Proton re-irradiation of unresectable recurrent head and neck cancers

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Research

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Abstract

Purpose: This study presents a retrospective analysis (efficacy and toxicity) of outcomes in patients with unresectable recurrence of previously irradiated head and neck cancers, treated with proton therapy.

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 base of the 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 EQD_2 of 57.6 Gy (α/β=10). Radiation-induced toxicity was recorded according to the RTOG/EORTC criteria.

Results: The 1- and 2-years LC, RFS, and 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 1 patient (3.3%). There were 5 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.

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 of the patients have a high risk of locoregional recurrence or second metachronous tumors, occurring in-field or 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 make to 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 quite 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 with increasing rates of severe toxicities, 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 the goals of recurrence treatment 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 the results of a pencil beam proton therapy for the second irradiation of in-field recurrence of head and neck cancer in patients who were not eligible to undergo surgery neither before PT, or after, 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 a H&N cancer with a proton beam to a previously irradiated site, between November 2015 and January 2020, was approved for a retrospective analysis by a local institution ethics committee, 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 at least 6 months, and without signs of severe (grade 3-4) persistent toxicity. All patients included in the study, have 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 course of RT was delivered via a spot-scanning proton beam in a seated position [12]. A daily image-guidance was performed with a built-in cone-beam computer tomography (CB-CT). Simulation CT was obtained without intravenous contrast, with 1-mm slice thickness. The patient was immobilized using a standard thermoplastic mask. Both MRI with contrast and ^{18}FDG-PET/CT scans in non-treatment position were obligatory 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 2D technique, via non-MLC 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 seeing on MR-images and ^{18}FDG-PET/CT scans, co-registered to the simulation CT. Additionally, by using molecular imaging, we reduced a clinical volume (CTV) to a 5-mm margin, adapted to the patient's CT anatomy. For the planning target volume (PTV) generation, the corresponding CTV was expanded by 3-mm margin to the skull base site, and with 5-mm in 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 completely relay on reconstructed doses to OARs. So, the strategy for critical structures sparring was to achieve as low dose as reasonably achievable (ALARA principle, described in the WHO paper) [13].

The total doses in the case of prior conformal RT to the OARs were based on QUANTEC- group articles and calculated to its BED (a/b= 3) to estimate the risk of toxicities in the normal tissues. Parallel OARs (i.e., spinal cord, visual nerves, chiasma, and brain stem) were allowed to receive additionally no more than 20-25% from its QUANTEC-proposed tolerance minus already received dose [14].

Proton therapy was delivered once a day, 5 times per week, by 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. A 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 (a/b= 10) of 57.6 Gy [range, 42.1 to 68.0].

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 3 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), recurrence-free survival (RFS) and overall survival (OS), measured from the time of PT completion (LC, OS) or the date of remission (RFS). 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) received 20% (n=6) of the patients.

Twenty-three (76.7%) of recurrent tumors were squamous cell carcinoma, with 13,3% (n=4) of adenocarcinomas and 10% (n=3) have 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 previous diagnosis, had a secondary primary tumor. According to the largest recurrence tumor extension, all patients were also categorized based on anatomical site: aerodigestive tract (n=18, 60%) and skull base (n=12, 40%), with the view for more specific reporting of treatment outcomes.

The median treated tumor volume was 158.1 cm3 [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 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 v 1.1 criteria.

Tumor control and outcomes.

The 1- and 2-year rates of local control were 52.6% and 21%, respectively (Figure 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 or 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 recurrence-free survival (RFS) rates were 21.9% and 10.9%, respectively (Figure 3). The 1-year overall survival (OS) was 73.4%, with a rapid fall in the following year, with a 2-year OS rate of 8.4% (Figure 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% C.I. 0,1590 to 1,020; p=0.03) (Figure 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.

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 have grade 1, and in 10 cases occurred grade 2. 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 1 temporal lobe damage) and 1 new incidence of chewing trismus; with 1 death caused (carotid bleeding), after 3 months of re-irradiation. The second review of treatment plans showed a possibility of those incidences, 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 $^{2}/_{3}$ of incidences [15]. Almost 15% of H&N patients are at risk of developing secondary primary cancer, with an increasing incidence rate within long-term survival [7].

Maximal surgical resection remains to be the treatment of choice, with 5-years OS reached 40% reported [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, the success of the operation always linked with tumor location (better outcomes for laryngeal cancer and neck nodes) and extension, alongside with co-morbidity [18]. For those patients, who are not operable, chemotherapy alone has only a median survival of 7.4 months, with quite low impact of cetuximab addition (to 10.1 months) [19]. It is obvious that in the final results of most studies, dedicated to the H&N re-irradiation, surgery plays a remarkable role. Meanwhile, poor outcomes of our cohort at the second year corresponds 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, and 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 points of re-irradiation 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 determination of actual tumor extent, delivering high doses (>60 Gy), and sparing normal tissue. In the last decade, an increasing use of IMRT-technique shows promising outcomes, with 32% 5-years 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 course of radiotherapy. Proton therapy advantages (i.e., precise dose distribution, rapid dose fall, biological and immune features) may potentially 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 32.7%, with 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 3 related deaths [25]. A multi-institutional report, published in 2016 by Romesser et al., with 91 patients involved, described 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 were not able to undergo surgery, so the initial prognosis was quite poor. The patterns of relapse are in agreement with other studies: with mostly in-field or marginal recurrences and relative low risk of distant progression [26]. Bulky tumors (prevailed in our cohort) or CTV>50 cm3 are shown to be associated with higher toxicity and poor outcomes [11, 23]. Though, the lower toxicity rate of protons is usually being 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-radiation 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. Balance between RT-treatment intensification and adverse events is quite challenging in H&N re-irradiation. Recommended re-RT dose for tumor growth control might be ≥ 60-66 Gy, whereas the most of critical OARs located at H&N area, are 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 $D1_{cc}$<65 Gy or brain stem $D1_{\%<}$78 Gy) and desirable doses (e.g., optic nerve 78 Gy, temporal lobe $D1_{cc}$<84.5 Gy) [28]. In contrast, some authors maintain more conservative doses (e.g., myelon BED < 100-120 Gy) [9].

Generally, however, because of poor survival chances with recurrent H&N cancer, many patients may not survive long enough to meet potential adverse effects. We observed 1 death related to carotid bleeding, which is one of the most morbid toxicities associated with re-irradiation in the head and neck area [29].

Nevertheless, dose constraints for the carotid artery are used mostly for SBRT (with value from 32.5 to 34.0 Gy for hypofractionation) [30].

As re-treatment of H&N cancers is extremely controversial and complicated, defining significant prognostic factors to divide patients into several groups, which could guide for therapy choice, is important. Thus, Mattew C. et al., based on the results of IMRT of 412 patients, identified 3 groups of patients: 1) >2 years from RT and resected tumor (2-year OS, 61.9%); 2) >2 years from RT and unresected tumor, in a 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 for a better understanding of patient 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 for those who are not suitable for surgery. Physical and radiobiological advantages of PT provide a good compromise between the delivery of higher radiation doses, and sparing previously irradiated zones. We achieved an adequate 1-year tumor control with reasonably low rates of toxicity. Meanwhile, further investigations in the field of re-irradiation (e.g., flash-protons), combination with novel systemic therapy agents for intensification of adjuvant treatment, are required.

Declarations

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

Consent for publication: As corresponding author, I confirm that the manuscript has been read and approved for submission by all named authors.

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

Ethical standards: The accompanying manuscript does not contain any studies carried out by the authors on humans or animals. The study was approved for a retrospective analysis by a local institution ethics committee, including waivers of informed consent due to the retrospective nature of the study

Authors' contributions: K.G., I.G., A.S. conceived and planned the study. K.G., A.S., O.G., S.K. carried out the treatment. K.G., I.G. contributed to the interpretation of the results. K.G, I.G. took the lead in writing the manuscript. S.I., A.K. made the final approval. All authors provided critical feedback and helped shape the research, analysis and manuscript.

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Abbreviations

IMPT intensity-modulated proton therapy

EQD_2 equivalent Dose In 2-Gy Fractions

Gy gray

GyRBE cobalt gray equivalents

RTOG/EORTC toxicity criteria of the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer

LC local control

RFS progression-free survival

OS overall survival

H&N head and neck

SBRT stereotactic body radiation therapy

RT radiation therapy

QoL quality of life

PT proton therapy

CB-CT cone-beam computed tomography

CT computed tomography

MRI magnetic resonance imaging

^{18}FDG 2-(fluorine-18)-fluoro-2-deoxy-D-glucose

PET/CT positron emission tomography–computed tomography

TPS treatment planning system

MLC multi-leaf collimator

2D two-dimensinal

GTV gross tumor volume

CTV clinical target volume

PTV planning target volume

ALARA as low as reasonably achievable

WHO World Health Organization

QUANTEC quantitative analyses of normal tissue effects in the clinic

RBE relative biological effectiveness

RECIST response evaluation criteria in solid tumors

K-M Kaplam-Meyer

OAR organ at risk

C.I. confidence interval

SB skull base

AD aerodigestive tract

GORETEC Groupe d'Oncologie Radiothérapie Tête et Cou

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Tables

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 ($\alpha/\beta = 10$)	69.1
Median EQD_2 ($\alpha/\beta = 10$)	57.6

Figures

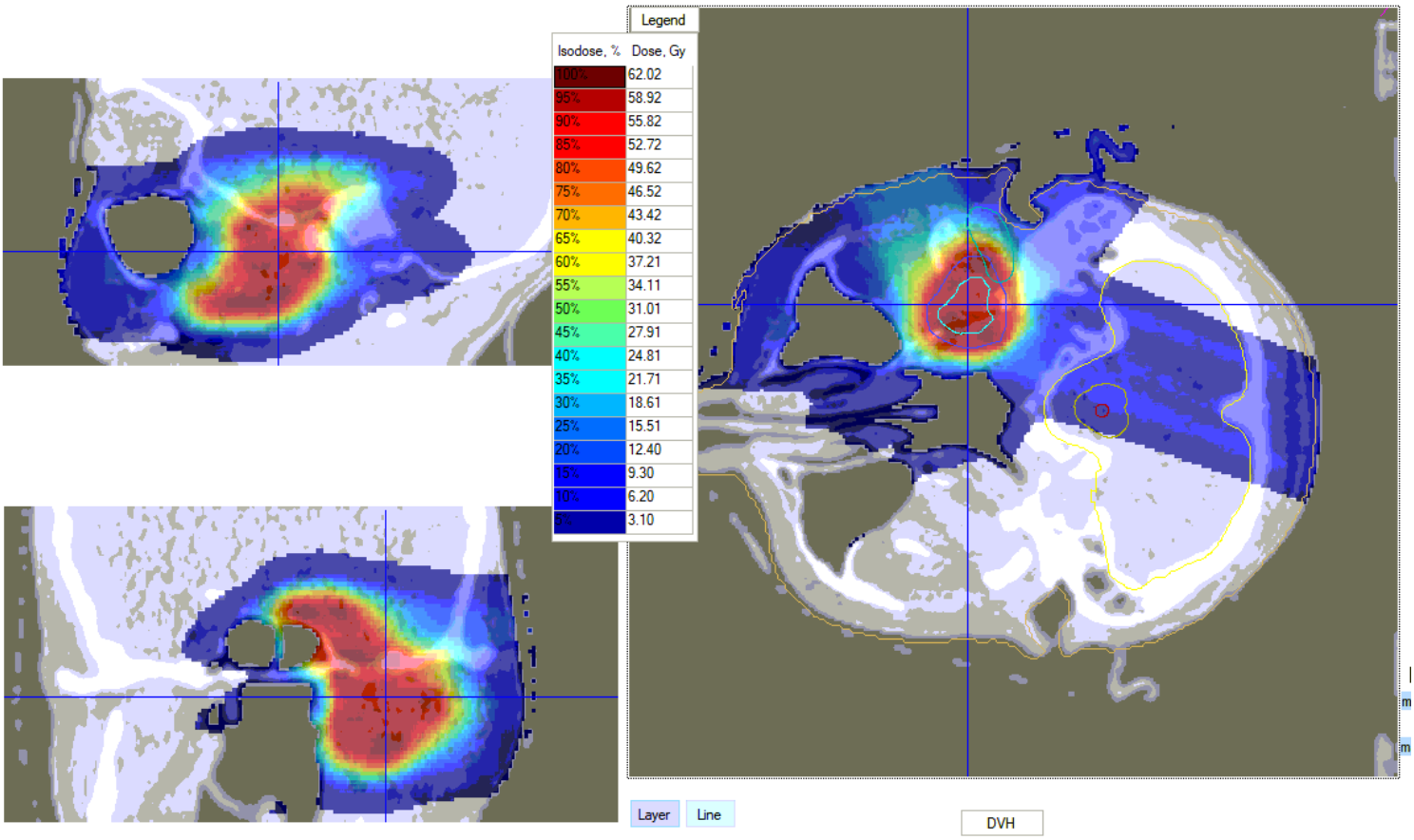

Figure 1

Representative proton reirradiation plan (IMPT).

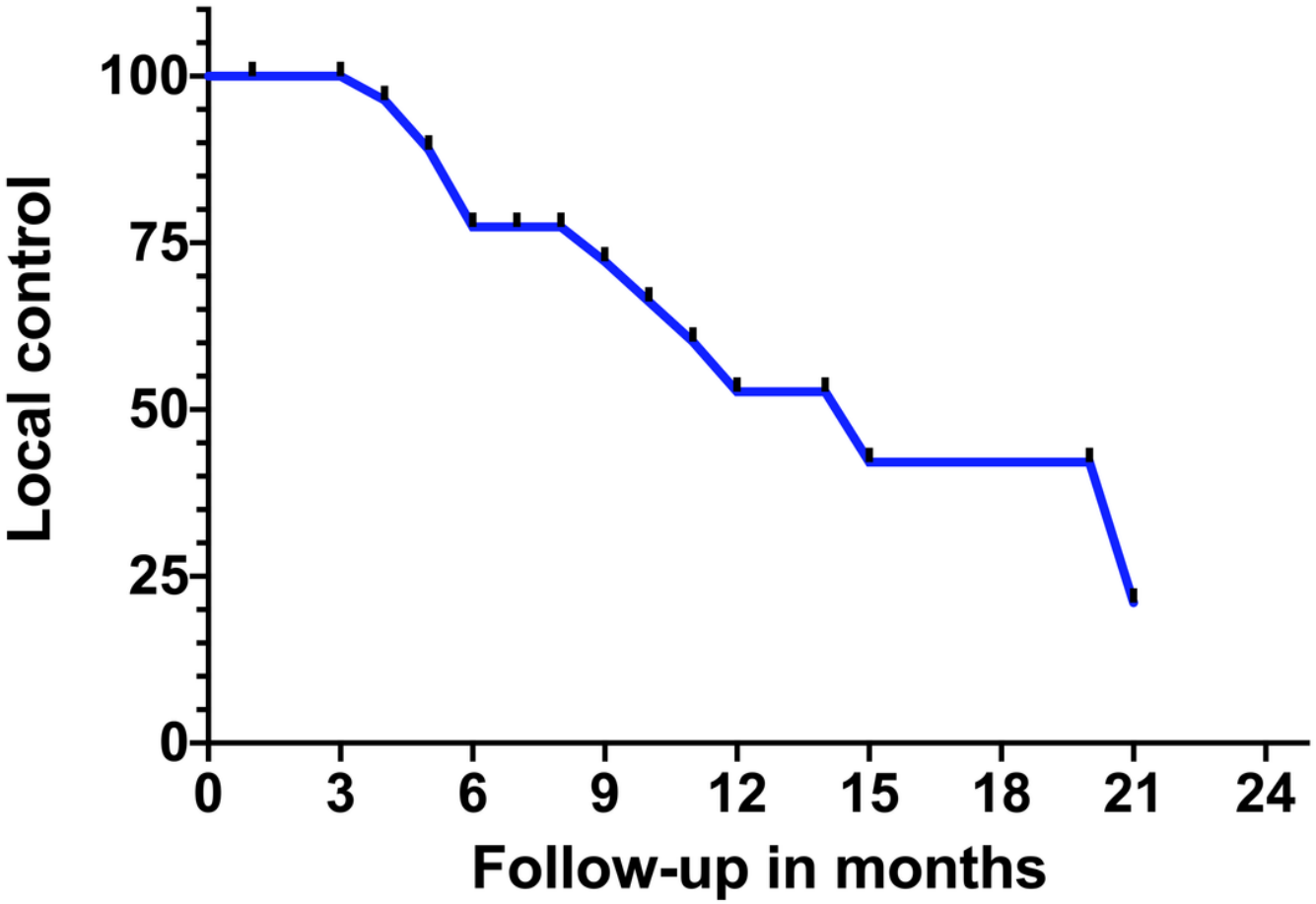

Figure 2

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

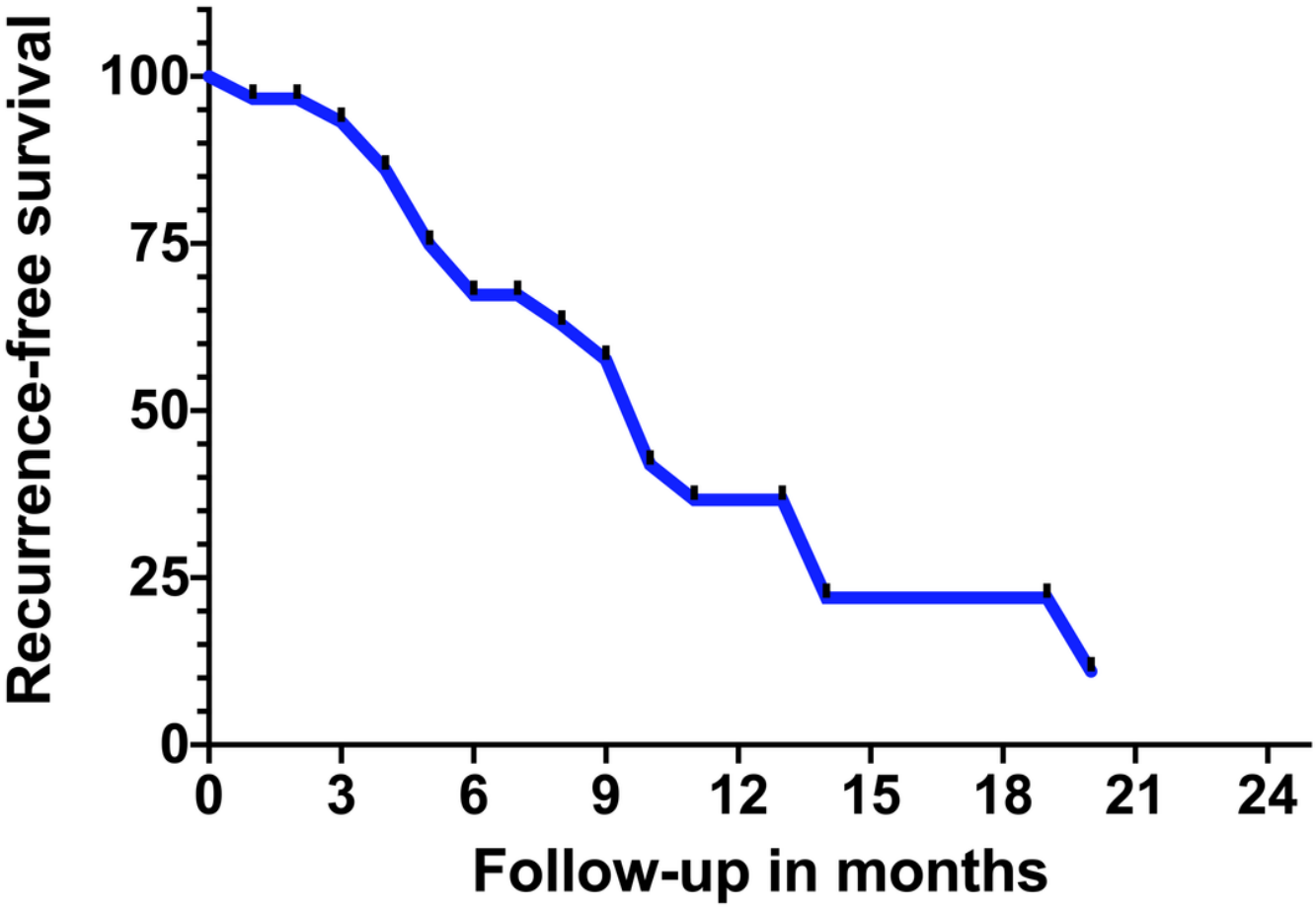

Figure 3

Recurrence-free survival after proton re-irradiation (Kaplan-Meier Plot).

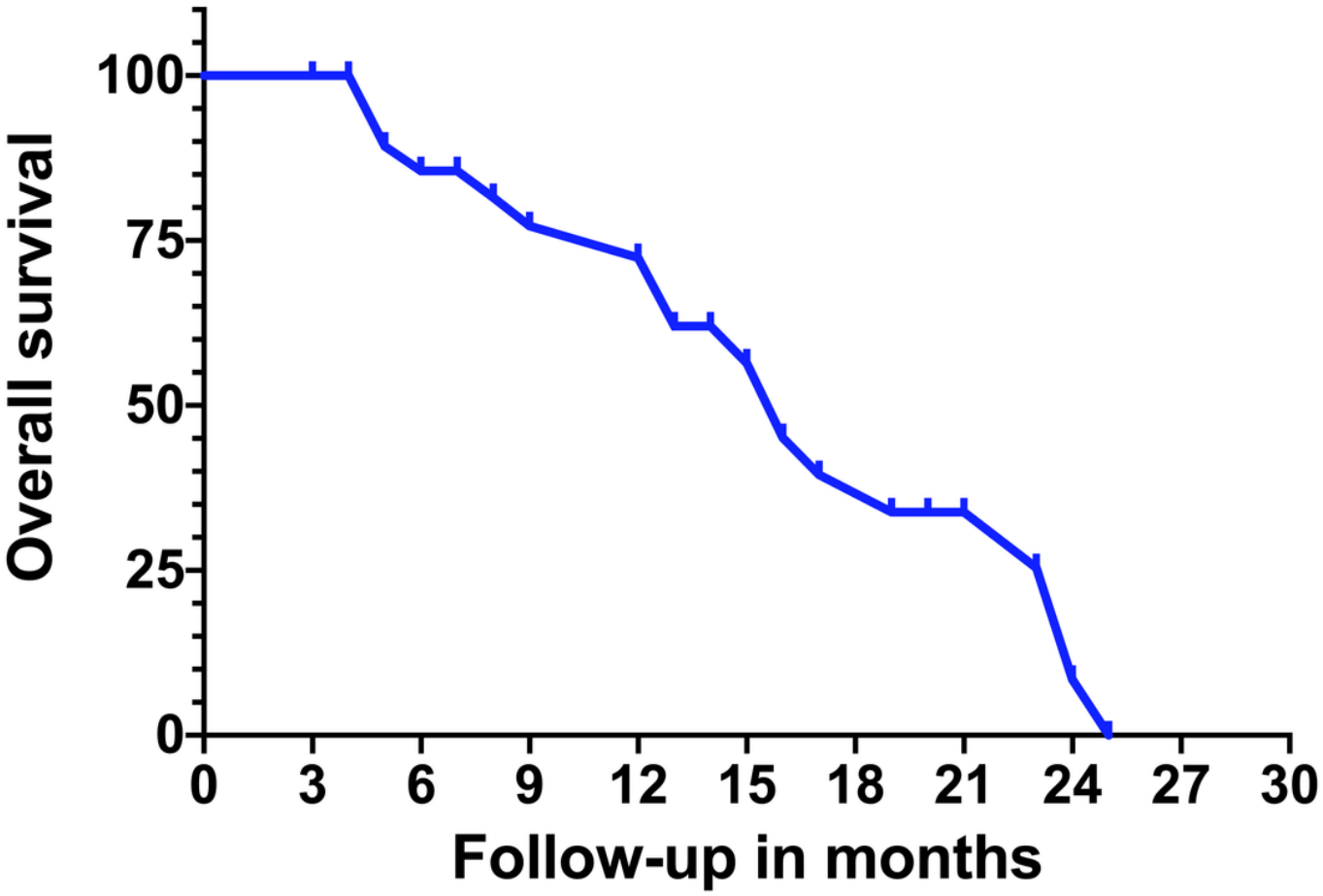

Figure 4

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

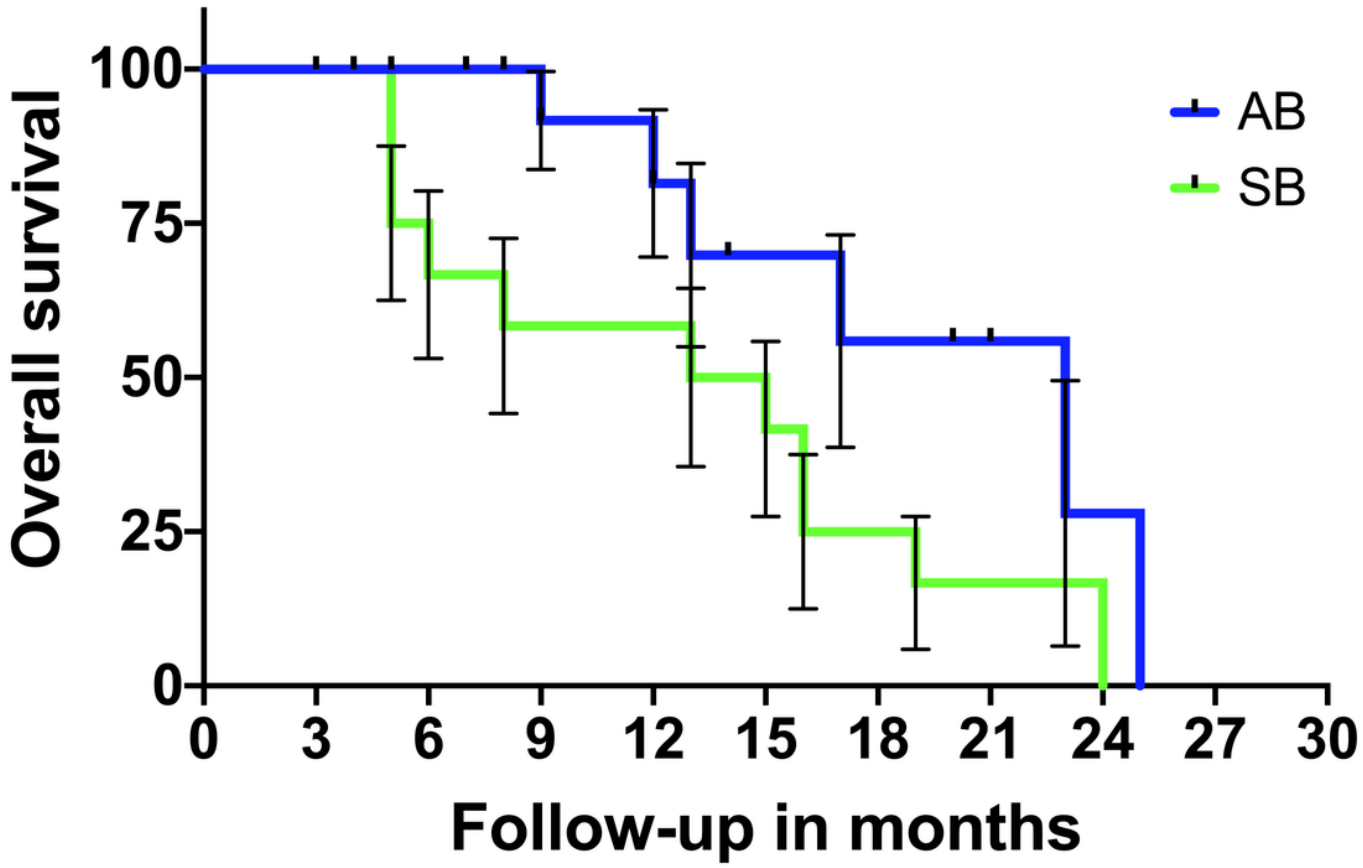

Figure 5

Overall survival from retreatment site* * note: AB – aerodigestive tract, SB – skull base; H.R. 0.40, 95% C.I. 0,1590 to 1,020; p=0.0399