International Journal of Dermatology

Report

HDR brachytherapy with individual epithetic molds for facial skin cancer: techniques and first clinical experience

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Access to Data/Data analysis: Drs. Diefenhardt, Chatzikonstantinou, and Tselis had full access to all the data in the study and take responsibility for the integrity and accuracy of the data analysis.

Conflict of interest: None.

Funding source: Projekt DEAL

doi: 10.1111/ijd.15492

Abstract

Background Facial skin cancer lesions in close proximity to critical organs require further development of radiotherapeutic techniques for highly conformal treatment, especially when treating elderly frail patients. We report on our treatment technique and first clinical experience for patients with perinasal/periorbital skin cancer treated with individualized epithetic mold high-dose-rate brachytherapy (BRT).

Methods From January 2019, patients with complex shaped or unfavorably located skin cancer not eligible for surgery or external beam radiotherapy (RT) were screened for mold-based BRT. Six patients were identified. Toxicity and clinical response were documented during therapy and posttreatment follow-up.

Results Median patient age was 80 years (74–92 years). Median prescription dose was 42 Gy (range, 33–44 Gy) delivered in once-daily fractions of 3 or 4 Gy. Two patients had treatment interruptions caused by acute conjunctivitis grade 2 and a nontreatment-related cardiac event, respectively. At a median follow-up of 335 days (96–628 days), no $\geq$ grade 2 late toxicity was documented with all patients showing complete clinical response.

Conclusions High-dose-rate BRT with individualized epithetic molds for perinasal/periorbital skin cancer is a well-tolerated and safe treatment option for patients not eligible for primary surgery or definitive external beam RT because of comorbidities or tumor location.

Introduction

The incidence of skin cancer has increased globally over the past decades[1,2] with basal cell cancer (BCC) being the most common cutaneous malignancy accounting for about 80% of all non-melanoma tumors.[3] At the same time, demographic aging has a significant impact in daily clinical routine leading to new challenges especially for oncologic specialties treating elderly frail patients.[4]

First-line treatment of localized nonmelanoma skin cancer (NMSC) is surgery. Radiotherapy (RT) as definitive treatment is recommended for patients with inoperable lesions or those who are considered nonsurgical candidates because of comorbidities. National Comprehensive Cancer Network (NCCN) guidelines recommend external beam radiotherapy (EBRT) with either photons or electrons and doses ranging from 35 to 64 Gy using fractional doses of 2–7 Gy.[3] In addition, definitive RT can be considered as a viable alternative in nonsurgical patients with malignant melanoma *in situ* or lentigo maligna with dosing regimens ranging from 32 to 70 Gy.[5]

Despite its curative potential,[6] definitive EBRT is associated with some technique-specific aspects that should be taken into account: Standard fractionated EBRT takes several weeks,

International Journal of Dermatology 2021, **60**, 717–723

which may challenge treatment adherence especially in frail elderly patients. Furthermore, in anatomical locations of close proximity to critical organs at risk (OARs) and irregular shape or strong curvatures, such as the perinasal/periorbital region, EBRT cannot achieve sufficient target coverage without compromising conformity leading to unavoidable higher dose exposure of healthy surrounding structures. At this, brachytherapy (BRT) is an established modality for contact RT of skin malignancies with surface cone applicators for small lesions and catheter flaps for large and irregularly-shaped tumors being commercially available since many years. For anatomical locations difficult to access with standard applicators, individually adapted molds have been described.[7,8] Even if several BRT trials have reported excellent local control and good cosmetic outcome for NMSC,[6,9] NCCN guidelines recommend BRT only for highly selected cases without further defining dose and fractionation.[10,11] Filling this gap, the ESTRO recommendations for skin BRT suggest treatment schedules at 3–5 Gy per fraction, twice-daily to twice-weekly, up to a total physical dose of 40–60 Gy. The authors emphasize that in cases of very thin skin or with underlying cartilage, lower fractional doses may result in better cosmetic results without impairing oncological outcome.[12]

In order to address the clinical scenario of nonsurgical candidates with perinasal/periorbital skin tumors who are not amenable to EBRT, we introduced a new BRT technique implementing individualized epithetic molds. In contrast to existing cone applicator, flap, or classical mold concepts, we used individually designed epithetic molds for improved dose conformity and OAR sparing. In this report, we present our experience with this technique in terms of safety and early clinical outcome.

Material and methods

After the introduction of epithetic mold-based BRT in 2019, six selected patients were treated with this technique. All patients had skin cancer located in the perinasal/periorbital region and were assessed for operability by a specialized dermatologic surgeon and were deemed inoperable either because of excessive comorbidities or because complete local resection would be mutilating requiring extensive plastic reconstruction. Patients diagnosed with an SCC received a cranial and cervical MRI prior to BRT, in order to exclude nodal metastases as well as for macroscopically assessment of tumor depth infiltration. After written informed consent, patients were referred to the

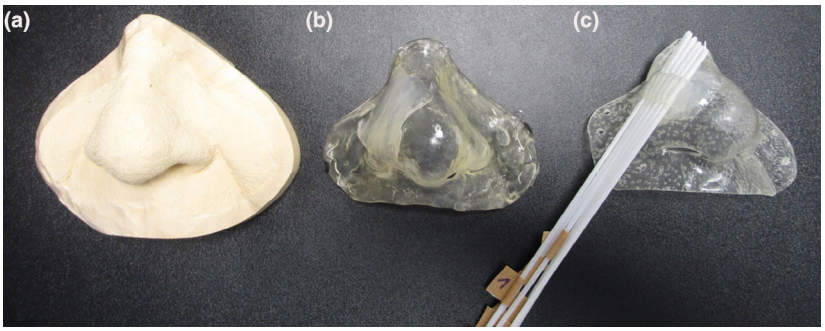

Figure 1 Plaster model of the target region for brachytherapy (BRT) applicator placement (a), mold without BRT applicators (b), and mold with flexible BRT applicators in parallel arrangement (c)

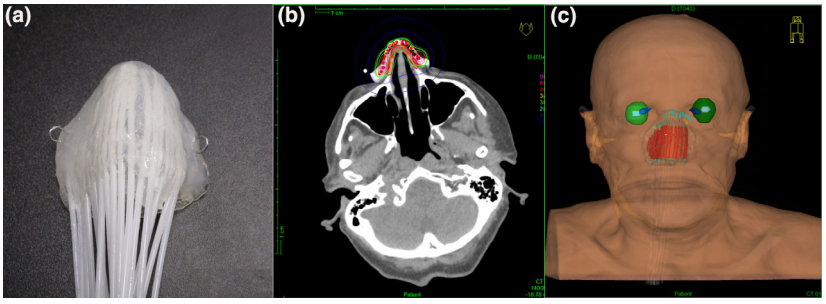

Figure 2 A 92-year-old patient with an extensive basal cell cancer extending from the right nasal wing over the ridge of the nose to the left nasal wing. (a) Epithetic mold with 18 embedded catheters. (b) Planning CT of the patient depicting the target volume (red). Prescription dose was 39.0 Gy to a target of 7.8 ml at 4.0 mm depth in once-daily fractional doses of 3.0 Gy delivered through 18 catheters. The 0.25 Gy isodose per fraction (not shown) is encompassing the lower part of the eyeballs resulting in a cumulative dose of 3.25 Gy to this part of the eyes. (c) Three-dimensional reconstruction of the planning CT depicting both eyes (green), the lenses (light blue), and the optic nerves (dark blue). The target volume on the skin is projected in red along with the reconstructed catheters and the calculated dwell positions of the radioactive source (red dots along the catheters)

epithetic division of the Department of Oral and Maxillofacial Surgery for individualized mold customization. The preparation of every mold by the cooperating anaplastologist (epithetist) required several successive work steps with an overall manufacture time of 1 week. The technique has been successfully evaluated by our group regarding dosimetric reproducibility/robustness, and the respective work is in the publication process. Concerning the clinical workflow, the facial target region was molded with liquid silicone, and the resulting negative was casted with plaster in order to obtain a positive model (Fig. 1a). Then, the layer of plastic mold material was formed to this positive plaster cast (Fig. 1b). Finally, flexible 6F ProGuide (Elekta, Sweden) BRT applicators of 200 or 240 mm length were glued on the mold with ultraviolet light curable acrylic resin resulting in an embedment of the applicators into the final construct (Fig. 1c). The applicators were arranged equally spaced (2–5 mm), covering at least the entire target surface. The minimum bending radius to ensure transfer of the Ir-192 source cable was kept when nonparallel applicator arrangement was indicated. Figure 1 depicts the work steps for mold preparation with one example of parallel applicator arrangement.

For BRT treatment planning, a CT dataset of the patient with the mold fixed by elasticated head bands was acquired with a Philips Brilliance Big Bore oncology system (120 kV tube voltage, 1 mm slice reconstruction with a high-resolution head and neck protocol). ProGuide CT markers (Elekta, Sweden) were inserted into the BRT applicators to visualize the BRT source paths. The tumor lesions were marked with a tin wire in a secondary CT acquisition of the same specifications. Both CT datasets were consecutively merged in the treatment planning system, and the PTV as well as relevant OARs including the eyeballs and lenses were delineated (Fig. 2). Dose was prescribed to 3–5 mm under the skin surface in accordance with international recommendations, depending on the histopathologic described infiltration depth and specific histology, and delivered in once-daily fractions over 5 days a week. Planning treatment volume was defined in accordance with international recommendations taking under consideration the histopathologic described infiltration depth, the specific histology as well as the pretreatment cranial CT scan. After inverse treatment planning optimization, minor graphical optimization was also performed. All treatments were performed using a 192-Iridium HDR afterloading system (Flexitron, Elekta, Sweden).

Follow-up consisted of clinical examination performed initially at 6 weeks after BRT and every 3 months thereafter. Toxicity was assessed according to CTCAE version 5 criteria.

Results

Patient and tumor characteristics are shown in Table 1. Median age was 80 years (range, 74–92). Among the six patients treated,

Table 1 Patient and treatment characteristics

No	Gender	Age	UCC Board Recommendation	Diagnosis	Tumor localization	Reason for Moulage BRT	Treatment time[c] [days]	Treatment dose/per fraction [Gy]	PTV [cm^3]	Treatment adherence	Follow-up/oncological outcome
1	M	75	Yes	LM	Nasofacial angle	Functional inoperable	15	44/4	1.8	Complete, no interruption	628 days no recurrence
2	M	74	Yes	BCC	Nasofacial angle	R0 resection not possible	21	42/3	5.5	Complete, no interruption	570 days no recurrence
3	F	79	Yes	MIS	Root of the right nose	Functional inoperable	34	42/3	3.0	Complete, interruption >3 days[a]	96 days died without evidence of recurrence
4	M	81	Yes	SCC	Right inner eye corner	Mutilating surgery	17	42/3	6.8	Complete, no interruption	346 days no recurrence
5	F	92	Yes	BCC	Nasal bridge	Functional inoperable	22	42/3	5.4	Complete, no interruption	325 days no recurrence
6	F	86	Yes	BCC	Left inner eye corner	Functional inoperable	34	33/3	3.0	Complete, interruption >3 days[b]	308 days no recurrence

BCC, basal cell carcinoma; BRT, brachytherapy; F, Female; LM, lentigo maligna; M, Male; MIS, melanoma *in situ*; PTV, planned target volume; RD, radiation dermatitis; SCC, squamous cell carcinoma; UCC, University Cancer Center.

[a]Patient was hospitalized because of cardiac complaint in an external hospital.

[b]Patient had grade 2 conjunctivitis leading to treatment interruption.

[c]Time from treatment planning CT until completion of BRT.

three were male and three female, one patient had malignant melanoma *in situ*, one lentigo maligna, three BCC, and one squamous cell carcinoma. Treatment time ranged from 15 to 34 days (median 21 days), single dose from 3 to 4 Gy (median 3 Gy), and total dose from 33 to 44 Gy (median 42 Gy). Two patients had treatment interruptions; one related to a major cardiac event necessitating hospitalization for interventional treatment (patient no. 3) and one the result of radiation-induced acute conjunctivitis requiring treatment (Fig. 3, patient no. 6). In both cases, the time from treatment planning CT until completion of BRT increased from 3 to 5 weeks. Within 90 days after treatment completion, no > grade 1 late toxicity was documented. At the end of BRT, all patients developed an erythema in terms of acute radiation dermatitis grade 1 (Fig. 4), which completely resolved within 30 days after treatment completion. At a median follow-up of 335 days (range, 96–628 days), all patients showed complete clinical response. One patient died after heart surgery at 5 months after BRT without evidence of local recurrence. In all treated cases, target coverage was adequate with a median D90 of 98.9%.

Discussion

Our analysis explores the role of epithetic mold-based BRT in the treatment of patients with perinasal/periorbital skin cancer, who are not candidates for surgery or definitive EBRT. Although there is some clinical experience with HDR BRT in the former setting,[13,14] this is, to the best of our knowledge, the first report on an individualized epithetic mold procedure. Our experience shows that the technique is feasible, well tolerated, with low rate of treatment-related adverse events, and encouraging initial oncologic outcome. Especially for frail elderly patients not eligible for radical surgery or EBRT, it poses a meaningful alternative option.

Despite the anatomically challenging locations, our toxicity profile was expectedly low with only one grade 2 acute conjunctivitis and grade 1 acute radiation dermatitis. Our findings corroborate the results reported in the current literature[14–17] confirming the safety and effectiveness of HDR BRT in the treatment of facial skin cancer. In a review by Delishaj et al.[17] regarding the role of HDR BRT in the treatment of skin cancer covering different techniques, toxicity was reported in the same range with predominantly grade 1 and 2 acute and late toxicity. Of note, it appears that there is no difference with respect to toxicity even in “very” frail elderly patients as shown in the study of Lancellotta et al.,[14] where median age was 86 years and only late grade 1 adverse events were observed.

Although randomized data are lacking, HDR BRT appears at least comparable in terms of toxicity with EBRT by means of

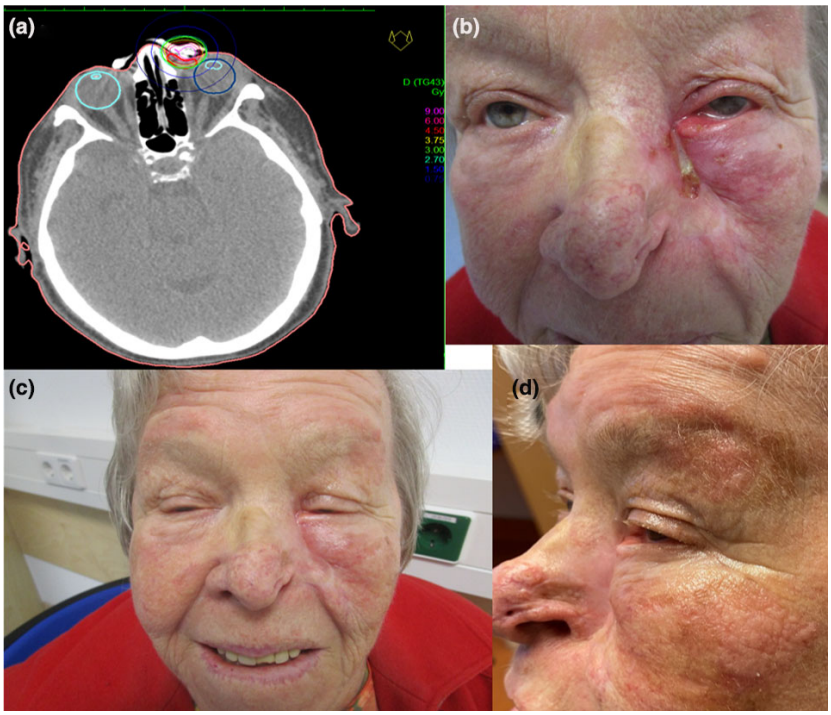

Figure 3 An 86-year-old patient with a basal cell cancer in the left corner of the eye. (a) Planning CT of the patient depicting the target volume (red) and critical structures (both eyeballs and lenses) in axial view. Prescription dose was 33.0 Gy to a target of 2.99 ml in once-daily fractional doses of 3.0 Gy delivered using seven embedded applicators. The 1.5 Gy isodose per fraction is encompassing the medial part of the eyeball resulting in a cumulative dose of 16.5 Gy to this part of the eye. (b) Conjunctivitis grade 2 on treatment day 14 as acute adverse event of the radiation dose exposure to the eyeball; (c, d) follow-up on day 70 (c) and on day 127 (d) with complete resolution of the radiation-induced toxicity

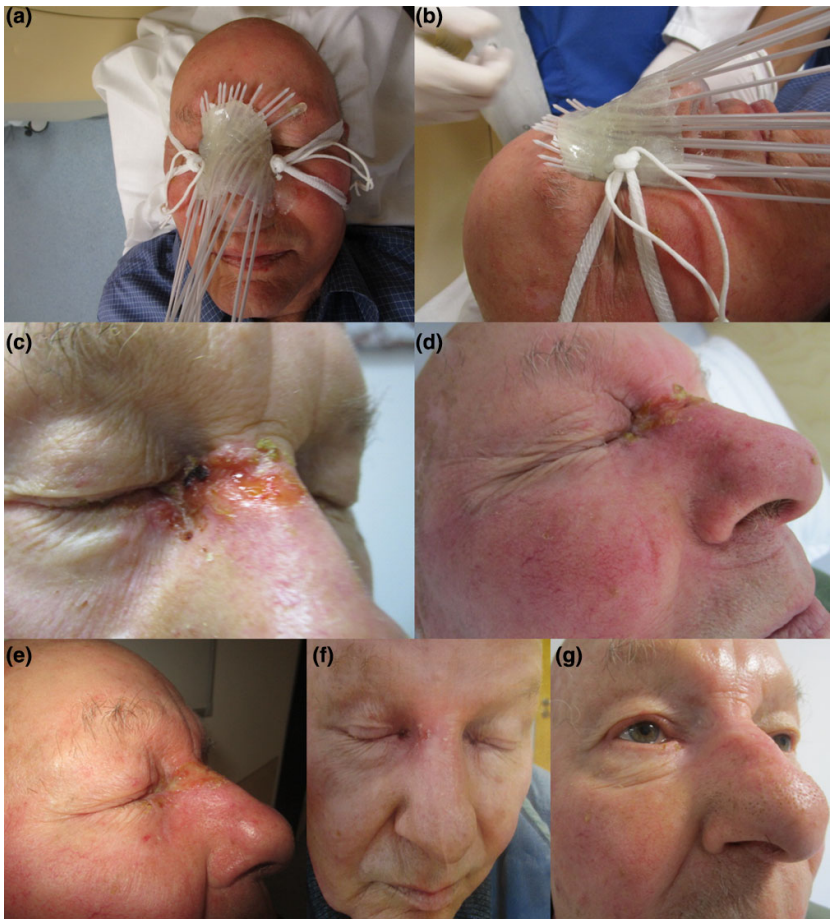

Figure 4 Exemplary clinical course of an 81-year-old patient with an extensive SCC expanding from the left corner of the right eye to the left-sided bridge of the nose. (a, b) Individualized epithetic mold fixed on the patient's face; (c) clinical manifestation before treatment; (d) clinical changes during treatment; (e) status at end of treatment; (f) status at follow-up day 53; (g) status at follow-up day 172

electrons.[18,19] At this, Vyas et al.[19] performed a matched pair analysis with respect to age, stage, anatomical site, and histology of a total of 25 lesions of early stage head and neck NMSC treated with electrons from 2008 to 2012, which were compared with 25 lesions treated with HDR BRT from 2010 to 2013. Acute as well as late toxicity were lower with BRT. The noninferior toxicity of HDR BRT was also noted in a retrospective analysis by Rosen et al.,[18] consisting of patients with early stage NMSC treated with orthovoltage x-rays, electrons, or HDR BRT. No acute or late toxicity differences were documented among the treatment modalities, although HDR BRT was utilized for anatomically more challenging locations not suitable for other modalities.

When treating skin cancer, cosmesis is an essential part of the overall clinical outcome. In our analysis, the cosmetic outcome so far is very satisfying in all patients. In line with our results, reported rates of good/excellent cosmesis after HDR BRT[15–17,20,21] are in the order of 80% or higher. Zaorsky et al.[21] reported a meta-analysis comparing HDR BRT and EBRT in the treatment of skin cancer with regard to cosmetic outcome. A total of 9965 patients with early stage NMSC treated with EBRT and 553 with HDR BRT across 24 studies were included. The primary endpoint was post-treatment cosmesis, categorized as "good," "fair," or "poor." With a mean age of 73 years, a median follow-up of 36 months, and a median total dose of 45 Gy in 10 fractions at 4.5 Gy/fraction, the authors concluded that BRT had favorable cosmesis over EBRT at common fractionation regimens.

An excellent local control in patients with NMSC treated with HDR BRT has been shown in several studies.[14–17,20–23] In a recent meta-analysis published by Lee et al.,[23] local recurrence rates among 21,000 patients with NMSC treated with conventional excision (CE), Mohs micrographic surgery (MMS), EBRT, or HDR BRT were compared. One-year and 5-year recurrence rates were low throughout treatment modalities at 0.8%, 0.2%, 2%, 0%, and 2.1%, 1.8%, 6.7%, 2.5% for CE, MMS, EBRT, and HDR BRT, respectively. Of note, both 1- and 5-year recurrence rates for EBRT were significantly higher in comparison to

CE and MMS, whereas no difference was noted between latter ones and BRT.

Another aspect that should always be considered, especially when treating frail elderly patients, is treatment adherence. Fewer treatment visits and shorter treatment time are of importance for this patient population. At this, BRT was tolerated well without any inconveniences. Our mold-based procedure was carried out in an outpatient setting; no hospitalization at any time of the process was required. Fraction duration ranged from 3 to 7 minutes with the patients treated in supine position and feeling comfortable with the fitted mold device. There were no cases of treatment interruption triggered by break or constriction of the BRT applicators. The feasibility of HDR BRT is well documented in the studies of Guix et al.[15] and Maronas et al.[16] In both studies, HDR irradiation was well tolerable with each treatment fraction lasting less than 8 minutes. Treatment adherence in consistence with our experience was immaculate.

Concerning treatment availability, a Canadian retrospective trial of 59 patients with SCC and BCC in an elderly patient collective (median age 82 years) treated most commonly with 40 Gy à 4 Gy found no grade 3–5 toxicity and presented a 3-year progression-free survival of 71.5% using surface mold BRT.[24] However, only 7/41 registered Canadian radio-oncology centers practiced surface mold BRT,[25] illustrating that even if general agreement in the indication of BRT for skin cancer exists, the therapy cannot be offered because of the lack of availability. On the other side, referring dermatologists are likewise often not aware of the advantages HDR BRT can offer their patients; therefore, more interdisciplinary communication and cooperation are desirable. Characteristically, the American Academy of Dermatology recommends HDR BRT, in contrast to electronic BRT, as an effective treatment option for patients with SCC[26] not suitable for other modalities.

Notwithstanding the technical novelty, our clinical analysis has some limitations that have to be addressed. Firstly, its retrospective nature is associated with intrinsic bias and the patient number is relatively low. Furthermore, although all patients showed an enduring complete clinical response with no late toxicity, our follow-up reflects a first clinical experience but not long-term oncological outcome. On the other hand, the presented workflow has led to further developments of our individualized mold-based approach. The workflow with externally commissioned mold manufacture in an epithetic center is certainly feasible for clinical routine, but the adequate positioning of BRT applicators as part of the final construct depends strongly on result-oriented communication between physician, medical physicist, and epithetician. In our experience, this can be a weak point with impact on dosimetry and treatment initiation in case of necessary mold modifications. Therefore, we proceeded to a workflow that allows planning of mold applicator arrangement through image-based anatomy-oriented treatment preplanning. Hence, position, number, and orientation of embedded applicators can be *ab initio* adapted to the clinical intent. By using iterative optimization prior to mold adaptation, this process has a direct dose distribution benefit in terms of conformity. On the other hand, based on the acquired preplan, the physician may also compare the intended mold-based contact BRT with other RT techniques such as interstitial BRT. After thorough preparation and extensive verification of treatment accuracy, in January 2020 we finally started treating selective skin cancer patients with 3D-printed molds, and until now five patients have been treated with this technique. Our aim, as results mature, is to perform and subsequently present a comparison of the oncological outcomes of the two techniques in order to provide the optimal BRT treatment for patients with perinasal/periorbital skin cancer.

Conclusions

HDR contact BRT for perinasal/periorbital skin cancer with individualized epithetic molds is a well-tolerated and safe treatment option for patients not eligible for primary surgery or definitive EBRT because of comorbidities or tumor location. With increasing incidence of skin cancer in elderly patients, interdisciplinary cooperation between dermatologists and radiation oncologists is crucial to enable the best treatment strategy for these patients. Possible improvement of this treatment modality through the use of 3D-printed molds is currently studied in our department.

Acknowledgments

Open Access funding enabled and organized by Projekt DEAL. [Corrections added on March 8, 2021, after first online publication. Acknowledgment section has been added.]

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