Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Initial experience of hypofractionated radiation retreatment with true beam and flattening filter free beam in selected case reports of recurrent nasopharyngeal carcinoma

Filippo Alongi, Elena Clerici, Sara Pentimalli, Pietro Mancosu, Marta Scorsetti*

Radiotherapy and Radiosurgery Department, Humanitas Cancer Center, Istituto Clinico Humanitas, Via Manzoni 56, 20089 Rozzano, Milan, Italy

ARTICLE INFO

Article history:
Received 10 December 2011
Received in revised form
30 April 2012
Accepted 17 July 2012

Keywords:
Reirradiation
Hypofractionation
Nasopharyngeal carcinoma
Flattening filter free beam

ABSTRACT

Aim: To show our preliminary experience in using TrueBeam with RapidArc technology and FFF beam for stereotactic re-irradiation of nasopharyngeal carcinoma.

Background: Thanks to new advanced techniques, as well as intensity modulated radiation therapy, it is possible to approach head and neck recurrences in selected patients. Volumetric Modulated Arc Therapy (VMAT) in its RapidArc® format, permits to reduce significantly the time to deliver complex intensity modulated plans, allowing to treat hypofractionated regimes within a few minutes. With TrueBeam it is possible to perform photon beams without usage of the flattening filter. It seems possible to expect a reduction of out-of-field dose when flattening filter free (FFF) beams are used. While research into the physics domain for FFF beams is increasing, there are very few clinical data where FFF beams are applied in clinical practice.

Materials and methods: We present here the cases of 4 patients with local or regional recurrence of nasopharyngeal carcinoma. All patients were treated using TrueBeam with RapidArc technology and FFF beam for stereotactic hypofractionated re-irradiation.

Results: All patients concluded SBRT and showed good tolerability. During follow-up, complete response at imaging evaluation (PET and/or MRI) for all treated patients was documented.

Conclusions: Our preliminary experience using TrueBeam with RapidArc technology and FFF beam for stereotactic hypofractionated re-irradiation of nasopharyngeal carcinoma was safe and effective in all 4 treated patients. Longer follow-up and a larger population of study is needed to confirm these promising results.

1. Background

Systemic therapy is increasing survival in several subsets of patients with head and neck cancer. Locoregional recurrence remains the predominant pattern of failure after treatments in head and neck cancer patients; it also represents the most common cause of death.[1] Thus, local reirradiation is considered as a possible treatment option in case of recurrence in the site of disease.

* *Corresponding author*. Tel.: +39 0282248522; fax: +39 0282248509.
E-mail address: filippo.alongi@libero.it (F. Alongi).

1507-1367/$ – see front matter
http://dx.doi.org/10.1016/j.rpor.2012.07.012

Radiation retreatment is a problematic issue to resolve in clinical practice: it requires knowledge on the possibility of unforeseen toxicity risks in healthy tissue. "Dose sculpting" on active tumor with IMRT is a helpful approach to minimize the radiation dose to previously irradiated tissues.[2] Image-guided radiation therapy (IGRT) reduces repositioning errors and is used to monitor the treatment region and/or to adapt dose distribution to the possibly changing target and organs at risk during radiotherapy.[3] Recently, two new technological platforms have been made available to clinical practice. Firstly, Volumetric Modulated Arc Therapy (VMAT) in its RapidArc® format permits to reduce significantly the time needed to deliver complex intensity modulated plans, allowing to treat hypofractionated regimes within a few minutes.[4] Secondly, there has been increasing attention on the clinical use of linear accelerators (LINAC) with photon beams generated without the usage of a flattening filter.[5–8] It seems possible to expect a reduction of out of-field dose when flattening filter free (FFF) beams are used.[33–36] This is mainly due to reduced head scatter and residual electron contamination. FFF beams should, therefore, lead to reduced peripheral doses and patients may benefit by decreased exposure of normal tissue to scattered doses outside the field. Removal of the flattening filter implies also the possibility to deliver treatments with higher dose rates, up to the factor 4 at 10 MV, and with a much higher dose per pulse. This, beside further improving time efficiency for delivery, might have subsequent potential radiobiologic implications still unclear and deserving dedicated investigations. While research into the physics domain for FFF beams is increasing, there are very few clinical data where FFF beams are applied in clinical practice,[32] particularly in stereotactic hypofractionated head and neck re-treatments.

2. Aim

We present herein our preliminary experience in 4 patients using TrueBeam with RapidArc technology and FFF beam used for stereotactic hypofractionated re-irradiation on local or regional recurrence of nasopharyngeal carcinoma.

3. Materials and methods

TrueBeam™ is a new LINAC designed to deliver flattened, as well as flattening filter-free (FFF) photon beams. In TrueBeam™, many key elements including the waveguide system, carousel assembly, beam generation, and monitoring control system differ from the preceding LINAC series as described in.[9] All patients were treated with RapidArc® using 10 MV FFF beams. The maximum dose rate enabled for FFF beams was 2400 MU/min for 10 MV. RapidArc® plans were individually designed using full or partial single or multiple arcs chosen to obtain the best adherence to planning objectives for each patient.[10] Treatment was delivered in 5 fractions in 3 patients with recurrence in nasopharynx region and in 18 fractions in one patient with lymph node relapse, both over consecutive working days. Treatment delivery included stereotactic frame localization and CBCT in the first session aiming at a preliminary isocentre positioning while for the following fractions, patient set-up was done by means of a daily CBCT image guidance with eventual on-line couch adjustment at each fraction. Image matching was performed on bones and, when visible, on tumors and other soft tissue structures. Clinical evaluations were planned on the first day of treatment, before radiation FFF session (visit 0); visit 1 in the course of the treatment; visit 2 at the end of the last session; visit 3 within 60–90 days from the end of the treatment. Unscheduled visits could be performed if necessary. Acute radiation induced toxicities were scored according to NCI Common Terminology Criteria for Adverse Events (CTCAE version 3.0).[11] A first assessment of treatment outcome, although obviously very early, was made at first and second follow up visits and are reported in terms of degree of response.

3.1. *Case 1*

Female patient, 41 years old. No other important concomitant diseases were recorded in anamnesis. In July 2007, a diagnosis of G2 carcinoma was made after a nasopharyngeal biopsy. Concomitant presence of neoplastic cells at needle aspiration exam in lateral right lymph node enlargement was confirmed. A cisplatin and 5-FU-based chemotherapy regimen was administered for two cycles and a partial response was shown at MRI after 2 months. A subsequent concomitant radiochemotherapy was performed, delivering 56 Gy by means of external beam radiotherapy to the whole neck and a boost by brachytherapy with doses of 9 Gy in 3 fractions. In 2009, CT detected local failure in the left nasopharyngeal region during follow-up. A biopsy confirmed the recurrence of nasopharyngeal Grade 3 carcinoma. Taxotere chemotherapy was administered for 6 cycles with further local progression shown on CT with contrast enhancement. In June 2010, a PET/CT confirmed the local failure with an exclusive FDG pathologic accumulation in the left region of the nasopharynx. In August 2010, Cetuximab was administered as salvage therapy. A CT for re-evaluation four months later showed further local progression of disease on the left side. In March 2011, the patient was referred to our Department of Radiotherapy and Radiosurgery where it was decided to re-irradiate the patient. PET/CT and MRI were used as imaging tools for image fusion with CT during a virtual simulation procedure. Stereotactic body radiotherapy was performed by means of TrueBeam with the RapidArc technique in 5 fractions of 6 Gy with a cumulative dose of 30 Gy. The treatment was completed without acute side effects. In June 2011, at the first clinical and instrumental evaluation during follow-up, PET/CT showed significant reduction of FDG accumulation in the treated area (see Fig. 1). No side effects were recorded. In September 2011, a complete metabolic response was shown at PET/CT and the same result of the absence of signs of recurrence/persistence was confirmed morphologically at the last MRI control in November 2011. During follow-up controls, the otorhinolaryngologist detected a congestion and thickening of the mucosa on the left side. With a minimum follow-up of 9 months, the patient is free of relapse and only moderate earache and sore throat were clinically recorded.

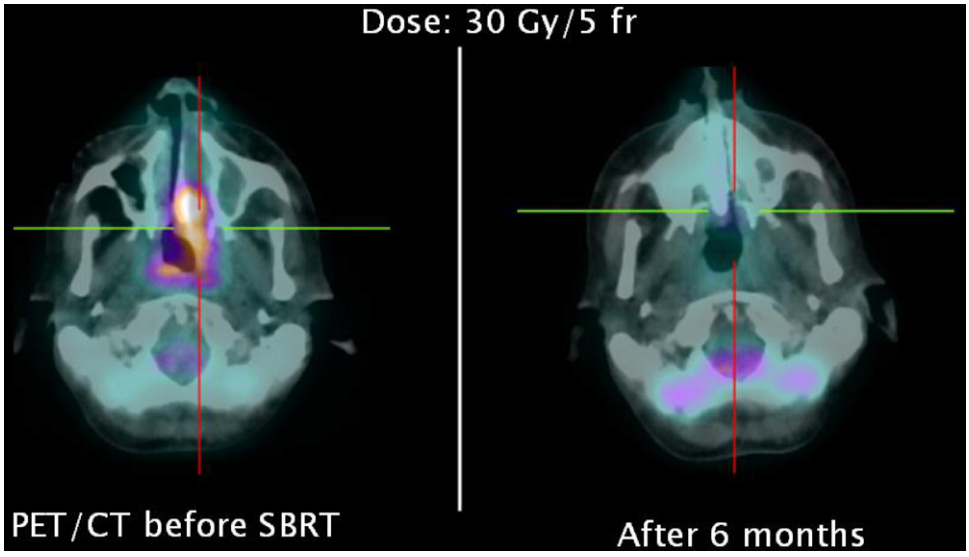

Fig. 1 – Case 1: Direct comparison of PET/CT axial images before and 6 months after the SBRT re-treatment (30 Gy in 5 fractions), showing a complete response of nasophaynx recurrence.

3.2. *Case 2*

Male patient, 43 years old. In June 2009, metastases of carcinoma were diagnosed during a neck level IIA–IIB dissection after the first negative nasopharynx biopsy. A subsequent biopsy in the nasopharynx region confirmed carcinoma of Grade 2. MRI showed multiple bilateral lymph node enlargement on Level II and an infiltration of the parapharyngeal space on the left side. In July–August 2009, two cycles of TPF chemotherapy was administered. Between September and November 2009 the patient was submitted to radiotherapy: 56 Gy were delivered to the whole neck with a sequential boost for a cumulative dose of 70 Gy to the rhinopharynx and positive node involved in the neck bilaterally. Concomitant cisplatin (100 mg/mq) was administered weekly. In January 2010, MRI showed a complete response. The patient was free from recurrence until March 2011, when MRI evidenced pathological tissue on the nasopharynx on the left side toward the nasal cavity. A nasal cavity biopsy confirmed focal infiltration of nasopharynx carcinoma. In April 2011, the patient was referred to our Department of Radiotherapy and Radiosurgery and it was decided to re-irradiate the patient. PET/CT and MRI were used as imaging tools for image fusion with CT during a virtual simulation procedure. Stereotactic body radiotherapy was performed by means of TrueBeam with the RapidArc technique in 5 fractions of 6 Gy with a cumulative dose of 30 Gy. The treatment was completed without acute side effects. In May 2011, at the first clinical and instrumental evaluation during follow-up, PET/CT showed a significant reduction of FDG accumulation in the treated area in the posterior part of the rhinopharynx region (see Fig. 2). Earache, lachrymation increasing reduction of visual activity of the right eye

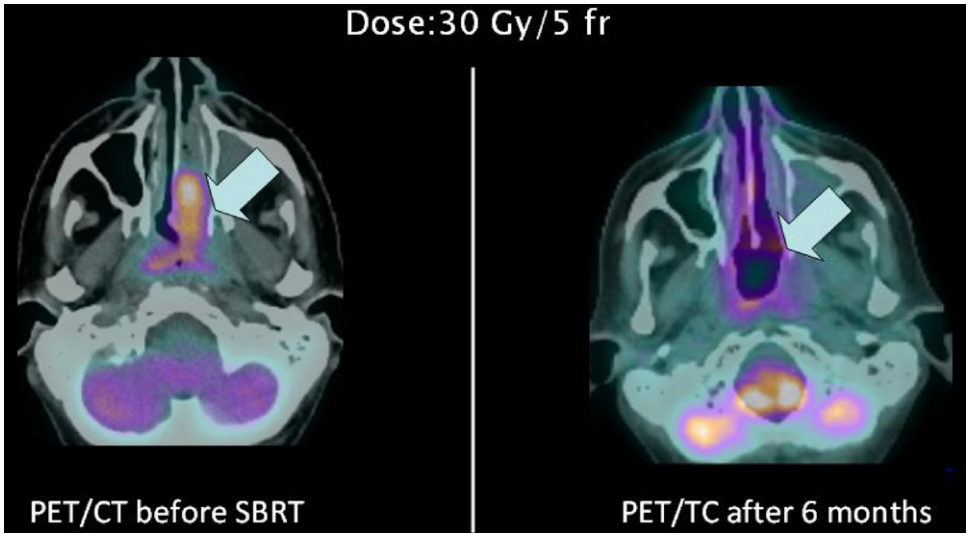

Fig. 2 – Case 2: Direct comparison of PET/CT images before and 6 months after the SBRT treatment (30 Gy in 5 fractions), showing (with white arrows) a complete response in the site of nasophaynx relapse.

were recorded. A visit to the optometrist was recommended. During follow-up controls, the otorhinolaryngologist detected some crusting mucus on the roof of the nasopharynx that was aspirated. No suspicion of recurrence was found. In November 2010, PET/CT showed a complete metabolic response. With a minimum follow-up of 8 months the patient is free of relapse and only moderate earache and sore throat were clinically recorded.

3.3. *Case 3*

Male patient, 53 years old. In March 2008, the patient complained of diplopia and headache. In April 2008, MRI detected an infiltration by neoplastic tissue in the clivus region towards sphenoidal bone and nasopharyngeal mucosa on the left side. With the suspicion of neoplasm of the clivus the patient was submitted to a neurosurgery procedure to remove the lesion: the histological specimen revealed undifferentiated carcinoma of the nasopharynx, related to EBV infection. Post-surgical MRI confirmed residual tissue in the nasopharyngeal mucosa and left latero-cervical lymph node (Level II) enlargement greater than 1 cm in diameter. Between May and August 2008, three cycles of TPF chemotherapy were administered. MRI showed stable disease and the patient was referred to the Radiation Oncology Department to undergo radical treatment to the nasopharynx and pathological lymph node at II level (70 Gy) and precautional irradiation of the whole neck with 54 Gy. The treatment was not well tolerated and the patient complained of a high grade of mucositis with mucosal ulceration of the mouth. In January 2009, a complete response was found at MRI. In May 2009, the MRI performed during follow-up evidenced inhomogeneous intensity signal for new tissue on the upper part of the nasopharynx towards the pre-vertebral region. A biopsy performed in the suspicious region was negative and the patient was followed up with MRI to evaluate the change in the suspicious tissue. Minimal progression was found in January 2010 but the patient refused treatment until March 2010 when three cycles of TPF-based chemotherapy were administered. In July 2010, a severe episode of epistaxis with tinnitus and anemization occurred needing hospitalization. Desametasone was administered during support therapy and a remission of symptoms was achieved after a few days.

In August 2010, MRI showed stable disease. PET/CT confirmed the disease with a pathological accumulation of FDG on the nasopharynx, close to the temporal bone. In September 2010, the patient was referred to our Department of Radiotherapy and Radiosurgery and, after a multidisciplinary discussion with medical oncologists and head and neck surgeons, it was decided to re-irradiate the patient. PET/CT and MRI were utilized as imaging tools for image fusion with CT during a virtual simulation procedure. A stereotactic body radiotherapy was performed by means of TrueBeam with the RapidArc technique in 5 fractions of 6 Gy with a cumulative dose of 30 Gy. After treatment, the patient complained of just a mild headache and clinical situation was stable. At the first clinical and instrumental evaluation during follow-up in December 2010, PET/CT showed a complete metabolic response in the treated area (see Fig. 3). This pattern of the absence of disease was confirmed at MRI after three months. The patient was free from failure during instrumental and clinical evaluation for 14 months until an episode of stroke cerebri. It was not possible to correlate this acute episode to the vascular damage of previous local and systemic treatments.

3.4. *Case 4*

Male patient 60 years old. In August 2005, nasopharyngeal carcinoma was diagnosed and treated with radical radiochemotherapy: 70 Gy to the nasopharynx, 54 Gy to neck bilaterally. Concomitant cisplatin (100 mg/mq) was administered weekly. The patient was free from recurrence until March 2011 when MRI detected lymph nodal enlargement of the IB/IIA level on the right side of the neck, in the right parapharyngeal region. Biopsy revealed nasopaharyngeal carcinoma. In April 2011, PET confirmed pathologic accumulation of FDG in the same region. In May 2011, the patient was referred to our Department of Radiotherapy and Radiosurgery and, after a multidisciplinary discussion with medical oncologists

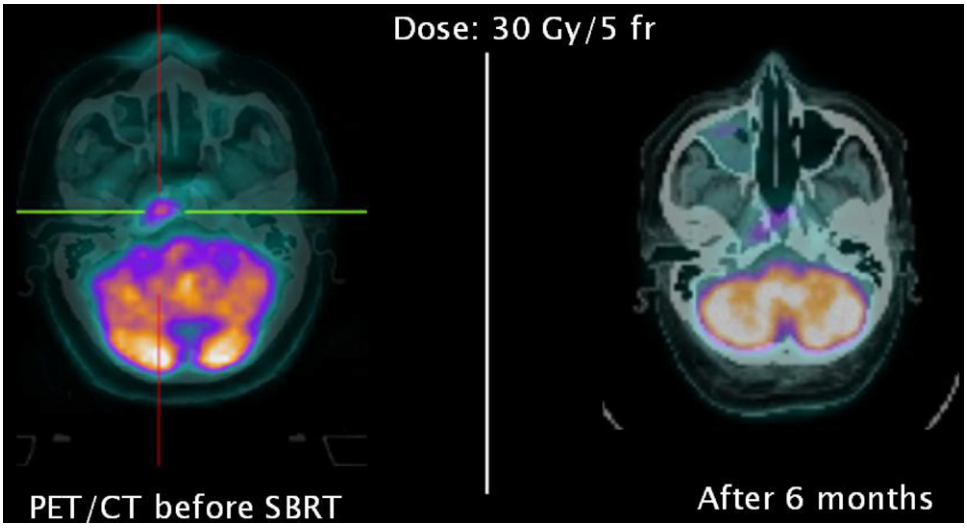

Fig. 3 – Case 3: Direct comparison of PET/CT axial images before and after the SBRT treatment (30 Gy in 5 fractions), showing a complete response in the site of nasophaynx recurrence.

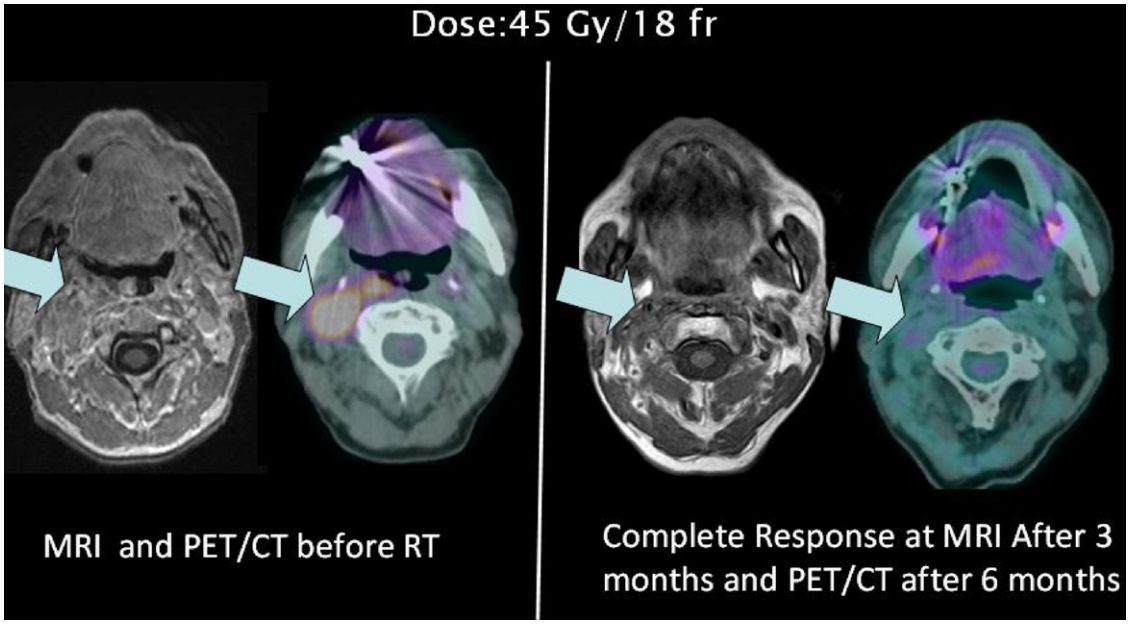

Fig. 4 – Case 4: Direct comparison of MRI and PET/CT axial images performed before re-irriadiation (45 Gy in 18 fractions) and after the re-treatment, showing a complete response in the irradiated lymph nodal site of recurrence.

and head and neck surgeons, it was decided to re-irradiate the patient. PET/CT and MRI were utilized as imaging tools for image fusion with CT during a virtual simulation procedure. Hypofractionated radiotherapy was performed by means of TrueBeam with the RapidArc technique in 18 fractions of 2.5 Gy with a cumulative dose of 45 Gy. The treatment was well tolerated. Only mild dysphagia was reported. In August 2011, at the first clinical and instrumental evaluation during follow-up, MRI showed a complete response in the treated area (see Fig. 4). Otorhinolaryngologist evaluation was negative for recurrence. In November 2011, PET/CT confirmed a complete metabolic response in the treated area. At the time of analysis, the patient was free from failure after 6 months from reirradiation.

4. Discussion

Radiation oncologists must consider several parameters before prescribing retreatment with radiation. The feasibility of reirradiation, especially in head and neck disease, depends on previous doses and fields, the time between irradiation and reirradiation, the general condition of the patient related to life expectancy, and alternative treatment options. With regard to dose tolerance in reirradiation, there is no consensus about the dose limits to normal tissue involved in the field of previous radiotherapy. Concerning the current 4 cases, for each patient a description of: (a) the dose delivered to the nasopharynx during each course of RT, (b) the BED calculation (biologically effective dose) for the different tissues ($\alpha/\beta = 15$ for tumour; $\alpha/\beta = 10$ for acute response tissues as well as mucosa; $\alpha/\beta = 4$ for late responding tissues as well as nerves) during each course of RT (c) the BED calculation of cumulative doses for the two courses of RT, are shown in detail in Table 1. The maintenance of functional activity in the pre-irradiated field should be an absolute priority.[12] The few clinical data available in the literature are extremely heterogeneous and not only about head and neck district[13–22]: various techniques (3-dimensional conformal radiotherapy, intraoperative radiotherapy, brachytherapy, IMRT, stereotactic radiotherapy) were reported in the same review; curative-intent and palliative intent retreatments. Radiation side effects were also recorded with various toxicity scales in different centers. The prescribed retreatment doses are consequently decided upon on a purely empirical basis. A cumulative toxicity risk evaluation with the overlap of field/isodose curves of the two treatments or with the analysis of modern biological parameters, if available, could be a way to minimize uncertainty regarding toxicity. In three out of 4 of the presented cases we decided to prescribe an extreme hypofractionation as scheduled for re-irradiation in the nasopharynx primary tumour region.

The choice of the prescription dose in hypofractionated schedule with a high focused technique of radiotherapy, as a stereotactic radiation therapy approach, was related also to the paucity of experiences published recently on this subject.[21,23] However, a well known radiobiologic assumption can support the approach of large dose per fraction in head and neck retreatment with SBRT: the oral mucosa is an acute responding tissue and it could be more damaged after a larger cumulative dose (delivered for example by 1.8–2 Gy per fraction) than in the cases when the cumulative dose is reduced (delivered for example by 6 Gy per fraction).[24] Compared to the 3 cases of extreme hypofractionation here reported, in case 4, lymph nodal recurrence was treated with a more careful dosage of 45 Gy in 18 fractions. We adopted the choice of a moderate hypofractionation to avoid at maximum the damage of cumulative doses of the two courses to soft tissues and mucosa, in this case too close to other types of various healthy tissues: carotid vessels, mandible and vertebral bones, spine, parotid gland. Few data on the time interval

Table 1 – Description for each patient of: (a) the dose delivered to the nasopharynx during each course of RT, (b) the BED calculation (biologically effective dose) for the different tissues($\alpha/\beta = 15$ for tumour; $\alpha/\beta = 10$ for acute response tissues as well as mucosa; $\alpha/\beta = 4$ for late responding tissues as well as nerves) during each course of RT (c) the BED calculation of cumulative doses for the two courses of RT.

Case number	Nominal dose in Gy of the first RT course to the nasopharynx region	BED of first RT course to the nasopharynx region	Nominal dose in Gy of the second RT course to the nasopharynx region	BED of the second RT course to the nasopharynx region	Cumulative BED of the two RT courses to the nasopharynx region
1	56 Gy + 9 Gy (boost)*	* Not applicable	30 Gy	42($\alpha/\beta = 15$) 48($\alpha/\beta = 10$) 75($\alpha/\beta = 4$)	* Not applicable
2	70 Gy	79($\alpha/\beta = 15$) 84($\alpha/\beta = 10$) 105($\alpha/\beta = 4$)	30 Gy	42($\alpha/\beta = 15$) 48($\alpha/\beta = 10$) 75($\alpha/\beta = 4$)	112($\alpha/\beta = 15$) 132($\alpha/\beta = 10$) 180($\alpha/\beta = 4$)
3	70 Gy	79.3($\alpha/\beta = 15$) 84($\alpha/\beta = 10$) 105($\alpha/\beta = 5$)	30 Gy	42($\alpha/\beta = 15$) 48($\alpha/\beta = 10$) 75($\alpha/\beta = 4$)	112($\alpha/\beta = 15$) 132($\alpha/\beta = 10$) 180($\alpha/\beta = 4$)
4	70 Gy	79($\alpha/\beta = 15$) 84($\alpha/\beta = 10$) 105($\alpha/\beta = 4$)	45 Gy	42($\alpha/\beta = 15$) 48($\alpha/\beta = 10$) 75($\alpha/\beta = 4$)	112($\alpha/\beta = 15$) 132($\alpha/\beta = 10$) 180($\alpha/\beta = 4$)

issue are available in the literature and most are from preclinical analyses: the minimum interval between two radiation treatments has not been clearly established. It might be considered a sound approach to allow for an interval longer than the period in which the most common late side effects would be expected.[23] This depends, however, on previous doses to organs at risk and the type of tissue damage repair. Complete restoration of early radiation damage in some tissues, such as skin or oral mucosa, ranges from 12 to 90 days.[2,23] For late damage, tissue recovery is variable and 5–6 months may be necessary for many tissue types, as reported in preclinical studies.[25–27] In our four cases reported herein, a minimum period of one year between prior radiotherapy and the new course was guaranteed. Obviously, when the period is longer than one year, the possibility of recovery from damage of the previous treatment is higher making it more possible to prescribe more effective doses and record less toxicity. The ideal modalities of reirradiation involve other critical points, including a better definition of the target to be reirradiated.[28] In most cancer patients, PET/CT could be highly useful before reirradiation for better definition of disease recurrence and disease restaging.[29] In all of the cases here presented, PET/CT was performed during target definition and during follow-up. Setup accuracy is another crucial point: immobilization devices are essential to reduce setup errors.[3] "Dose sculpting" on active tumor site with IMRT, as volumetric modulation arc therapy with the RapidArc technique of the four current cases, is a helpful approach to minimize the radiation dose to previously irradiated tissue.[4,30,31] Image-guided radiation therapy (IGRT) reduces repositioning errors and is used to monitor the treatment region.[3] TrueBeam is a platform for advanced radiotherapy that combines the RapidArc technique and IGRT by means of ConeBeam CTs, with the innovative possibility to deliver high doses per fraction in a few minutes. The capacity of TrueBeam to reduce treatment time is related to the FFF modality that allows the LINAC to perform a dose rate four times greater than a classic beam. Reduction of treatment time is crucial to reduce uncertainties of positioning during delivery, especially when very high doses per fraction are delivered close to organs at risk.[5–9,32] Obviously, in re-irradiation, this can be even more important. Considering the continuous advances in more detailed cancer imaging and safer radiation technology, promising clinical data, such as the cases herein presented, suggesting new possibilities to re-irradiate cancer patients in selected cases are still awaited. Thus, cases of re-irradiation will be even more usual for new generation of Radiation Oncologists in the next few years and they must be more conscious about the risks of retreatments but also on new potential weapon to face these challenging situations.

Conflict of interest

None declared.

REFERENCES

1. Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and neck cancer. *N Engl J Med* 1993;**328**:184–94.
2. Sulman EP, Schwartz DL, Le TT, et al. IMRT reirradiation of head and neck cancer—disease control and morbidity outcomes. *Int J Radiat Oncol Biol Phys* 2009;**73**:399–409.
3. Alongi F, Di Muzio N. Image-guided radiation therapy: a new era for the radiation oncologist? *Int J Clin Oncol* 2009;**14**:568–9.
4. Otto K. Volumetric modulated arc therapy: IMRT in a single gantry arc. *Med Phys* 2008;**35**:p310–7.
5. Poenisch F, Titt U, Vassiliev O, et al. Properties of unflattened photon beams shaped by a multileaf collimator. *Med Phys* 2006;**33**:1738–46.
6. Vassiliev ON, Kry SF, Chang JY, et al. Stereotactic radiotherapy for lung cancer using a flattening filter free Clinac. *J Appl Clin Med Phys* 2009;**10**:2880.
7. Georg D, Knoos T, McClean B. Current status and future perspective of flattening filter free photon beams. *Med Phys* 2011;**38**:1280–93.
8. Kragl G, Wetterstedt S, Knausl B, et al. Dosimetric characteristics of 6 and 10 MV unflattened photon beams. *Radiother Oncol* 2009;**93**:141–6.
9. Hrbacek J, Lang S, Kloeck S. Commissioning of photon beams of a flattening filter free linear accelerator and the accuracy

of beam modeling using an anisotropic analytical algorithm. *Int J Radiat Oncol Biol Phys* 2012.
10. Fogliata A, Clivio A, Nicolini G, et al. Intensity modulation with photons for benign intracranial tumours. A planning comparison of volumetric single arc, helical arc and fixed gantry techniques. *Radiother Oncol* 2008;**89**:254–62.
11. National Cancer Institute. *Cancer Therapy Evaluation Program. Common terminology criteria for adverse events. Version 3.0.* DCTD, NCI, NIH, NHHS; 2003, http://ctep.cancer.gov.
12. Stewart FA, Dörr W. Milestones in normal tissue radiation biology over the past 50 years: from clonogenic cell survival to cytokine networks and back to stem cell recovery. *Int J Radiat Biol* 2009;**85**:574–86.
13. Mendenhall WM, Mendenhall CM, Malyapa RS, Palta JR, Mendenhall NP. Re-irradiation of head and neck carcinoma. *Am J Clin Oncol* 2008;**31**:393–8.
14. Jereczek-Fossa BA, Kowalczyk A, D'Onofrio A, et al. Three-dimensional conformal or stereotactic reirradiation of recurrent, metastatic or new primary tumors. Analysis of 108 patients. *Strahlenther Onkol* 2008;**184**:36–40.
15. Combs SE, Debus J, Schulz-Ertner D. Radiotherapeutic alternatives for previously irradiated recurrent gliomas. *BMC Cancer* 2007;**7**:167.
16. Mayer R, Sminia P. Reirradiation tolerance of the human brain. *Int J Radiat Oncol Biol Phys* 2008;**70**:1350–60.
17. Grosu AL, Andratschke N, Nieder C, Molls M. Retreatment of the spinal cord with palliative radiotherapy. *Int J Radiat Oncol Biol Phys* 2002;**52**:1288–92.
18. Das P, Delclos ME, Skibber JM, et al. Hyperfractionated accelerated radiotherapy for rectal cancer in patients with prior pelvic irradiation. *Int J Radiat Oncol Biol Phys* 2009;**77**:60–5.
19. Maranzano E, Trippa F, Pacchiarini D, et al. Re-irradiation of brain metastases and metastatic spinal cord compression: clinical practice suggestions. *Tumori* 2005;**91**:325–30.
20. Alongi F, Di Muzio N, Schipani S, Fazio F. Helical tomotherapy in radiation retreatments. *Radiother Oncol* 2006;**81**:S520 [Abstract ESTRO 25, Leipzig, Germany, October 8–12, 2006].
21. Comet B, Lartigau E. Reirradiation of head and neck cancers. *Cancer Radiother* 2010;**14**:416–20.
22. Chojnacka M, Skowrońska-Gardas A, Pędziwiatr K, Morawska-Kaczyńska M, Perek M, Perek D. Reirradiation of relapsed brain tumors in children. *Rep Pract Oncol Radiother* 2012;**17**:32–7.
23. Alongi F, Di Muzio N, Scorsetti M. Reirradiation: hopes and concerns of the radiation oncologist. *Tumori* 2010;**96**:792–3.
24. Kubicek GJ, Heron DE. In Regard to "ACR Appropriateness Criteria of Recurrent Head-and-Neck Cancer After Prior Definitive Radiation." (Int J Radiat Oncol Biol Phys 2011;80:1292–1298). *Int J Radiat Oncol Biol Phys* 2012;**82**: 1322–3.
25. Ang KK, Jiang GL, Feng Y, Stephens LC, Tucker SL, Price RE. Extent and kinetics of recovery of occult spinal cord injury. *Int J Radiat Oncol Biol Phys* 2001;**50**:1013–20.
26. van der Kogel AJ, Sissingh HA, Zoetelief J. Effect of X rays and neutrons on repair and regeneration in the rat spinal cord. *Int J Radiat Oncol Biol Phys* 1982;**8**:2095–7.
27. Terry NH, Tucker SL, Travis EL. Residual radiation damage in murine lung assessed by pneumonitis. *Int J Radiat Oncol Biol Phys* 1988;**14**:929–38.
28. Trojanowska A. Squamous cell carcinoma of the head and neck – the role of diffusion and perfusion imaging in tumor recurrence and follow-up. *Rep Pract Oncol Radiother* 2011;**16**(6):207–12.
29. Messa C, Di Muzio N, Picchio M, Gilardi MC, Bettinardi V, Fazio F. PET/CT and radiotherapy. *Q J Nucl Med Mol Imaging* 2006;**50**:4–14.
30. Scorsetti M, Fogliata A, Castiglioni S, et al. Early clinical experience with volumetric modulated arc therapy in head and neck cancer patients. *Radiat Oncol* 2010;**5**:93.
31. Kumar SAS, Vivekanandan N, Sriram P. A study on conventional IMRT and RapidArc treatment planning techniques for head and neck cancers. *Rep Pract Oncol Radiother* 2012;**17**(3):168–75.
32. Scorsetti M, Alongi F, Castiglioni S, et al. Feasibility and early clinical assessment of flattening filter free (FFF) based stereotactic body radiotherapy (SBRT) treatments. *Radiat Oncol* 2011;**6**(September 12):113.
33. Nicolini G, Ghosh-Laskar S, Shrivastava SK, et al. Volumetric Modulation Arc Radiotherapy With Flattening Filter-Free Beams Compared With Static Gantry IMRT and 3D Conformal Radiotherapy for Advanced Esophageal Cancer: A Feasibility Study. *Int J Radiat Oncol Biol Phys* 2012 Mar 2 [Epub ahead of print].
34. Lang S, Reggiori G, Puxeu Vaquee J, et al. Pretreatment quality assurance of flattening filter free beams on 224 patients for intensity modulated plans: a multicentric study. *Med Phys* 2012;**39**(Mar 3):1351–6.
35. Reggiori G, Mancosu P, Castiglioni S, et al. Can volumetric modulated arc therapy with flattening filter free beams play a role in stereotactic body radiotherapy for liver lesions? A volume-based analysis. *Med Phys* 2012;**39**(Feb 2):1112–8.
36. Mancosu P, Castiglioni S, Reggiori G, et al. Stereotactic body radiation therapy for liver tumours using flattening filter free beam: dosimetric and technical considerations. *Radiat Oncol* 2012;**Feb 7**:16.