Strahlenther Onkol
https://doi.org/10.1007/s00066-018-1400-5

ORIGINAL ARTICLE

# Incidence of second primary cancers after radiotherapy combined with platinum and/or cetuximab in head and neck cancer patients

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Received: 6 July 2018 / Accepted: 8 November 2018


## Abstract

**Purpose** The second primary cancer (SPC) incidence after treatment with platinum-based chemotherapy and cetuximab in combination with radiotherapy has not been previously reported. Our aim was to compare SPC risk following radiotherapy in combination with these agents for the treatment of head and neck squamous cell carcinoma (HNSCC).

**Methods** The charts of 296 cases treated for loco-regionally advanced HNSCC between 2009 and 2015 were retrospectively reviewed for patient, tumor, and procedural characteristics. All patients were planned to undergo radiotherapy either with platinum compounds (group: Platinum) or monoclonal antibody cetuximab (group: Cetuximab). A third group of patients switched from platinum compounds to cetuximab due to toxicity (group: Switch). Treatment groups were evaluated for the incidence of SPC with log-rank test. Possible confounders were investigated with multivariate Cox's proportional hazards model. All tests were two-sided, and a $p < 0.05$ was set to indicate statistical significance.

**Results** Median follow-up was 36 months. Platinum, Cetuximab, and Switch groups consisted of 158, 101, and 37 patients, respectively. Three-year overall survival in the whole cohort was 70%. The rate of SPC was comparable between Platinum (9.2%) and Cetuximab (11.5%) groups ($p = 0.98$), whereas the patients in the Switch group were exposed to a significantly higher incidence of SPC (23.3%) in 3 years ($p = 0.01$). The multivariate model indicated Switch to be the only variable correlating with an increased risk for SPC.

**Conclusions** The Switch strategy may expose the patients to an increased risk of developing SPC. The use of switch should be advocated with caution until robust pre-clinical and clinical data are available.

**Keywords** Squamous cell carcinoma · Radiation · Anti-epidermal growth factor receptor · Cisplatin · Carboplatin · Secondary malignancies

**Availability of data and material** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Published online: 21 November 2018

## Inzidenz von metachronen Zweitkarzinomen nach Strahlentherapie in Kombination mit Platin und/oder Cetuximab bei Patienten mit Kopf-Hals-Tumoren


### Zusammenfassung

**Zielsetzung** Über die Inzidenz von metachronen Zweitkarzinomen („second primary cancer", SPC) nach platinbasierter Chemotherapie und Cetuximab in Kombination mit einer Radiotherapie ist bisher nichts bekannt. Ziel war es, das SPC-Risiko bei Patienten mit Plattenepithelkarzinomen des Kopf-Hals-Bereichs (HNSCC) nach durchgeführter kombinierter Radiotherapie mit den genannten Substanzen zu evaluieren.

**Methoden** Zwischen 2009 und 2015 wurden 296 Patienten aufgrund eines lokoregionär fortgeschrittenen HNSCC behandelt und bezüglich patienten-, tumor- und therapieassoziierten Charakteristika retrospektiv analysiert. Alle Patienten wurden entweder für eine Radiotherapie mit platinbasierter Chemotherapie (Platin-Gruppe) oder Antikörpertherapie mit Cetuximab (Cetuximab-Gruppe) eingeplant. Die dritte Gruppe bestand aus Patienten, die aufgrund einer Platinunverträglichkeit einen Substanzwechsel auf Cetuximab vollzogen (Switch-Gruppe). Die Inzidenz des SPC wurde mit dem Log-rank-Test errechnet. Mögliche Confounder wurden durch das multivariate Cox-Regressionsmodell (Cox's proportional hazards model) detektiert. Alle Tests erfolgten zweiseitig; ein $p$-Wert <0,05 galt als statistisch signifikant.

**Ergebnisse** Die mediane Nachbeobachtungszeit betrug 36 Monate. In der Platin-Gruppe waren 158, in der Cetuximab-Gruppe 101 und in der Switch-Gruppe 37 Patienten. Die 3-Jahres-Gesamtüberlebensrate der gesamten Kohorte war 70%. Die SPC-Raten waren zwischen der Platin- (9,2 %) und Cetuximab-Gruppe (11,5 %) vergleichbar ($p = 0{,}98$). In der Switch-Gruppe ließ sich hingegen nach 3 Jahren eine signifikant höhere Inzidenz ($p = 0{,}01$) von SPC (23,3 %) nachweisen. Im multivariaten Modell korrelierte ein Substanzwechsel als einzige Variable mit einem erhöhten SPC-Risiko.

**Schlussfolgerung** Der Substanzwechsel von einer platinbasierten Substanz auf Cetuximab könnte für Patienten ein erhöhtes Risiko für eine SPC-Entwicklung darstellen. Ein Substanzwechsel sollte aufgrund fehlender, robuster präklinischer und klinischer Daten vorsichtig ausgeübt werden.


**Schlüsselwörter** Plattenepithelkarzinom · Radiotherapie · Anti-epidermal growth factor receptor · Cisplatin · Carboplatin · Systemische Therapie

**Abbreviations**

| | |
|---|---|
| EGFR | Epidermal growth factor receptor |
| HNSCC | Head and neck squamous cell carcinoma |
| HPV | Human papillomavirus |
| OS | Overall survival |
| SPC | Second primary cancer |
| UICC | Union for International Cancer Control |

## Introduction

For two decades, the combination of platinum-based chemotherapy and radiotherapy has remained the first-choice non-surgical curative treatment for locally advanced head and neck squamous cell carcinoma (HNSCC) [1–3]. Alternative to cytotoxic chemotherapy, cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor (EGFR) showed success by increasing the loco-regional control and overall survival (OS) in this patient population [4]. However, neither a survival advantage nor a better toxicity profile could be directly demonstrated with cetuximab compared to platinum-based chemotherapy. Recently presented results of the GORTEC 2007-01 study revealed a significant improvement in progression-free survival and loco-regional control when carboplatin and 5-fluoruracil were added to concomitant cetuximab and radiotherapy [5]. However, with a similar but opposite design, the previously published RTOG 0552 failed to show a similar effect when cetuximab was added to cisplatin and radiotherapy [6]. These findings suggest that the positive effect of cetuximab may be dominated by platinum compounds, which is also supported by the findings of various retrospective case series [7, 8]. Therefore, cetuximab remains an alternative for patients who are not able to tolerate cytotoxic chemotherapy. Since the success of cetuximab, no other targeted agent has shown any clinical benefit when combined with radiotherapy alone or in combination with cytotoxic chemotherapy. In spite of contradicting data [9], efforts to demonstrate a superior efficacy or better toxicity profile through anti-EGFR strategies are ongoing [10].

Despite the abundance of literature about oncologic outcome of platinum compounds, cetuximab, and their combination, there are no published literature reports comparing the second primary cancer (SPC) incidence between platinum agents and cetuximab. Although there is no sound biological rationale for any expected difference, our aim was to explore and compare the incidence rates of SPC in a retrospective series of patients treated with radiotherapy and platinum compounds and/or cetuximab in our institution.

## Methods

The charts of the patients who were treated for Union for International Cancer Control (UICC) stage III–IVB HNSCC between 2009 and 2015 were retrospectively reviewed for patient, tumor, and procedural characteristics. Other eligibility criteria were: having been treated definitively or post-operatively with a combination of radiotherapy and systemic treatment with either cisplatin, carboplatin, or cetuximab; no previously diagnosed head and neck cancer; no previously untreated malignancy or synchronous malignancy at the time of diagnosis; and no induction chemotherapy prior to the concomitant treatment of the HNSCC. All tumors were biopsy proven and staged with panendoscopy, multimodal imaging with $^{18}$F-fluorodeoxyglucose positron emission tomography combined with computed tomography ($^{18}$F-FDG PET/CT) scan, and/or a combination of head and neck magnetic resonance imaging (MRI) and chest CT scans according to the UICC 7th edition. Evaluation of the human papillomavirus (HPV) status was not part of the routine diagnostic work-up in our institute before 2017. If occurred before the last follow-up, data about local, regional, and distant recurrence, death, and SPC were obtained. The follow-up time was not censored at a given timepoint. The post-treatment follow-up for HNSCC consisted of regular hospital visits every 3 months for the first 2 years, every 4 months in the 3rd year, every 3 months until the end of the 5th year, and annually thereafter. Additionally, head and neck MRI and chest CT examinations were performed at the 3rd, 12th, and 24th month after treatment. In case of detection of SPC, each patient was presented in the corresponding organ center's multidisciplinary tumor board of our university hospital. All SPCs had to be histologically verified and anatomically separate from the initial tumor (HNSCC). The diagnostic modalities, treatment, and further follow-up were organized according to the site, histology, and stage, in line with the institutional guidelines. The differential diagnosis between metachronous pulmonary metastases of HNSCC and primary squamous cell carcinoma of lung and the final decision in this regard relied on the cased-based information exchange between the attending pathologist, radiologist, and nuclear medicine specialist at the multidisciplinary thoracic oncology tumor board.

Radiotherapy was delivered in 2 Gy daily fractions with a volumetric modulated arc technique up to a total dose of 72 Gy to the macroscopically detectable tumor, 66 Gy to post-operative positive or close resection margin and to the lymph node region(s) with pathologic extracapsular extension, and 54 Gy to the elective nodal basin as previously described [11]. The concomitant systemic treatment consisted of either cisplatin 100 mg/m$^2$ every 3 weeks, weekly carboplatin (area under the curve: 2), or weekly cetuximab (400 mg/m$^2$ the week before radiotherapy and then 250 mg/m$^2$ weekly during radiotherapy). For the practical purposes of this study, patients receiving only platinum compounds and only cetuximab were grouped as "Platinum" and "Cetuximab", respectively. In the treatment timeframe of this cohort, our institutional policy was to switch from platinum agents to cetuximab if a patient became unable to receive the remaining platinum cycles due to treatment toxicity. Such patients were grouped under the category "Switch". In an auxiliary exploratory analysis, we compared the SPC incidence in these three systemic treatment groups with a previously published series [12] of UICC 7th edition stage I–II glottic laryngeal HNSCC ($n=201$) treated with radiotherapy alone as a reference for SPC incidence without systemic agents.

The log-rank test was used to evaluate the time to event endpoints, calculating from the date of histopathological diagnosis of the initial HNSCC. Readily available potentially confounding variables for SPC risk were considered as age, gender, surgery (due to the possible effect of radiotherapy dose and volume reduction), smoking pack-years, and documented alcohol abuse were investigated with multivariate Cox's proportional hazards model. All tests were two sided, and a $p<0.05$ was considered to indicate a statistically significant difference. Analyses were performed with JMP (version 13.0; SAS Institute, Cary, NC, USA).

## Results

A total of 296 patients who met the eligibility criteria were included in the final analysis. Patient and disease characteristics are provided in Table 1. Platinum, Cetuximab, and Switch groups consisted of 158, 101, and 37 patients, re-

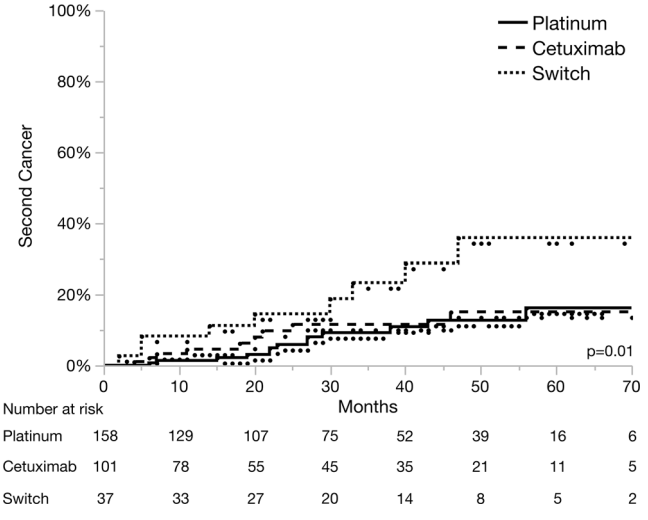


**Fig. 1** Incidence of second primary cancers after concomitant radiotherapy and systemic treatment for loco-regionally advanced head and neck squamous cell carcinoma

**Table 1** Patient and disease characteristics

| Parameter | Whole cohort ($n=296$) | Platinum ($n=158$) | Cetuximab ($n=101$) | Switch ($n=37$) | $p$-value |
|---|---|---|---|---|---|
| Median age (SD) | 62 (9.7) | 60 (9.9) | 67 (8.5) | 60 (8.7) | <0.01 |
| Female | 25.3% | 26.6% | 21.8% | 29.7% | 0.55 |
| *Tumor subsite* | | | | | 0.01 |
| Oral cavity | 16.9% | 20.3% | 11.9% | 16.2% | |
| Oropharynx | 50.7% | 53.7% | 45.5% | 51.4% | |
| Hypopharynx | 11.8% | 7% | 18.8% | 13.5% | |
| Larynx | 15.2% | 13.3% | 19.8% | 10.9% | |
| Nasal/paranasal | 1% | 1.9% | 0% | 0% | |
| Nasopharynx | 1.4% | 2.5% | 0% | 0% | |
| Multiple subsites[a] | 3% | 1.3% | 4% | 8% | |
| *UICC stage* | | | | | 0.77 |
| III | 15.5% | 14.6% | 15.8% | 18.9% | |
| IVA | 78.4% | 78.5% | 80.2% | 73% | |
| IVB | 6.1% | 6.9% | 4% | 8.1% | |
| Median KPS (range) | 90 (60–100) | 90 (60–100) | 90 (60–100) | 90 (60–100) | 0.10 |
| Median smoking py (SD) | 40 (30) | 30 (29) | 40 (30) | 40 (36) | 0.15 |
| *Smoking after diagnosis* | | | | | 0.42 |
| Still smoking | 51% | 50.4% | 51.6% | 52.8% | |
| Stopped smoking | 33% | 29.8% | 36.6% | 36.1% | |
| Never smoked | 16% | 19.8% | 11.8% | 11.1% | |
| Alcohol abuse | 71.3% | 67.1% | 75.3% | 78.4% | 0.21 |
| Primary surgery | 20.6% | 26.6% | 10.9% | 21.6% | 0.01 |

*KPS* Karnofsky performance Status, *py* pack-years, *SD* standard deviation, *UICC* Union for International Cancer Control
[a]Multiple subsites do not refer to synchronous tumors but a relatively large tumor extending to more than one subsite, which makes it impossible to define the subsite of origin.

spectively. In the Platinum group, 6 patients received carboplatin. The remaining 152 patients were planned to receive cisplatin, but 19 of them had to change to carboplatin after the administration of at least 1 cycle of cisplatin. Information regarding the systemic treatment cycles is given in Table 2.

The median follow-up of the surviving patients was 36 months (range: 2–79) in the whole cohort, and 35 (3–79), 39 (2–76), and 41 (7–74) in the Platinum, Cetuximab, and Switch groups, respectively ($p=0.61$). The rates of event-free patients who refused or ignored further regular visits before completing 2 years of follow-up were 21/13%, 7/7%, and 3/8% in the Platinum, Cetuximab, and Switch groups, respectively ($p=0.22$). Until their last follow-up visits, all patients adhered to the regular clinical and imaging examination plan mentioned in the Methods section.

Three-years OS was 70% in the whole cohort, and 74, 60, and 82% in the Platinum, Cetuximab, and Switch groups, respectively. The OS difference between the Platinum and Cetuximab groups was statistically significant ($p=0.02$). Three-year loco-regional control was 89% in the whole cohort, and 88, 88, and 97% in the Platinum, Cetuximab, and Switch groups, respectively ($p$ values >0.18). Three-year disease-free survival was 61% in the whole cohort, and 66, 49, and 74% in the Platinum, Cetuximab, and Switch groups, respectively. The Cetuximab group had a significantly lower disease-free survival compared to the Platinum ($p<0.01$) and Switch ($p=0.01$) groups.

The actuarial rates of SPC between the Platinum (9.2%) and Cetuximab (11.5%) groups were comparable ($p=0.98$), whereas the patients in the Switch group (23.3%) were exposed to a significantly higher incidence of SPC in 3 years ($p=0.01$), as depicted in Fig. 1. The multivariate model (Table 3) indicated Switch to be the only factor correlating with an increased risk of SPC. In the auxiliary multivariate analysis including the stage I–II cohort, only the Switch strategy compared to radiotherapy remained as an independent risk factor for increased SPC incidence vs. radiotherapy alone (HR: 5.39; 95% CI: 2.31–12.18, $p<0.01$), vs. Platinum (HR: 3.16; 95% CI: 1.35–7.18, $p<0.01$), and vs. Cetuximab (HR: 2.59; 95% CI: 1.04–6.53, $p=0.04$). The other two systemic treatment strategies did not yield a statistically significant risk for SPC: Platinum vs. no systemic agent ($p=0.17$), Cetuximab vs. no systemic agent ($p=0.10$), or among themselves ($p=0.65$).

The SPC are categorized as head and neck and non-head and neck SPC in Table 4. All (6) head and neck SPC were

**Table 2** Fractions of planned systemic treatment received in each treatment group

| Treatment group | Administered fractions of systemic treatments | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cisplatin, in % | | | Carboplatin, in % | | | Cetuximab, in % | | |
| | 1/3 | 2/3 | 3/3 | 1/3 | 2/3 | 3/3 | 1/3 | 2/3 | 3/3 |
| Platinum | 11 | 33 | 56 | 78 | 14 | 8 | – | – | – |
| Cetuximab | – | – | – | – | – | – | 5 | 35 | 60 |
| Switch[a] | 74 | 26 | – | 66 | 33 | – | 52 | 48 | – |

[a]There were no patients in the Switch group who received all three treatments. The switch was either between cisplatin and cetuximab, or between carboplatin and cetuximab

**Table 3** Multivariate Cox proportional hazards model for second primary cancer risk

| Parameter | HR | 95% CI | *p*-value |
|---|---|---|---|
| Age ≥62 vs. <62 years | 1.79 | 0.85–3.84 | 0.13 |
| Gender (male vs. female) | 2.25 | 0.87–7.18 | 0.10 |
| Smoking (yes vs. no) | 3.62 | 0.95–23.93 | 0.06 |
| Alcohol abuse (yes vs. no) | 0.56 | 0.23–1.57 | 0.25 |
| Primary surgery vs. none | 1.42 | 0.59–3.09 | 0.42 |
| Treatment group | – | – | 0.02[a] |
| Cetuximab vs. Platinum | 1.09 | 0.43–264 | 0.86 |
| Switch vs. Platinum | 3.40 | 1.42–8.04 | <0.01 |
| Switch vs. Cetuximab | 3.13 | 1.21–8.25 | 0.02 |

*CI* confidence interval, *HR* hazard ratio, *SPC* second primary cancer
[a]Effect summary for the parameter with three variables

**Table 4** Distribution of second cancers

| Treatment Group | HNC-SPC, in % (*n*) | non-HNC-SPC, in % (*n*) |
|---|---|---|
| Whole cohort | 2 (6) | 8.8 (26) |
| Platinum | 1.3 (2) | 7 (11) |
| Cetuximab | 3 (3) | 5.9 (6) |
| Switch | 2.7 (1) | 24.3 (9) |

*HNC* head and neck cancer, *SPC* second primary cancer

squamous cell carcinomas clearly belonging to subsites distinct from the initial HNSCC (e. g., first hypopharynx, later oral cavity). All non-head and neck SPC were also solid tumors: lung cancer (9 squamous cell carcinoma, 4 adenocarcinoma, 1 large-cell carcinoma), non-melanoma skin cancer (3 basal cell carcinoma, 1 squamous cell carcinoma), gastric adenocarcinoma (1 intestinal type, 1 signet ring, 1 mixed type), esophagus squamous cell carcinoma (2), colon adenocarcinoma (2), and papillary thyroid carcinoma (1). Concerning the previously mentioned issue of differential diagnosis between pulmonary HNSCC metastases and primary squamous cell carcinomas of the lung, 2, 4, and 3 cases were diagnosed with squamous cell carcinoma of the lung in the Platinum, Cetuximab, and Switch groups, respectively. All patients except for one (in the Switch group) were recurrence-free at the time of SPC diagnosis and did not receive any other oncologic treatments in between. This particular patient developing recurrent HNSCC 12 months after initial diagnosis was treated with salvage neck dissection. She developed a pT3 pN2 cM0 squamous cell carcinoma of the lung 21 months after salvage surgery.

## Discussion

To our knowledge, there is no previously published literature comparing the SPC risk in patients treated with platinum compounds and cetuximab for any cancer type, neither in the curative nor in the recurrent/metastatic setting. Regarding the Switch strategy for the treatment of HNSCC, there is so far only one published retrospective study by Peddi et al. [7], who reported the outcome of patients treated with Platinum, Cetuximab, and Switch. Their reasons for Switch were medical conditions similar to those observed in our collective. However, the authors of this study focused on toxicity and progression-free and overall survival endpoints in a cohort of 96 patients, and did not report on SPC.

Despite a relatively modest cohort size, our retrospective series revealed an interesting and original finding indicating a possibly increased risk of SPC when both platinum-based chemotherapy and cetuximab were combined with radiotherapy. The rate of SPC was significantly lower and comparable among patients who were treated with either platinum-based chemotherapy or cetuximab only. It is also

worth noting that the SPC incidence in the Platinum and Cetuximab groups was comparable and in line with the SPC risk reported in the literature [12–15]. High second malignancy rates in HNSCC patients are a major problem. With each passing year, about 3% of the treated HNSCC patients are expected to develop a second primary malignancy [13, 14].

Except for the possibility of a statistical type I error, it is quite difficult to explain the biological rationale of this observation. One hypothesis might be that the Switch group did not receive the full planned dose of either platinum or cetuximab. However, this explanation is quite problematic, considering the fact that a substantial number of patients in the Platinum and Cetuximab groups also did not receive the full doses as planned. Moreover, the Platinum and Cetuximab groups indicate an SPC incidence similar to previously published case series treated with radiotherapy alone [16–18]. In other words, the risk of SPC is already not expected to decrease by means of concomitant systemic treatment added to radiotherapy. In order to confirm this, we performed the auxiliary analysis and compared the Platinum, Cetuximab, and Switch groups with a previously published cohort of stage I–II laryngeal cancer patients treated with radiotherapy alone. There was no statistically significant difference in SPC incidence between these cohorts, except for the significantly higher incidence in the Switch group. Another hypothesis could be based on the possibility of a synergistic carcinogenic effect of radiotherapy when combined with both drugs instead of one. But then, contradictory to the pattern of SPC observed in the Switch group, we would rather expect to see a prominent increase of head and neck SPC and not non-head and neck SPC due to the radiation dose distribution.

Despite being original, due to the obvious reasons related to its retrospective nature, our results should be interpreted carefully and considered as hypothesis-generating findings. Important limitations of our cohort are especially the short follow-up period to observe late SPC incidence, co-morbidities, and the lack of histopathological information about HPV status, which became a part of the routine diagnostic work-up in 2017 with the implementation of the UICC 8th edition. The rate of SPC is known to be significantly lower in patients treated for HPV-positive compared to HPV-negative HNSCC [19].

## Conclusions

Our findings may result from a statistical type I error and/or unknown confounding variables. However, we cannot completely rule out that the Switch strategy form a single systemic concomitant platinum-based treatment to cetuximab during radiotherapy might expose patients to an increased risk of developing SPC. Although quite controversial, our current results suggest recommending the investigators of the RTOG 0552 [6] and GORTEC 2007-01 [5] trials to perform post-hoc analyses on both study populations regarding the incidence of SPC in the control and experimental arms, which consisted of single-agent platinum or cetuximab vs. combinations of cetuximab and a platinum agent, respectively. If our results can be reproduced in these prospectively randomized study cohorts, further systematic research on a possible carcinogenic effect of the radiotherapy, cetuximab, and platinum combination would be necessary.

**Acknowledgements** We thank Dr. Emanuel Stutz for his valuable input to the manuscript.

**Authors' contributions** Conception and design of the study: OE; data acquisition and quality control of data: BS, BB, MS, OE; statistical analysis: OE; manuscript preparation, editing, review and approval: all co-authors.

## Compliance with ethical guidelines

**Conflict of interest** O. Elicin received honoraria for his consulting role in the advisory boards of AstraZeneca, Merck, and Merck Serono. B. Sermaxhaj, B. Bojaxhiu, M. Shelan, R. Giger, D. Rauch, and D.M. Aebersold declare that they have no competing interests.

**Ethical standards** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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