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Proton re-irradiation of unresectable recurrent head and neck cancers

Konstantin Gordon[1], Igor Gulidov[2], Alexey Semenov[1], Olga Golovanova[3], Sergey Koryakin[3], Tatyana Makeenkova[1], Sergey Ivanov[4], Andrey Kaprin[5]

[1]Department of Proton and Photon Therapy, A. Tsyb Medical Radiological Research Center, Obninsk, Russia
[2]Radiation Therapy Department, A. Tsyb Medical Radiological Research Center, Obninsk, Russia
[3]Radiophysics Department, A. Tsyb Medical Radiological Research Center, Obninsk, Russia
[4]A. Tsyb Medical Radiological Research Center, Obninsk, Russia
[5]National Medical Research Center of Radiology, Obninsk, Russia

ABSTRACT

Background: This study presents a retrospective analysis (efficacy and toxicity) of outcomes in patients with unresectable recurrence of previously irradiated head and neck (H&N) cancers treated with proton therapy. Locoregional recurrence is the main pattern of failure in the treatment of H&N cancers. Proton re-irradiation in patients with relapse after prior radiotherapy might be valid as promising as a challenging treatment option.

Materials and methods: From November 2015 to January 2020, 30 patients with in-field recurrence of head and neck cancer, who were not suitable for surgery due to medical contraindications, tumor localization, or extent, received re-irradiation with intensity-modulated proton therapy (IMPT). Sites of retreatment included the aerodigestive tract (60%) and the base of skull (40%). The median total dose of prior radiotherapy was 55.0 Gy. The median time to the second course was 38 months. The median re-irradiated tumor volume was 158.1 cm^3. Patients were treated with 2.0, 2.4, and 3.0 GyRBE per fraction, with a median equivalent dose (EQD_2) of 57.6 Gy ($\alpha/\beta = 10$). Radiation-induced toxicity was recorded according to the RTOG/EORTC criteria.

Results: The 1- and 2-year local control (LC), progression-free survival (PFS), and overall survival (OS) were 52.6/21.0, 21.9/10.9, and 73.4/8.4%, respectively, with a median follow-up time of 21 months. The median overall survival was 16 months. Acute grade 3 toxicity was observed in one patient (3.3%). There were five late severe side effects (16.6%), with one death associated with re-irradiation.

Conclusion: Re-irradiation with a proton beam can be considered a safe and efficient treatment even for a group of patients with unresectable recurrent H&N cancers.

Key words: re-irradiation; proton therapy; head and neck cancer; disease control; toxicity; unresectable

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Introduction

Head and neck (H&N) cancers are among the most common cancers, accounting for more than 500,000 new cases, with around 300.000 deaths each year [1]. Despite treatment intensification in the last decades, the 5-year overall survival still varies between 40% to 50% [2]. Most patients have a high risk of locoregional recurrence or second metachronous tumors occurring marginal or

Address for correspondence: Konstantin Gordon, Ph.D. Senior Researcher, Radiation Oncologist , Department of Proton Therapy, A. Tsyb Medical Radiological Research Centre, 249036, Korolev str. 4, Obninsk, Russia, tel: 0079105184148; e-mail: dr_gordon@yahoo.com; gordon@mrrc.obninsk.ru

close to previously irradiated volume [3, 4]. Surgery as a salvage option for relapse is considered to be highly efficient, with 5-year overall survival approaching 40% [5]. Surgery can provide additional benefit by removing radio- and chemoresistant tumor cells that create a higher possibility of a combined cure. However, many patients are not candidates for surgical approaches because of the recurrent tumor extent or medical contraindications [6, 7]. With chemotherapy alone, which has been the most common option for inoperable patients, the response rate is relatively low, limited to a median survival time of 7–8 months [8]. Re-irradiation with conventional or hypofractionation (SBRT) showed promising results as a potentially curative treatment, although increasing severe toxicities rates up to 40% [9, 10].

While locoregional failure after the second radiotherapy (RT) course is still common, some patients might be irradiated again. It has become critically important to spare normal tissue as much as possible, owing to its impact on the quality of life (QoL) and further treatment.

Since recurrence treatment goals are not only to cure the patient but also to provide acceptable QoL, proton therapy (PT) becomes more frequently used as a re-irradiation approach over the last decades [11]. Dosimetric and radiobiological advantages of protons offer better organs at risk sparing and may benefit previously irradiated patients.

In this study, we present a proton therapy with pencil beam results for the second irradiation of in-field recurrence of head and neck cancer in patients who were not eligible to undergo surgery neither before nor after PT, due to comorbidity and/or tumor extent. Disease control, treatment-related toxicity, and influencing factors were analyzed.

Materials and methods

A group of 30 patients treated for a local recurrence of H&N cancer with a proton beam to a previously irradiated site, between November 2015 and January 2020, was approved for retrospective analysis by a local institutional review board, including waivers of informed consent due to the retrospective nature of the study. All patients were more than 18 years old, with biopsy-confirmed diagnosis, both at initial treatment and recurrence, with a period from a prior RT of at least six months, and without signs of severe (grade 3–4) persistent toxicity. All patients included in the study had a minimum of 3 months of follow-up time. Before the treatment, the patient's medical history and current possible options were discussed at the multidisciplinary tumor board.

The second RT course was delivered via a fixed horizontal, spot-scanning proton beam, in a seated position [12]. A daily image-guidance was performed with built-in cone-beam computer tomography (CB-CT). Simulation CT was obtained without intravenous contrast, with a 1-mm slice thickness. The patient was immobilized using a standard thermoplastic mask. Both MRI with contrast and ^{18}FDG-PET/CT scans in a non-treatment position were obligatorily fused.

If it was possible, previous RT-plans were registered in the treatment planning system (TPS) to the new CT. The problem of radiation therapy in Post-Soviet states is that there are still hospitals providing treatment with the 2D technique, via non-multileaf collimator linear accelerators or ^{60}Co-units. So, some of our patients received conventional RT. In such a situation, field setup and treatment parameters were reconstructed in TPS, according to the patient's RT medical records.

The gross tumor volume (GTV) was delineated by a combination of a tumor recognized on MR-images and ^{18}FDG-PET/CT scans, co-registered to the simulation CT. Additionally, we reduced a clinical volume (CTV) to a 5-mm margin adapted to the patient's CT anatomy by using molecular imaging. For the planning target volume (PTV) generation, the corresponding CTV was expanded by a 3-mm margin to the skull base site, and by 5 mm in the case of the aerodigestive tumor localization, for covering setup uncertainties.

As almost half of our patients had previously received conventional radiotherapy, it was risky to relay reconstructed doses to OARs completely. So, the strategy for critical structures sparring was to reduce the dose as much as achievable [13].

The total doses in the case of prior conformal RT to the OARs were based on QUANTEC group articles and calculated to its biologically effective dose (BED) ($\alpha/\beta = 3$) to estimate the risk of toxicities in the normal tissues. Serial OARs (i.e., spinal cord, optic nerves, chiasma, and brain stem) were allowed to receive a cumulative dose < 120–125% from its QUANTEC-proposed tolerance, as nerve

tissue was shown to recover 20–25% tolerance after one year from RT [14].

Proton therapy (PT) was delivered once a day, five times per week, by the intensity modulation technique, always supported with CB-CT imaging before each field. PT dose was prescribed to the PTV with a goal of at least 95%. According to the re-irradiation nature and additional CTV margin presence, OAR dose constraints took priority over PTV coverage, in instances where both were not achievable. Relative biological effectiveness (RBE) of 1.1 for protons was assumed. Patients were treated with 2 (n = 3), 2.4 (n = 9) and 3 GyRBE (n = 18) per fraction, with the median EQD_2 (α/β = 10) of 57.6 Gy [range, 42.1 to 68.0]. Fractionation schedules were based on a tumor volume and a patient's performance status.

Adjuvant systemic therapy was delivered by the prescriptions of the treating medical oncologist.

All patients were screened first in 4–6 weeks after finishing PT, and then every three months, unless the patient has required another frequency due to progression or severe toxicity. Both MR imaging with intravenous contrast and ^{18}FDG PET/CT, if necessary, were used to estimate the local efficacy, according to RECIST 1.1 criteria. Acute and late side effects were assessed by a radiation oncologist and recorded based on the RTOG/EORTC schema. Late toxicity was defined as an occurred event > 12 weeks after PT end.

Statistical methods

Clinical endpoints were to evaluate local control (LC), progression-free survival (PFS), and overall survival (OS), measured from the time of PT completion (LC, OS) or the date of remission (PFS). Each value was calculated using the Kaplan-Meier method (and reverse K-M for median follow-up time) with analysis performed in GraphPad Prism 8 (p-value < 0.05, assumed as statistically significant). A log-rank test was applied to a comparison between analyzed factors.

Results

Patient characteristics and treatment parameters

The median follow-up time from the finishing of proton re-irradiation was 21 months [range, 3 to 25]. Patient, tumor, and treatment characteristics are described in Table 1. The median time from previous RT was 38 months [range, 8 to 285]. Conformal prior radiotherapy received 21 patients (70%). None of the patients were operable, both before and after the PT, due to medical contraindications or recurrence extent, or both factors. Adjuvant systemic treatment (i.e., chemotherapy, target, or immune therapy) was given to 20% (n = 6) of the patients.

Twenty-three (76.7%) of recurrent tumors were squamous cell carcinomas, with 13.3% (n = 4) of adenocarcinomas and 10% (n = 3) having neuroendocrine histology, all of them localized in the field of the first RT course. Re-irradiated sites included: nasopharynx (n = 10, 33.4%), oral cavity (n = 9, 30%), parotid glands (n = 6, 20%) and maxillary sinuses (n = 5, 16.6%). Two patients (6.6%), with the longest period from the first RT course (126 and 285 months) and morphology differences from the previous diagnosis had a secondary primary tumor. According to the largest

Table 1. Patient and treatment characteristics

Patient characteristics	Number
Total patients	30
Median follow-up time in months	21
Gender	
Female	18 (60%)
Male	12 (40%)
Median age in years	62,5
Median Karnofsky score	70
Median prior RT dose in Gray	55
Median interval from initial RT in months	38
Conformal prior RT	21 (70%)
Non-conformal prior RT	9 (30%)
Histology	
Squamous cell carcinoma	23 (76.7%)
Adenocarcinoma	4 (13.3%)
Neuroendocrine cancer	3 (10%)
Retreatment site	
Aerodigestive tract	18 (60%)
Skull base	12 (40%)
PT dosimetry	
Median irradiated volume in cm^3	158.1
Median D_{95}	90.4
Median BED (α/β = 10)	69.1
Median EQD_2 (α/β = 10)	57.6

RT — radiotherapy; PT — proton therapy; BED — biologically effective dose; EQD_2 — equivalent dose

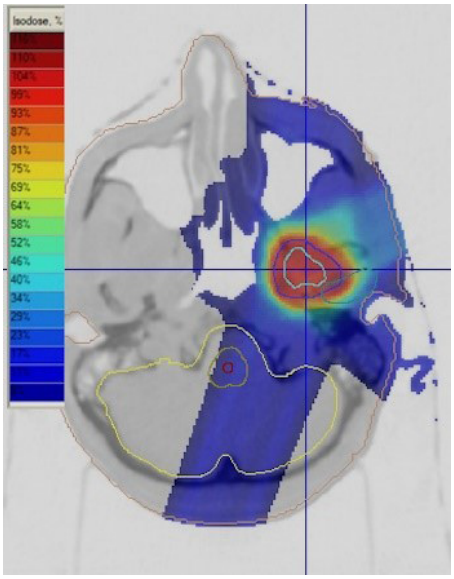

Figure 1. Representative proton reirradiation plan (IMPT)

recurrence tumor extension, all patients were also categorized based on anatomical site: aerodigestive tract (n = 18, 60%) and skull base (n = 12, 40%), with a view to obtain more specific reporting of treatment outcomes.

The median treated tumor volume was 158.1 cm^3 [range, 13.2 to 280.1]. Despite prioritizing OAR-sparing over PTV coverage, the median D_{95} was 90.4% [range, 85.3 to 100]. The example of the proton dose distribution is illustrated in Figure 1.

Treatment outcomes of tumor control were assessed by regular MR imaging and clinical examination, with medical oncologists and surgeons enrolled. For suspicious findings, PET/CT with ^{18}FDG or ultrasound-guided biopsy were used. Radiographic findings were described following the RECIST v1.1 criteria.

Tumor control and outcomes

The 1- and 2-year local control rates were 52.6% and 21%, respectively (Fig. 2). The median local control was 15 months. Eighteen patients (60%) have a locoregional recurrence. The majority of the recurrence (n = 15) occurred in-field/marginal, with regional node metastasis observed in 3 patients (10%), out of the irradiated field. Only one patient (3.3%) had distant metastasis (in the brain stem). The 1- and 2-year PFS rates were 21.9% and 10.9%, respectively (Fig. 3). The 1-year OS was 73.4%, with a rapid fall in the following year, with a 2-year OS rate of 8.4% (Fig. 4). Meanwhile, one patient had a non-cancer death (myocardial infarction), and one patient died from treatment-related late toxicity (carotid blow-out syndrome). The median overall survival was 16 months. The comparison between retreatment sites showed significant differences in the groups, with skull base localization associated with lower overall survival (hazard ratio 0.40, 95% CI: 0.1590 to 1.020; p = 0.03) (Fig. 5). This occurrence might be linked to PTV coverage decreasing to spare OARs in this complicated anatomical area (SB median D_{95} — 91.3% *vs.* AD median D_{95} — 97.7%), though no significant correlation has been confirmed.

Following correlation analyses of recurrent tumor histology, systemic therapy, proton irradiation parameters (i.e., total dose, tumor volume, fractionation, or time to prior RT), as much as performance status, gender, or age were not significantly associated with outcomes.

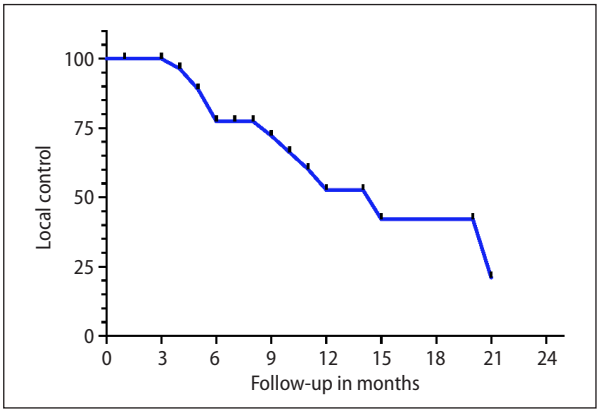

Figure 2. Local control rate after proton re-irradiation (Kaplan-Meir Plot)

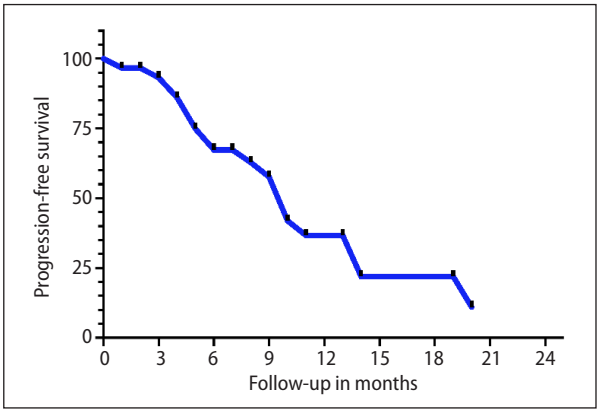

Figure 3. Progression-free survival after proton re-irradiation (Kaplan-Meier Plot)

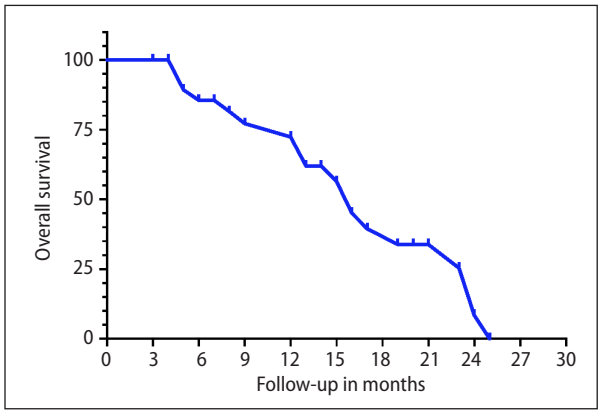

Figure 4. Overall survival after proton re-irradiation (Kaplan-Meier Plot)

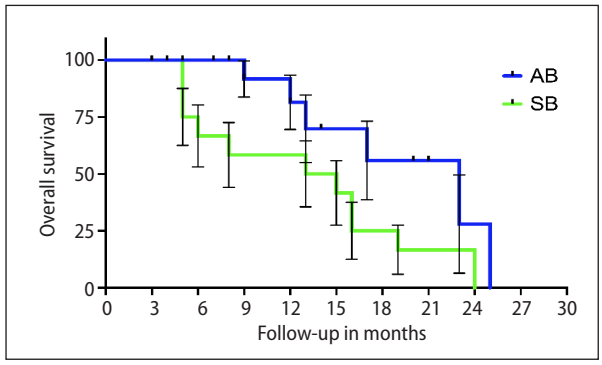

Figure 5. Overall survival from retreatment site. AB — aero-digestive tract; SB — skull base; HR = 0.40, 95% CI: 0.1590–1.020; p = 0.0399

Treatment-related toxicity

All of our patients tolerated proton irradiation well, without any treatment gaps. Radiation dermatitis was observed in 11 patients, with 2 cases of grade 2 toxicity, and grade 1 in the rest. Mucositis grade 1–3 was recorded in 29 patients: 18 patients had grade 1, and in 10 cases, grade 2 toxicity occurred. One patient (3.3%) experienced grade 3 mucositis. Persisting xerostomia after initial radiation therapy was observed in 100% of patients. Twenty patients (66.7%) additionally had chewing trismus and swallowing difficulties before PT. Nonetheless, none of these patients described an increase in the symptoms after the retreatment. Severe late toxicity occurred in 5 cases (16.6%): 3 radiation-induced necrosis (including one temporal lobe damage) and one new incidence of chewing trismus, with one death caused (carotid bleeding), after three months of re-irradiation. The second review of treatment plans showed a possibility of those incidences being due to prior non-conformal treatment with a range of dosimetry uncertainties, and recurrent tumors' growth close to OARs. No correlations between late toxicity and retreatment side were observed.

Discussion

Thirty inoperable patients with recurrent H&N cancer, treated with IMPT for the second course, were selected for retrospective analysis. For this study group, we evaluated treatment efficacy and related toxicity using IMPT for re-irradiation.

Locoregional recurrence after H&N therapy continues to be the most frequent pattern of failure, especially in locally advanced tumors, so it causes death in most of the cases. The highest period at risk is the first two years after the treatment, with more than 2/3 incidences [15]. Almost 15% of H&N patients are at risk of developing secondary primary cancer, with an increased incidence rate within long-term survival [7].

Maximal surgical resection remains the treatment of choice, with 5-year OS reaching 40% [5, 16]. Janot et al. showed in GORETEC phase III trial adjuvant chemoradiation improved both locoregional control ($p < 0.0001$) and disease-free survival ($p = 0.01$), without significant influence on overall survival ($p = 0.50$). However, significantly higher toxicity rates were observed (grade 3 in 28% cases, and 39% with late grade 4 complications) [17]. Nevertheless, salvage surgery can only be provided for around 30% of all such patients. However, surgical success is always linked with tumor location (better outcomes for laryngeal cancer and neck nodes) and extension, alongside comorbidity [18]. For those patients, who are not operable, chemotherapy alone has only a median survival of 7.4 months, with relatively low impact of cetuximab addition (to 10.1 months) [19]. It is evident that in the final results of most studies dedicated to the H&N re-irradiation, surgery plays a remarkable role. Meanwhile, our cohort's poor outcomes during the second year correspond to the lack of up-front surgery, as all of our patients were inoperable.

Two randomized trials, RTOG 9610 [10] and RTOG 9911 [20], had positive outcomes combining RT and chemotherapy. These studies showed that 1/3 of patients were locoregionally controlled, with 10 to 30% 2-year OS rate, yet with severe toxicities

grade 3–4 observed in around 40% of re-irradiated patients. At the same time, 10% of patients suffered from toxicity-related death.

The most complicated re-irradiation points are persistence radioresistant tumor cells (even after high-dose RT) and reduced tissue tolerance [14, 21, 22]. So, the main challenges in re-irradiation are to determine the actual tumor extent, deliver high doses (> 60 Gy), and spare normal tissue. In the last decade, IMRT-technique shows promising outcomes, with 32% 5-year OS, but with a severe toxicity risk of up to 48% [23]. However, even with IMRT, the high doses cannot be delivered, being met with OAR constraints from the previous radiotherapy course. Proton therapy advantages (i.e., precise dose distribution, rapid dose fall, biological and immune features) may benefit H&N patients with recurrence [24].

In 2016, Phan et al. published the retrospective data about proton re-irradiation with 60 patients included, demonstrating 1-year OS 83.8% and 16.7% of grade 3 late toxicity [11]. After completing PT, 58% of the patients received upfront surgery, and 73% received concurrent and adjuvant systemic therapy, though without significant consequences for the outcomes. The multi-institutional study by McDonald et al. included 61 patients, re-treated with PT for H&N recurrence or second primary tumor. Authors reported 2-year estimated OS of 32.7%, with a remarkable impact of surgery on outcomes: median OS with salvage surgery was 25.1 months *vs.* 10.3 months without operation, p = 0.008. Acute grade ≥3 toxicities were seen in 14.7% and 24.6% in the late setting, including three related deaths [25]. A multi-institutional report, published in 2016 by Romesser et al. with 91 patients involved, described a 25.1% risk of failure in 12 months and a favorable toxicity profile.

In our study group, we observed 73.4% of 1-year OS, while all of our patients could not undergo surgery, so the initial prognosis was relatively poor. The relapse patterns are in agreement with other studies: with mostly in-field/marginal recurrences and relatively low risk of distant progression [26]. Bulky tumors (prevailed in our cohort) or CTV > 50 cm^3 are shown to be associated with higher toxicity and poor outcomes [11, 23]. Though the lower toxicity rate of protons is usually accounted for in its dose distribution, recent experimental studies reported lower expression of factors involved in lymph- and angiogenesis, inflammation, and immune tolerance [27].

Adverse events from re-irradiation play a significant role in decreasing the QoL in H&N patients. Besides, conventional radiotherapy is associated with severe complications. Even with novel photon RT approaches, second irradiation still causes a significantly higher toxicity rate. The low toxicity outcomes observed in proton studies are promising, although longer follow-up of long-term survivors is necessary to estimate tissue damage risks related to re-irradiation. A balance between RT-treatment intensification and adverse events is quite challenging in H&N re-irradiation. The recommended re-RT dose for tumor growth control might be ≥ 60–66 Gy, whereas most critical OARs located at the H&N area could already exceed their limits after prior radiotherapy. Furthermore, there is still no consensus about dose constraints for re-irradiation. Chan et al. published data about re-irradiation of recurrent T_3/T_4 nasopharyngeal cancer, dividing OAR's limits into absolute (i.e., spinal cord D_{1cc} < 65 Gy or brain stem $D_{1\%}$ < 78 Gy) and desirable cumulative doses (e.g., optic nerve 78 Gy, temporal lobe D_{1cc} < 84.5 Gy) [28]. In contrast, some authors maintain more conservative doses (e.g., myelon BED < 100–120 Gy) [9].

Generally, many patients with recurrent H&N cancer may not survive long enough to meet potential adverse effects because of low survival chances. We observed only one death related to carotid bleeding, one of the most morbid toxicities associated with re-irradiation in the head and neck area [29]. Nevertheless, the carotid artery dose constraints are used mostly for SBRT (with a value from 32.5 to 34.0 Gy for hypofractionation) and rarely assessed in a fractionated RT [30].

As the retreatment of H&N cancers is extremely controversial and complicated, it is essential to define significant prognostic factors to divide patients into several groups, which could guide for therapy choice. Thus, Mattew C. et al., based on the results of IMRT of 412 patients, identified three prognostic groups: 1) >2 years from RT and resected tumor (2-year OS, 61.9%); 2) >2 years from RT and unresected tumor, in good performance status (2-year OS, 40.0%) and 3) the rest of patients, who do not meet these criteria, with a poor prognosis (2-year, 16.8%) [31]. This classification can potentially help better understand pa-

tient selection for re-RT and adjuvant treatment, following given indicators.

Conclusion

Although this study has a limitation in its retrospective nature, we demonstrate that proton beam therapy can be a safe and effective treatment for patients with recurrent H&N cancers, even with unresectable tumors. Proton's physical and radiobiological advantages provide a good compromise between delivering higher radiation doses and sparing previously irradiated zones. We achieved an adequate one-year tumor control with reasonably low rates of toxicity. Meanwhile, further investigations are required in the field of proton re-irradiation (e.g., flash-protons) in combination with novel systemic therapy agents for intensification of adjuvant treatment.

Conflict of interests

All authors know of no conflicts of interest associated with this publication.

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Ethical approval

The study was approved for a retrospective analysis by a local institution ethics committee, including waivers of patient's informed consent due to the retrospective nature of the study.

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