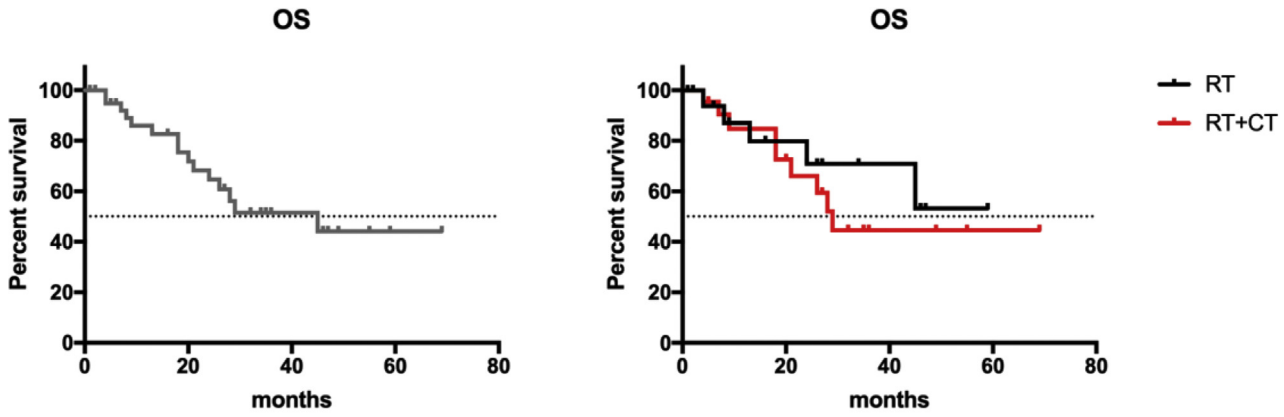

Fig. 2. Overall Survival (OS) for the entire sample (n = 41) and for patients who underwent RT-alone. (n = 19) or RT + CT (n = 22).

Table 5
Cumulative late sequelae. The table reports the number of patients and (%) that experienced late toxicities.

	G1	G2	G3	G4
Mucositis	1 (2.43)	1 (2.43)	1 (2.43)	
Dysphagia	3 (7.31)	3 (7.31)	2 (4.87)	
Xerostomia		2 (4.87)	1 (2.43)	
Dysgeusia		1 (2.43)		
Mandibular toxicity				1 (2.43)

Table 6
Overall response to treatments (n = 38).

Response	n (%)
Complete	21 (55.3)
Partial	11 (28.9)
Stable	5 (13.2)
Progression Disease	1 (2.7)

gressive disease (PD) in 1/38 (2.7%). No patient had post-treatment neck dissection. ORs are shown in Table 6.

The median follow-up (FU) for the entire sample of patients was 32 months (range 5–80), the median FU for the RT-alone and combined treatment groups was 26 and 35 months, respectively.

3.1. Local control

In the overall population, the 6-month and 1-year LC rate were 91.47% and 73.40%, respectively, while the 2-, 3-, 5-year LC rates were stable at 69.73% (Fig. 1). Subgroups analysis showed that there were no significant differences in LC rates between the RT-alone and combined treatment groups (p = 0.58, hazard ratio [HR] = 0.68, 95% CI: 0.18–2.54). The 6-month LC rates were 93.33% and 90.15% for the RT-alone and combined treatment arm, respectively. The 1-year LC was 77.70% and 70.83%, whereas the 2-, 3-, 5-year LC rates were stable at 77% and 64.39% for the RT-alone and combined treatment arm, respectively (Fig. 1).

3.2. Overall survival

The median OS for the overall cohort was 45 months. The 1-, 2-, 3-, 5-year OS rates were 85.93%, 64.66%, 51.49% and 44.14%, respectively (Fig. 2). The median OS was not reached in the radiotherapy (RT)-alone treatment arm and was 28 months in the combined treatment arm. Subgroups analysis showed that there were no significant differences in OS between the RT-alone and combined treatment groups (p = 0.55, hazard ratio [HR] = 0.71, 95% confidence interval [CI]: 0.25–2.06). In the RT-alone group, the 1-, 2-, 3-, 5-year OS rates were 87.05%, 70.93%, 70.93%, 53.20%, respectively. In the combined-treatment group, the 1-, 2-, 3-, 5-year OS rates were 84.78%, 60.56%, 40.88% and 40.88%, respectively (Fig. 2).

4. Discussion

The aim of our study was to evaluate clinical outcomes of locally-advanced (stage IV M0) HSNCC, including laryngeal cancers, considered inoperable for tumors extension and/or clinical conditions, and treated using VMAT/IMRT-SIB with or without concomitant systemic treatment in daily clinical practice. We choose

to treat HNSCCs patients using a moderately hypofractionated irradiation considering that these kinds of cancers present a high radio sensibility with an α/β ratio $\geq$10. In this regard, Mohan et al. proved that IMRT- SIB approach allows to simultaneously deliver high dose to the primary disease and lower dose to the subclinical disease or electively treated regions.[24] Butler et al. reported the first series of 20 patients treated with a SMART boost technique delivering a daily GTVp-n dose of 2.4 Gy and a prophylactic dose of 2 Gy per fraction. They reported a high early complete response rate in a heterogeneous series of patients with acceptable acute mucosal toxicity.[25]

In the present study, we observed an acceptable rate of acute toxicities mainly mucositis-related. To the best of our knowledge, only a few studies reported on the feasibility of association of concomitant boost/IMRT schedules with concomitant chemotherapy (or biotherapy). In a Phase II RTOG study, 72 Gy in 6 weeks concurrent with 2 cycles of cisplatin resulted mainly in severe acute toxicities.[26]Oral mucositis occurs in many HNSCC patients who undergo RT, especially when using hypofractionated schemes, and the adding of concurrent platinum-based chemotherapy increases this kind of toxicity. Therefore, in order to reduce toxicity profiles,[27,28] in particular mucositis, dysphagia, and pharyngoesophageal stricture, when SIB-IMRT is planned, the dose delivered on OARs should be evaluated carefully.

In our series we observed G3 mucositis in 8 patients (19.5%) and G3 dysphagia in 2 patients (5%) vs. 37-51% and 21-54%, respectively, found in literature.[29] The mild toxicities reported in our patients could be related to the systematic contouring of the oral cavity and the other mucosal structures (hard and soft palate, oropharyngeal mucosa) and the constrictor muscles outside the target volumes attempting at respecting the reference dose constraints with a medium-level of priority considering the proximity of GTV/GNV (Table 3). In fact, using a dose constraint on the oral mucosa outside the target volume, Sanguineti et al. reported a significant reduction of the mucosal volume in the high-dose region.[30]

Several reports support the efficacy of hypofractionated radiation schedules which provide a shorter overall treatment time on the basis of a lower recovery time of cell damage, despite a greater acute OAR toxicity.[31] On the other hand, superfractionated approaches, including concomitant boost and an escalated targets dose, have demonstrated a higher tumor control without increasing late tissue morbidity.[32]

In our series the clinical scenario due to age, comorbidity and clinical conditions of the patients permitted to deliver chemo/biotherapy in approximately half of them. We found OR rate in 84.2% of patients in line with recent studies.[33] These results are interesting considering the inclusion of only stage IV (M0) patients. Radiotherapy alone delivered with a SIB approach is a valid option for patients not suitable for systemic therapies due to comorbidities or other critical issues. However, combining chemotherapy with an altered fractionated radiation treatment has been reported to be feasible and effective in terms of loco-regional control and toxicity.[34,35]

In our study only one patient showed G4 toxicity (mandibular osteoradionecrosis). None developed trismus nor pharyngoesophageal stricture. Focusing on late salivary gland toxicity, we observed a gradual recovery after 2 years from the end of treatment. Additionally, the use of a rigorous preventive supportive care[36] could explain our better toxicity results.

In our series, 3-year LC and OS rates were 69.73% and 51.9%, respectively. These results may be considered acceptable in unselected patients treated in daily clinical practice out of protocol studies. Surprisingly our patients treated with concurrent chemo/bio-radiotherapy did not show neither better LC ($p = 0.58$, hazard ratio [HR] = 0.68, 95% CI: 0.18–2.54) nor OS ($p = 0.55$, hazard ratio [HR] = 0.71, 95% confidence interval [CI]: 0.25–2.06) with respect to patients treated with radiotherapy alone. These results could be due to the small sample size, even though our series was homogeneous since it included only unresectable stage IV (M0) HNSCC. However, multivariate analysis was not performed due to the small sample size and the related intrinsic limitations of the retrospective nature of the study.

Finally, the advantage of radiochemotherapy in this setting has been principally demonstrated in clinical trials that used a standard scheme of radiotherapy.[37]

Transferring experimental data in daily clinical practice is the test on the true feasibility of a therapeutic approach, as a preselection of patients is not possible in a real-life scenario.[38] The experience of patients and physicians in routine clinical practice is often different from that in a controlled clinical trial setting. In addition, “real world” presents a unique avenue for obtaining data on patients with characteristics outside those typically required for trial eligibility. Prospective and randomized clinical trials often enroll younger patients who lack comorbidities, have adequate organ functions, possess proper psychosocial support and are able to travel to study sites.[39]

Therefore, the combined treatment should be routinely delivered at least in every centre where there is a multidisciplinary team in clinical oncology. In conclusion, we can affirm that SIB-IMRT/VMAT is safe, with a good profile of tolerability, and can be used with concomitant chemotherapy/biotherapy in daily clinical practice.

However, further studies, focused on clinical practice, are warranted to confirm our observations.

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None declared.

Conflict of interest

None declared.

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