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Pre-treatment visualization of predicted radiation-induced acute alopecia in brain tumour patients

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ABSTRACT

Background and purpose: Temporary alopecia is a common side-effect in brain tumour patients receiving cranial radiotherapy with a significant psychological burden for the affected patient. The purpose of this study was to generate a method in our treatment planning system (TPS) to visualize the expected radiation-induced alopecia 4 weeks after treatment, in order to inform the patients thereupon before the start of radiotherapy.
Material and methods: A pilot study was conducted in ten patients receiving hypo- (HF) or conventionally fractionated (CF) photon beam Volumetric Modulated Arc Therapy (VMAT) for an intracranial lesion. Dose calculations were correlated to visible alopecia four weeks after the end of treatment to create a structure predictive of alopecia in our TPS. These alopecia structures for both fractionation schedules were validated in two cohorts of 69 HF and 78 CF patients undergoing radiotherapy between 2016 and 2019.
Results: In the pilot cohort, a total physical dose of 4 Gy for HF and 12.6 Gy for CF radiotherapy were found to be predictive of alopecia 4 weeks after treatment. Applying these doses to our validation cohort, we found an accurate prediction of alopecia in 59/69 (86%) HF and 73/78 (96%) CF patients. For the total patient group of 147 patients, the predicted amount of alopecia was accurate in 90% of the cases. All inaccurate predictions overestimated the expected extent of alopecia.
Conclusion: The presented straightforward method to visualize predicted alopecia 4 weeks after treatment has proven to predict the extent alopecia highly accurate in the vast majority of patients. Sharing these results with the patients pre-treatment may result in stress reduction before cranial irradiation.

Introduction

Alopecia is the partial or complete loss of hair, which can be a manifestation of a wide variety of disorders. In cancer patients, alopecia is one of the most common clinical presentations mainly due to cancer treatment. In patients receiving cranial radiation, acute and mostly temporary alopecia for several months is an example of a dose dependent side effect during radiotherapy [1]. The clinical presentation consists of non-scarring alopecia, which is often sharply demarcated in geometric shapes confined to the area of radiation [1,2]. The condition

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is mostly temporary, although permanent scalp alopecia is also reported [34]. The latter being one of the most feared side effects among many cancer patients.

A human scalp contains approximately 100,000 to 150,000 hair follicles, situated on average at 4 mm depth, with an individual cycle for each follicle [5,6,7]. Alteration of any part of the hair cycle can lead to abnormal or absent hair growth [8,9]. Radiation causes acute damage of actively dividing matrix cells. Mechanical damage to the matrix cells affects the hair follicles, causing reversible or permanent hair loss, depending on the type, depth, and dose fractionation of radiation treatment [9,10,11]. Low-dose radiation, such as 2 Gy in a single fraction, causes only premature entry transition of follicles, leading to temporary hair loss [12]. Temporary alopecia mostly occurs within 2–3 weeks after radiation exposure and usually resolves within 2–3 months after completion of radiation treatment [13]. Findings in mice models suggest that some follicular stem cells can survive radiation exposure in epithelial tissue, which are able to reproduce the complete follicle structure, explaining the possibility for hair regrowth [5]. High dose radiation causes shedding of hairs, ultimately leading to detachment from the hair follicle causing permanent hair loss [12]. Doses reported to cause permanent hair loss vary, ranging from more than 5 Gy in a single dose to more than 50–60 Gy in fractions of 1.8 or 2 Gy [6].

In the past two decades there have been major developments in radiation therapy. Volumetric Modulated Arc Therapy (VMAT) has become available, which allows for greater freedom in designing high-dose distributions that conform to the shape of the clinical target volume (CTV), and fall off rapidly beyond this [14,15]. This technique enables lowering the maximum dose to scalp and follicles, but the disadvantage is that a larger area receives lower doses of irradiation [16].

As part of a graduation project, a student conducted a pilot study in ten patients treated with hypo- (HF) or conventionally (CF) fractionated VMAT to find the absolute physical radiation dose predicting the amount of alopecia four weeks after VMAT. Treatment schedules with fractionation doses <3 Gy were part of the CF group and treatment schedules with fractionation doses >3 Gy were part of the HF group. These absolute dose levels for HF and CF, implemented in our TPS, were applied to a validation cohort of 147 patients undergoing cranial irradiation. Here, we present the results of the pilot and validation datasets.

Materials and methods

Pilot study

Originally, 22 patients were included in a single institution pilot study between March 2015 and June 2015. Patients were eligible if they received cranial irradiation for a primary brain tumour or brain metastases. Due to technical reasons, some data were not retrievable. Therefore, only ten patients were available for evaluation (see Table 1). All patients were treated with 10 MV photon beams administered with VMAT and varying fractionation schedules were used.

The validation dataset consisted of 318 patients, who received cranial radiation for brain tumours or cerebral metastases between March 2016 and April 2019. Eventually, 147 patients were found eligible in the prospective validation study (Table 2 and supplementary data 1).

Patients with complete androgenetic alopecia were excluded from the validation cohort.

During treatment planning, a structure representing the hair follicle at 4 mm below the skin was automatically generated by the TPS (Eclipse™ version 11.0 Varian Medical Systems, Palo Alto, CA) [4–6]. The patient's scalp was documented from four sides, i.e., anterior, right and left lateral and posterior, at four time-points, i.e., at baseline, once every two weeks during treatment and 1 month after treatment. When alopecia occurred, the maximum area was calculated using a ruler applied in two directions and the exact location was documented (Fig. 1). Moreover, a standardized picture of a human scalp was

Table 1
Characteristics of patients included in the dosimetric analysis of the pilot study.

	Absolute numbers	Percentage (%)
Gender		
Male	5	50
Female	5	50
Age, years		
20–50	2	20
50–75	8	80
Dose/fractionation		
3 × 8 Gy	4	40
1 × 24 Gy	1	10
1 × 24Gy + 3 × 8 Gy	1	10
30 × 1.8 Gy	1	10
33 × 1.8 Gy	3	10
Photon energy		
10 MV	10	100
Chemotherapy		
Prior to RT	0	0
During RT	1*	10
Indication		
Brain metastases	6	60
Primary brain tumour	4	40
Total	10	100

RT; Radiotherapy, *Temozolomide.

Table 2
Patient characteristics of the validation study (N = 147).

	Absolute numbers	Percentage %
Site		
Brain metastases	55	38
Meningioma	25	17
Glioblastoma	30	21
Vestibular schwannoma	12	8
Oligodendroglioma	5	3
Astrocytoma	6	4
Craniopharyngioma	2	1
High grade glioma NOS	3	2
Low grade glioma NOS	3	2
Pituitary adenoma	6	4
Hypofractionated schedules		
1 × 12,5 Gy	7	5
1 × 21 Gy	11	7
1 × 24 Gy	8	5
3 × 7,5 Gy	1	<1
3 × 8 Gy	43	29
5 × 5 Gy	4	3
Conventionally fractionated schedules		
15 × 2.66 Gy	3	2
26 × 1.8 Gy	8	6
28 × 1.8 Gy	9	6
30 × 1.8 Gy	21	14
30 × 2 Gy	5	3
33 × 1.8 Gy	27	19

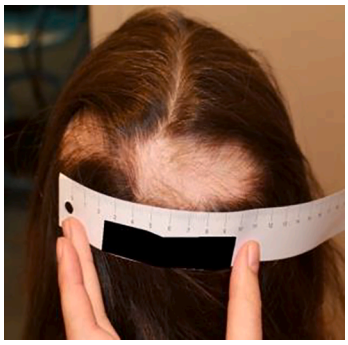

Fig. 1. Measuring the perpendicular diameters of alopecia four weeks after treatment in a pilot study patient.

demarcated (Fig. 2). These data were correlated to the delivered dose, in order to establish doses corresponding to the visually scored alopecia.

The location of the alopecia was compared with the planned, absolute physical dose using the corresponding TPS projected isodose lines. For both, HF and CF, independent dose levels were derived predictive of alopecia at four weeks after treatment. These absolute isodose lines were converted to a three-dimensional (3D) volume in the TPS corresponding to the observed alopecia, in this article referred to as alopecia volumes. As secondary outcome measure, each patient completed a short, in-house developed (KE), non-externally validated questionnaire, which encompassed the impact of alopecia on their general wellbeing and questions on their expected level of information (supplementary data 2). It was completed by 21 of the 22 originally included patients. The data of the pilot study was used to find absolute isodose lines, which are able to visualize expected alopecia four weeks after treatment in the TPS to show patients prior to their treatment. The pilot and validation studies were approved by the MAASTRO clinic institutional review board (IRB P0114).

Validation cohort

For each patient, two structures were created in the TPS:

1. A volume 4 mm below the body contour representing the hair follicle.
2. Alopecia volumes (HF_{xxGy} or CF_{xxGy}), found in the pilot study (Fig. 3).

A screenshot of the 3D predicted alopecia structure was stored in the electronic file of the patient, such that the radiation oncologist (LV, IC, DE) was able to compare this with the incidence and extent of alopecia of the patient's scalp at the first follow-up visit four weeks after completion of radiation therapy. Alopecia was scored according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 grading system. Furthermore, the scoring was performed two-fold:

In patients, in whom the predicted extent of alopecia four weeks after treatment corresponded to the observed extent, the scoring was either:

1. Observed extent of alopecia equal to predicted extent
2. Observed extent of alopecia less than predicted extent within a 25% margin

In patients, in whom the predicted extent of alopecia 4 weeks after treatment did not correspond to the observed extent, the scoring was either:

1. Observed extent of alopecia more than predicted extent
2. Observed extent of alopecia in the same area as predicted but >25% deviation of predicted extent (less or more alopecia)
3. Observed extent of alopecia in other areas than predicted.

Thinning of hair compared to start of treatment was also scored as alopecia.

Results

Pilot cohort

In ten patients of the pilot cohort, one month after radiation treatment, visible alopecia four weeks after treatment was found to correspond with an absolute follicle dose of 12.6 Gy in CF patients and of 4 Gy in HF patients administered over the total course of treatment.

Even though not all 22 patients were eligible for the dosimetric analysis, results of 21 were available for the questionnaire. In all patients, there was no evidence of alopecia other than androgenic alopecia before starting radiation therapy. Nine patients (43%) had a prior episode of hair loss, all due to prior chemotherapy or concurrent chemoradiation. Fourteen patients (67%) found hair loss to be a psychological burden for various reasons such as cosmetics and visibility of illness. Fifteen patients (71%) stated that information about expected hair loss due to treatment would have an added value for practical reasons such as ordering a hair piece/wig but also the feeling of having control over the course of their disease. The opinions about the way patients wanted to be informed varied between several options: verbal explanation by their radiation-oncologist, demonstration on the patients scalp or a visualisation model on the computer.

Validation cohort

Since the volume receiving an absolute physical dose of 4 Gy in the HF cohort and of 12.6 Gy in the CF cohort corresponded to the observed extent of alopecia in the pilot study, volumes encompassed by the respective isodose lines, i.e., HF_{4Gy} or $CF_{12,6Gy,}$ were generated for the validation cohort. For the total group, 132/147 (90%) predictions of alopecia in our model corresponded with the actual alopecia 4 weeks after treatment. Occurrence of alopecia was scored grade I for all patients. For the HF and CF group, 59/69 (86%) and 73/78 (96%) of the predictions, respectively, corresponded with the visible alopecia (Table 3). In 15/147 (10%) patients, the model did not predict the correct extent of alopecia. Interestingly, in those patients the extent of alopecia was overestimated in the model and less apparent than expected.

Discussion

In our study, we found that the absolute physical dose to the follicle depth (4 mm) of 4 Gy in HF schedules and 12.6 Gy in CF schedules were predictive of non-permanent alopecia 4 weeks after treatment in 90% of

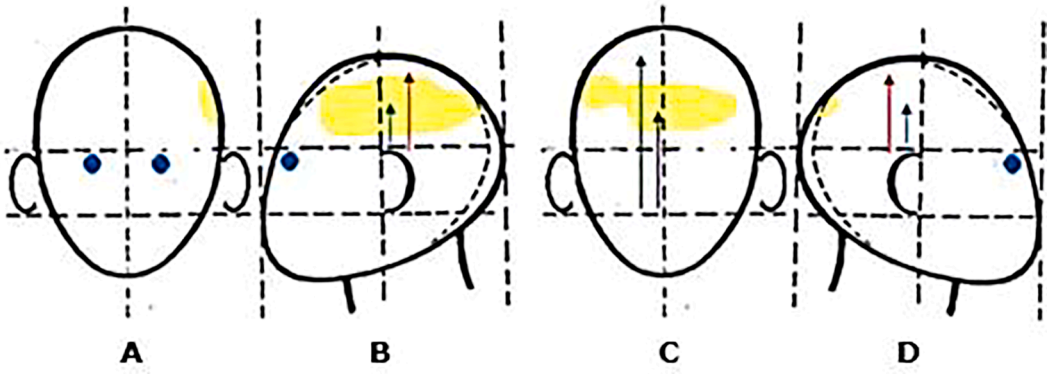

Fig. 2. Drawing of a pilot study patients scalp from different views (A: front, B: left, C: back, D: right) Visible alopecia was drawn on the different views in yellow.

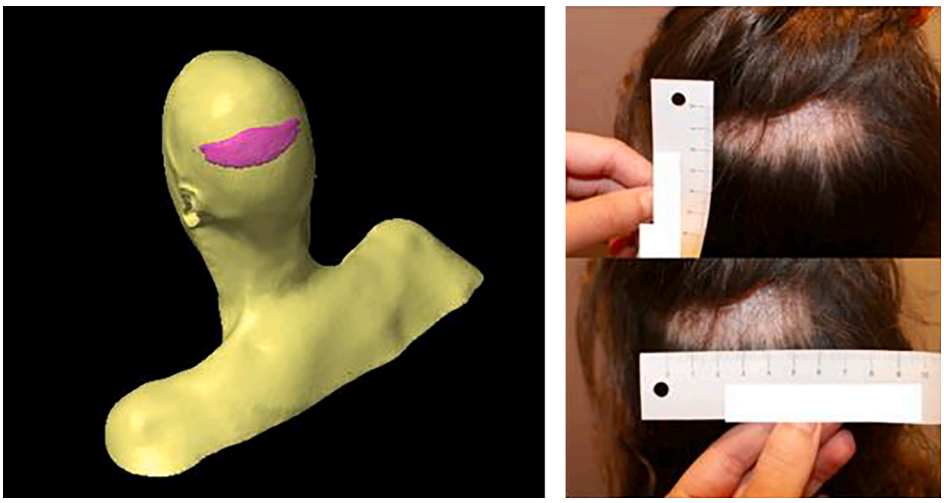

Fig. 3. Prediction of alopecia within the TPS (left) and clinical visible alopecia 4 weeks after treatment (right) in a pilot study patient treated with hypofractionated photon radiation therapy. In yellow the skin – 4 mm structure, in magenta the alopecia volume of 4 Gy.

Table 3
Results observed alopecia versus prediction in the validation study (n = 147 patients)

Alopecia	Hypofractionated schedule, threshold 4 Gy (n = 69)	Conventionally fractionated schedule, threshold 12,6 Gy (n = 78)	Total group (n = 147)
Equal to prediction	59 (86%)	73 (94%)	132 (90%)
Less than prediction	10 (14%)	5 (6%)	15 (10%)
More than prediction	0 (0%)	0 (0%)	0 (0%)

the investigated patients. This simplified model on absolute physical doses holds true even when applying different dose fractionation schedules. This model predicting the extent of alopecia is routinely and easily applied in our clinical practice at the moment. This information can be provided within a few minutes during consultation of the patient (supplementary data 3). As seen in the validation cohort our experience is that in most cases the prediction corresponds with the actual hair loss.

If radiation induced alopecia occurs, it is a substantial psychological burden for the affected patient. It sometimes is the first sign of illness, and a deviation from the accepted visual norms, which can eventually lead to impaired mental health [17,18]. *Can et al.* [19] found that patient body image and mental health were significantly affected by alopecia in an interview performed among 405 patients. Alopecia can also affect the social status of an individual regarding political status, religious belief and sexual attraction [20,21]. In our short questionnaire, we found that the majority of patients would consider it of additional value to be informed about expected alopecia. Our experience learned that if patients were aware of the predicted alopecia, they were prepared both mentally and practically. Patients were informed by their radiation oncologist who was able to show the predicted extent of alopecia during one of the consultation visits, preferably at start of treatment. Patients were able to take pictures to show to their relatives. During the recent COVID-19 crisis, when many consultations had to be done by phone or digitally, individual folders were made for each patient explaining the predicted alopecia, which were digitally sent out to the patients after the consultation. The fact that this corresponded with the actual alopecia seemed to be very reassuring for patients and family.

An important limitation of our study is the design of the pilot study. Unfortunately some data were irretrievable and the sample size was small. Another limitation of our study was the single institutional design using one TPS. Currently, this model is being externally validated at the Verbeeten institute Tilburg (the Netherlands) using the same TPS and dose threshold at 4 mm skin depth in a cohort of patients receiving photon radiotherapy for brain tumours or cerebral metastases. Our model used a 4 mm follicle depth based upon literature findings. It is also known that follicle depth can vary a little between individuals, which may influence the actual outcome of the alopecia and may account for the 10% overestimation of alopecia in the model [6]. If five mm for follicle depth had been used, in line with the recent EPTN contouring atlas, less amount of overestimation in our model could be expected [22]. Also, our model did not include differences between baldness or thinning of hair. Ultimately, thinning of hair was scored as alopecia in the model. Unfortunately, only acute onset alopecia is addressed in this model. In our CNS proton therapy cohort we aim for a long follow-up in order to develop a model for prediction of permanent alopecia as well.

The fact this model using only physical doses hold true even when used in different dose fractionation schedules argues for a dose range instead of a single absolute dose. In this study we identified the doses of 4 Gy and 12,6Gy only. Using a dose range might improve the accuracy of the model.

Several studies have looked at NTCP models for alopecia due to photon based cranial radiotherapy. *Scoccianti et al.* [23] recently published an article correlating dose constraints with alopecia in 101 brain tumour patients treated with VMAT. The scalp was drawn as a region of interest to spare during treatment planning. They found that the volumes receiving radiation doses of at least 20 Gy or 40 Gy, i.e. V_{20Gy} and V_{40Gy}, were the strongest predictors for acute and chronic grade 2 hair-loss, respectively. The low-dose bath typical of VMAT corresponded to large areas of acute but transient alopecia. Furthermore, It is important to note that TPS calculations are estimations at best which makes transfer of the above mentioned dose thresholds to other TPS systems subject of uncertainty. *Wang et al.* [24] recently showed that the Eclipse TPS has its limitations in predicting patient skin dose, which was calculated as mean dose to a contoured structure of 0.5 cm thickness from the surface. An underestimation of skin doses by up to 14% of prescription dose was reported for dose calculations with AAA (anisotropic analytical algorithm), when external body contour starts at the patient's skin. They also showed that the calculation accuracy can be considerably improved to an acceptable level by extending the external

body contour away from the skin with 1–2 cm without affecting the dose calculation accuracy to the treatment target and internal organs at risk. This solution has not been implemented in our institute but since we use AcurosXB® as dose calculation algorithm. However, Zhuang *et al.* [25] reported that Eclipse surface dose calculations are accurate enough to estimate surface doses, when using high accuracy commissioning data in the build-up region and a calculation grid size of 1 mm. The TPS used in this paper meets these conditions.

Also, in our data 10 MV photon beams were used, but thresholds may differ for other beam energies, such as 6 MV.

Follicle dose is the only predictor used in this model for alopecia developed within four weeks after start of radiotherapy. Other confounding variables such as chemotherapy, medication use and mental stress levels were not included. *Lawenda et al.* [4] reported the first human dose–response relationship describing the effect of the follicle dose on the subsequent development of permanent scalp alopecia after cranial irradiation with conventional radiation technique. The authors also analysed potential confounding variables that may contribute to the hair loss and found that only follicle dose was correlated to the presence of permanent alopecia. Age, gender, family history, beam energy, use of chemotherapy and personal history of alopecia were not found to be correlated. Confounding factors might influence these temporary alopecia outcomes. This study only reported on occurrence of permanent alopecia, while our study design aimed at predicting acute and most likely reversible alopecia 4 weeks after treatment. Lack of follow up data is a shortcoming in our study, disabling us to determine the percentage of permanent alopecia.

Our model was used in photon therapy plans. In proton therapy, the higher entry dose of the spread out Bragg peak may cause an increase in skin related side effects, which also encompasses hair loss [26]. *Palma et al.* [27] recently reported on data used for normal tissue complication probability (NTCP) model development for radiation-induced alopecia CNS patients treated with proton therapy. They reported on acute, late and permanent grade 2 radiation induced alopecia using dose surface histograms and found a dose corresponding to 50% probability to induce toxicity (TD50) of 22 Gy(RBE) for acute grade 2 alopecia. In another recent paper, the TD50 was 36 Gy(RBE) [26]. Once externally validated, these data can be used for individualized scalp sparing treatments in CNS patients.

Dutz et al. [28] investigated a cohort of 113 brain tumour patients treated with proton beam therapy and found prognostic parameters for occurrence of alopecia. The D2% was prognostic for alopecia grade 1, and the D5% was prognostic for alopecia grade 2. These results were successfully validated by two other cohorts with AUC > 0.75. Possibly, our visualization system for alopecia would also be applicable in these proton patients, since follicular dose is predictive of alopecia with likely the same dose effect in photons as protons. The limited experience of using the model in proton patients treated in our institute show that the model is accurate in protons as well predicting alopecia 4 weeks after start of treatment. However, further research, follow up data and validation in a proton patient cohort is necessary.

Conclusion

We developed and validated a way to visualize predicted alopecia four weeks after treatment in our TPS in patients receiving cranial photon beam radiation therapy for CNS tumours. The alopecia volumes predicted alopecia correctly in 90% of the included patients. In 10% of the patients, the extent of alopecia was overestimated. This method has proven to be accurate, helping clinicians to inform their patients about this troublesome side-effect. An external validation of our results is currently being performed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2022.02.003.

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