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Osteosarcoma Arising After Ewing Sarcoma or *Vice Versa*: A Report of 20 Affected Patients from the Cooperative Osteosarcoma Study Group (COSS)

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Abstract. *Background/Aim: Ewing sarcoma can arise in patients after osteosarcoma or vice versa. Our aim was to learn more about which patients develop these secondary tumors, which treatments may be effective, and which patients might survive. Patients and Methods: The database of the Cooperative Osteosarcoma Study Group (1980-09/2022) was searched for all patients with an osteosarcoma (including undifferentiated pleomorphic sarcoma of the bone) who also suffered from Ewing sarcoma (incl. peripheral neuroectodermal tumor) at any time, previously or thereafter. The identified patients were then analyzed for patient, tumor, and treatment-related variables as well as their disease- and survival-status at the last follow-up. Results: A total of 20 eligible patients [17 Ewing sarcoma prior to osteosarcoma, 3 vice versa; 10 males, 10 females; median age at 1st cancer 10.5 (2.4-20.6), at 2nd cancer 20.5 (9.9-42.4) years] were identified. None of the patients developed a 3rd cancer and none had a known tumor-predisposition syndrome. Sixteen/17 secondary osteosarcomas and no secondary Ewing sarcoma developed in sites that had previously been irradiated. Nineteen/20 (95%) patients received primary multi-agent chemotherapy for their 1st and 2nd cancers. Actuarial overall and event-free survival probabilities at five years after the diagnosis of the secondary cancer were 69% and 42%, respectively. Conclusion: Secondary osteosarcoma arising after Ewing sarcoma is almost exclusively associated with radiation. This is not the case vice versa. Either way, long-term survival is a realistic possibility with appropriate multidisciplinary treatment; thus, therapeutic negligence is clearly inadequate.*

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The combination of Ewing sarcoma with a later osteosarcoma is a feared complication in both pediatric and adult oncology. Osteosarcoma generally arises as the second tumor and is often assumed to be related to irradiation therapy for the first cancer (1-3). Secondary Ewing sarcoma, arising after an osteosarcoma, is also a possibility, but clearly represents the much less common order of events (4-10). This particular sequence of events is not assumed to be associated with tumor-predisposition syndromes or prior therapies.

To date, the low frequency of affected patients with both malignancies has limited analyses of epidemiological variables, apart from radiotherapy administered against the first cancer, and prognostic factors associated with better chances of survival of the second. The Cooperative Ewing Sarcoma Study Group CESS, like our group run under the auspices of the German Society of Pediatric Oncology and Hematology (GPOH), has very recently presented their experiences with both secondary malignancies arising after Ewing sarcomas (3) and secondary Ewing sarcomas (10), respectively. While there is considerable patient overlap between their group and ours, the clear focus on osteosarcomas, a detailed analysis of received therapies, and a presentation of long-term outcomes still make our analysis unique.

The Cooperative Osteosarcoma Study Group (COSS) has been running a comprehensive osteosarcoma registry for more than four decades (11-13). In addition to patients eligible for prospective trials, the registry has always been open for all other patients with osteosarcoma (14), thereby also enabling analyses of secondary tumors (15). Therefore, we searched the large, unselected COSS database for all patients who developed Ewing sarcoma at any time, be it prior to or after their osteosarcoma. Affected patients were then analyzed for epidemiological variables, treatments administered against both cancers, and, finally, outcomes after the second.

Patients and Methods

Eligibility. The database of the Cooperative Osteosarcoma Study Group COSS of osteosarcomas and biologically related bone-sarcomas (1980 - September 19, 2022; 5.403 patients) was searched for registered patients with both a diagnosis of high-grade osteosarcoma and Ewing sarcoma. Undifferentiated pleomorphic sarcoma of the bone (UPS) and peripheral neuroectodermal tumor (PNET) were considered sufficiently similar to osteosarcoma or Ewing sarcoma, respectively, and thus included in the search. These are summarized with the osteosarcomas or Ewing sarcomas in the following text, if not mentioned separately.

The osteosarcoma had to have been diagnosed prior to July, 2021. The sequence of tumors was irrelevant for this search. All registered COSS patients and/or their parents, whichever appropriate, were required to have given their informed consent into treatment, data capture, and unlimited follow-up. All COSS-study and -registry protocols were performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and approved by the appropriate ethics committee (Ethik-Kommission bei der Ärztekammer Hamburg nos. 500, 1147; Ethikkommission der Ärztekammer Westfalen-Lippe und der Westfälischen-Wilhelms Universität nos. 182/98 Biel2, 4IV Bie 2, 4 I Bielack, 5 V. Bielack; and Ethik-Kommission an der Medizinischen Fakultät der Eberhard-Karls-Universität und am Universitätsklinikum Tübingen no. 5 V Bielack).

Treatment. For osteosarcoma, patients were treated according to one of the various COSS-regimens active at the time of enrolment. These included neoadjuvant and adjuvant multidrug chemotherapy and complete surgery wherever feasible (11-13). Adjustment for previous Ewing sarcoma treatments was allowed and the COSS-study center was available for guidance.

Starting in the 1980s, treatment for Ewing sarcoma was generally performed within the cooperative infrastructure of the German Society of Pediatric Oncology and Hematology GPOH (16), but this was no prerequisite for study inclusion. These Ewing-sarcoma protocols also consisted of neoadjuvant and adjuvant chemotherapy. Local treatment included surgery and/or radiotherapy.

Analyses. Patients were coded for sex and age at Ewing sarcoma and osteosarcoma diagnosis. For each malignancy, its site (both in relation to the bone and the involved anatomical area), and the primary metastatic status (including metastatic sites, if applicable), were noted. Tumor surgery including type and timing (primary or following preoperative chemotherapy), radiotherapy (including its dose, if available), and chemotherapy (including drugs administered) were noted. A complete remission of the Ewing sarcoma was assumed following the treating institution's assessment. A complete remission of the osteosarcoma was only assumed if, according to the treating center, all tumor manifestations had been removed by surgery. The further history, particularly third and follow-up malignancies, was documented. Response of the osteosarcoma to preoperative chemotherapy, if administered, was coded according to Salzer-Kuntschik *et al*. (17), with a good response defined as <10% viable tumor.

Statistics. All patients were evaluated on an intent-to-treat basis. Chi^2 analysis was used to compare unrelated samples. Event-free survival was calculated from the date of diagnosis of the second cancer, irrespective of whether this was an osteo- or Ewing sarcoma, until recurrence of one of these cancers or death, whichever occurred first. Only recurrences occurring after diagnosis of the second cancer were considered. Overall survival was calculated from diagnosis of the secondary malignancy until the date last known to be alive or until death, respectively. The Kaplan–Meier method (18) together with standard errors was used to calculate osteosarcoma-free and overall survival. Statistical analyses were carried out using the SPSS statistical software package (IBM Corp. Released 2021, IBM SPSS Statistics for Windows, Spss version 29.0.0.0., IBM Corp. Armonk, NY, USA).

Results

A total of 20 eligible COSS patients with both an Ewing sarcoma (including PNET) and an osteosarcoma (including UPS) were identified (Table I). All patients were in complete remission of their first malignancy at the time their respective secondary cancer was diagnosed. Seventeen patients presented with Ewing sarcoma as their first malignancy and osteosarcoma as their secondary cancer, three did so vice versa.

Among the Ewing tumors, 17 (85%) tumors were classified as Ewing sarcomas and 3 (15%) as PNET. Eighteen (90%) of these tumors arose intra-osseously and two (10%) in the soft tissues. The 20 eligible patients also developed 19 (95%) high-grade osteosarcomas and 1 (5%) UPS. Nineteen (95%) of these arose intra- and one (5%) extra-osseously.

The study cohort consisted of 10 (50%) female and 10 (50%) male patients. Their median age at diagnosis of their respective first malignancy had been 10.5 (2.4-20.6) years. Age was 20.5 (9.9-42.4) years at diagnosis of the secondary malignancy. The median lag-time between the diagnoses of

Table I. *Characteristics, treatment, and follow-up of 20 patients who developed both an Ewing sarcoma and an osteosarcoma, sorted by number of malignancy and by tumor-histology.*

	By number of malignancies		By tumor histology	
	1st cancer	2nd cancer	Ewing sarcoma	Osteosarcoma
Patient & tumor characteristics				
Interval between malignancies (median±range)				
Lag-time (years)	n.a.	9.5 (2.9-27.1)	8.0 (2.9-20.1) (3 secondary)	10.1 (4.2-27.1) (17 secondary)
First cancer				
Osteosarcoma	3 (15%)	17 (85%)	-	20 (100%)
Ewing sarcoma	17 (85%)	3 (15%)	20 (100%)	-
Age (median±range)				
Median (min-max) in years	10.5 (2.4-20.6)	20.5 (9.9-42.4)	13.0 (2.4-25.1)	19.8 (5.0-42.4)
Mean (range) in years	10.9±5.6	22.6±9.2	12.5±6.3	21.0±10.4
Sex				
Male	10 (50%)	10 (50%)	10 (50%)	10 (50%)
Female	10 (50%)	10 (50%)	10 (50%)	10 (50%)
Tumor site				
Extremity	12 (60%)	10 (50%)	10 (50%)	12 (60%)
Trunk	8 (40%)	9 (45%)	10 (50%)	7 (35%)
Head & neck	-	1 (5%)	-	1 (5%)
Primary metastases				
Present	2 (10%)	1 (5%)	2 (10%)	1 (5%)
Absent	18 (90%)	19 (95%)	18 (90%)	19 (95%)
Treatment				
Surgery				
Yes	12 (60%)	17 (85%)	12 (60%)	17 (85%)
No	8 (40%)	3 (15%)	8 (40%)	3 (15%)
Radiotherapy				
Yes	16 (80%)	4* (21%)	19 (95%)	1* (5%)
No	4 (20%)	15 (79%)	1 (5%)	18 (95%)
Unknown	-	1	-	1
Chemotherapy				
Yes	19 (95%)	19 (95%)	19 (95%)	19 (95%)
No	1 (5%)	1 (5%)	1 (5%)	1 (5%)
Follow-up				
Median (min-max) in years	18.3 (5.8-40.3)	6.9 (0.4-23.2)	17.8 (1.0-40.3)	8.1 (0.4-37.1)
Mean (range) in years	20.0±10.2	8.4±7.1	18.5±10.1	10.0±9.3

n.a.: Not applicable. *Plus one case of targeted internal radiotherapy with ^{99m}samarium ethylenediamine tetra-methylene-phosphonic acid.

both malignancies was 9.5 (range=2.9-27.1) years, the mean 11.6±6.9 years. The corresponding values for the 17 secondary osteosarcomas were 10.1 (4.2-27.1) and 11.9±5.8 years, respectively. The three secondary Ewing sarcomas arose after 2.9, 8.0, and 20.1 years, respectively.

No patient was known to have carried a genetic cancer predisposition, but this was not systematically searched. No patient suffered from another, third malignancy. However, one female patient was known to develop a benign tumor, ovarian cystoma, between both malignancies.

Sixteen/17 (94%) secondary osteosarcomas were reported to have arisen within or adjacent to a former field of radiotherapy. The only exception was a left mandibular osteosarcoma arising secondarily to an operated Ewing sarcoma of the right chest. None of the three secondary Ewing sarcomas was reported to be radiation-associated.

Primary metastases were reported to have been present in two primary Ewing tumors. They affected the lungs in one and the lungs combined with the bone, bone-marrow, and central nervous system in the other. Primary osteosarcoma metastases to the lungs were reported for one of the 17 patients with secondary and none of those three with primary tumors.

All but one of the 20 patients (95%), a patient with an extra-osseous PNET, received chemotherapy for their first cancer. All but one of 20 patients (95%), a patient with a mandibular osteosarcoma, also did so for their secondary cancer. She was

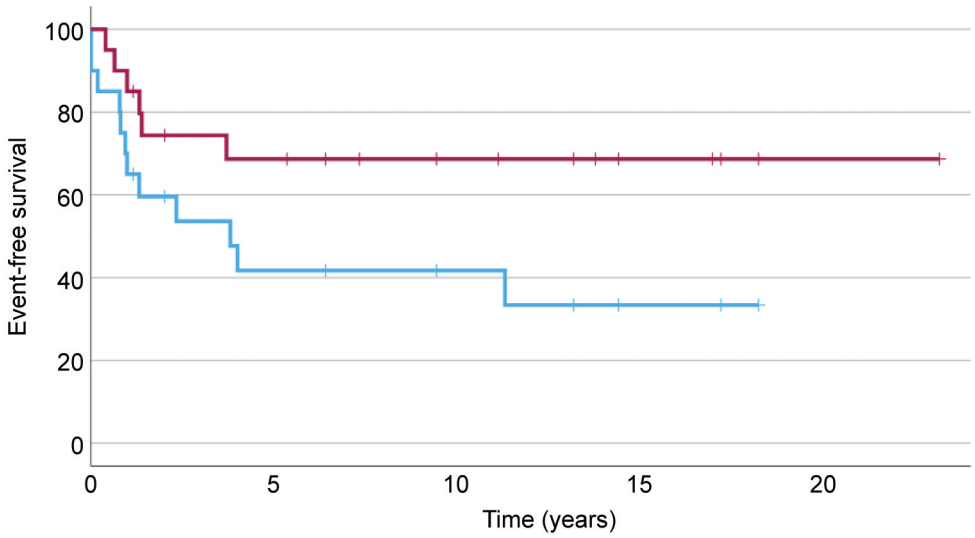

Figure 1. *Overall (red) and event-free (blue) survival of all 20 eligible patients from the date of diagnosis of their secondary bone-sarcoma.*

treated upon its recurrence. Agents used during primary therapy of Ewing sarcoma were known for 18/19 (95%) treated patients. They included vincristine (17; 94%), doxorubicin (16; 89%), ifosfamide (12; 67%), actinomycin D (12; 67%), cyclophosphamide (11; 61%), etoposide (10; 56%), and the combination of topotecan, irinotecan, and temozolomide (1; 6%). Two patients with primary metastatic disease also received high-dose therapy with busulfan and melphalan.

Nineteen/20 (95%) patients received first-line chemotherapy for their osteosarcoma (see above). Drugs documented in these 19 patients were high-dose methotrexate with leucovorin rescue (16; 84%), cisplatin (14; 74%), doxorubicin (13; 68%, 2 of these receiving the drug as a liposomal formulation), ifosfamide (12; 63%), etoposide (8; 42%), carboplatin (7; 37%), and cyclophosphamide, bleomycin, or actinomycin D (2 each; 11%). One patient received mifamurtide (5%).

The local therapy techniques used to treat both malignancies are detailed in Table I. The Ewing sarcomas were treated by surgery only in one (5%) patient, by radiotherapy only in eight (40%), and by a combination of both methods in 11 (55%) individuals. The type of surgery used was known for 11/12 (92%) operated tumors and was ablative in 1/11 (9%) and resection in 10/11 (91%). The radiotherapy dose was known for 13/19 (68%) irradiated patients. In these, the median dose was a 52 (30-64) Gy.

Seventeen (85%) osteosarcomas were operated upon, one (5%) was irradiated at a dose of 70 Gy, and two (10%) received no local therapy at all. Among the operated osteosarcomas, surgery was limb-saving resection in 4/17 (24%) and ablation in 13/17 (76%). Treatment began with this surgery in 7/17 (41%) operated osteosarcomas, and 10/17 (59%) received neoadjuvant chemotherapy. Response of the osteosarcoma to preoperative chemotherapy was documented for 9/10 (90%) and was good (<10% viable tumor) in 5/9 (56%) and poor in 4/9 (44%).

The 20 patients were followed for a median of 18.3 (5.8-40.3) years after diagnosis of their first and for 6.9 (0.4-23.2) years after the diagnosis of their second cancer (Table I). The corresponding values for 14 survivors were 20.1 (9.1-40.3) and 12.1 (1.1-23.2) years, respectively. Among the survivors, nine were in 1st remission of their osteosarcoma, four in 2nd, and one alive with disease at 2nd recurrence. One of the survivors with primary Ewing sarcoma developed an Ewing sarcoma recurrence after diagnosis of a secondary osteosarcoma. One further patient suffered an Ewing sarcoma recurrence prior to the development of a secondary osteosarcoma (not counted as an event upon lifetable-analyses).

Six patients, of whom five had a first diagnosis of Ewing and one of osteosarcoma, died after a median of 9.6 (5.8-28.0) years after diagnosis of their first cancer and 1.2 (0.4-3.7) years after diagnosis of their second. Causes of death were osteosarcoma in four individuals (one without ever achieving a remission, three at 1st recurrence), and secondary Ewing sarcoma in one. The remaining patient died of sepsis while being treated for a secondary osteosarcoma, without ever having achieved a remission.

Actuarial overall survival at 2, 5 and 10 years after diagnosis of the secondary cancer was 74% (standard-error: 10%), 69% (11%), and 69% (11%), respectively. The corresponding values for event-free survival were 60% (11%), 42% (12%), and 42% (12%), respectively (Figure 1). There was one late Ewing sarcoma recurrence in a patient with a secondary osteosarcoma.

Overall survival did not correlate with the order in which the sarcomas arose, with patient sex, age at first cancer, the interval between malignancies, or the age at second cancer ($p>0.1$, log-rank). There was a trend for better outcomes with extremity sites at presentation of the first ($p=0.065$) and better survival with extremity sites at presentation of the second malignancy ($p=0.038$). Of all these variables, none correlated significantly with event-free survival. A good response of the osteosarcoma to preoperative chemotherapy (<10% viable tumor) correlated significantly with event-free survival ($p=0.011$) and showed a trend favoring overall-survival ($p=0.059$) in the nine patients with available information on response.

Discussion

This report details therapy and outcomes of a considerably large cohort of patients developing both an Ewing sarcoma and an osteosarcoma. Neither of these tumors arose on the background of a known tumor predisposition syndrome. Secondary osteosarcomas, but not secondary Ewing sarcomas, were overwhelmingly often radiation-related. Of note, a sizeable minority of affected patients may still become long-term survivors with appropriate therapies despite their experience of a secondary bone sarcoma.

The COSS-database from which these patients were collected is probably the largest prospective osteosarcoma-database of any institution or cooperative group (14). As this is a prospective osteosarcoma registry and most Ewing sarcomas arose as first cancers, the information about these had, by necessity, to be collected retrospectively. It was nevertheless possible to collect most relevant data concerning both tumors. Our analysis is unique because it not only includes secondary osteosarcomas, but also secondary Ewing tumors. A long median follow-up of affected individuals even after their second malignancy adds considerable strength to the study. The inclusion of three tumors classified as PNET among the Ewing sarcomas and one osseous UPS among the osteosarcomas seems reasonable, as these tend to behave very similarly.

Osteosarcomas arising after Ewing sarcomas are very well recognized (1-3). The Cooperative Ewing Sarcoma Study-Group (CESS) has recently analyzed all of their groups' secondary malignancies. Among 4,518 Ewing sarcoma patients, they detected 101 of those, including 15 osteosarcomas (3). While there is certainly considerable patient redundancy as far as affected individuals are concerned, their study was largely epidemiological. Also, the clear focus on osteosarcomas and on individually received therapies presented here is unique.

Interestingly, we could not detect any patient with a known tumor-predisposition syndrome among these. However, our data confirms the overwhelming role of radiotherapy in this sequence of events. This has been previously observed by others (1-3). It may thus be wise to carefully analyze whether local Ewing sarcoma therapy truly requires irradiation or if the same quality of local control may be achieved by surgery. If the decision to use radiotherapy is contemplated, the increased risk of local recurrence without such therapy needs to be balanced against an increased risk of secondary osteosarcoma development.

Apart from radiotherapy as the vastly preferred mode of local treatment, we could not detect any other predisposing factors for later osteosarcoma development. Patients were as young as other Ewing sarcoma patients, mostly in their young adolescence (19). Like in the others, their distribution of sexes was even. The overwhelming absence of primary Ewing sarcoma metastases is best explained by the poor prognosis associated with such findings (20, 21), thereby often preventing any long-term observation of affected patients. All our patients were treated by systemic Ewing sarcoma chemotherapy, thereby preventing any statement about its potential contribution to osteosarcoma development.

The secondary osteosarcomas arose at a median of ten years, but as early as four and as late as 27 years after the Ewing sarcoma. The median lag-time from the first symptom to diagnosis lasted over two months - in the extreme up to almost ten months – in those 11 patients with appropriate information. This clearly demonstrates that patients at risk require a follow-up care which spans decades. The secondary osteosarcomas arose there where the primary Ewing sarcomas were located (19). This should come as no surprise given the impact of Ewing sarcoma irradiation on their development. Only one patient presented with primary metastatic secondary osteosarcoma, somewhat less than might be expected (22).

It is of interest that most of the secondary osteosarcomas were more or less treated appropriately (22) for this malignancy. This includes the use of appropriate local therapies where feasible. The high rate of ablative surgery observed should not come as a surprise, given that limb-salvaging methods had frequently been used for the Ewing sarcomas.

With the limitations on cumulative dosages associated with some anti-cancer agents, secondary osteosarcomas may be thought unlikely to once again be treated with intensive systemic chemotherapy. Anthracyclines, in particular, have strict cumulative dosage limitations (23). Nevertheless, most of our patients once again received what may be considered appropriate systemic treatment. This was probably aided by the fact that only doxorubicin and, within limits, ifosfamide, are in regular use against both malignancies, while this is not the case for many of the other drugs. Again, it should not be surprising that ablative surgery was a preferred treatment option.

Our series also confirms that, very rarely, Ewing sarcoma can arise as a secondary malignancy after osteosarcoma. The frequency in which we observed this order of events was, however, excruciatingly low. This is in accordance with the published literature: For instance, only five Ewing sarcomas

arising secondarily to any type of other sarcoma could be extracted from the SEER registry in 2013 (7). Published in 2019, a systematic review of secondary Ewing sarcomas reported only 62 such cases worldwide (9). The occurrence of only three patients with secondary Ewing sarcoma confirms that secondary Ewing sarcoma after osteosarcoma is indeed very rare. So far, neither we nor others have been able to define convincing risk-factors for their development. Among the secondary tumors, the use of local radiotherapy was more or less restricted to these very few Ewing sarcomas, which should not come as a surprise. The remarks made above relating to the renewed use of chemotherapy to treat secondary sarcomas are still valid when it comes to these secondary Ewing sarcomas.

The prognosis of the secondary bone sarcomas observed, may be considered surprisingly good, especially when these were in an extremity. Given the limitations of local and systemic treatments posed by procedures necessary to treat the first cancer, this positive impression seems especially remarkable. It demonstrates that all efforts must be made to treat a secondary bone-sarcoma appropriately. Therapeutic negligence is clearly inadequate.

Recurrent cancer after diagnosis of the secondary malignancy was, as expected, mostly related to this cancer. It should, however, be noted that there might be instances in which the first tumor recurs even after development of a secondary malignancy. Follow-up needs to take this into account.

In summary, secondary osteosarcomas after Ewing sarcoma were almost exclusively attributable to irradiation. We were not able to define similar risk-factors for the much rarer secondary Ewing sarcomas. The sometimes very long latency period between both tumors suggests that follow-up after bone cancer, at least if irradiated, needs to be life-long. Our results clearly prove that a history of prior bone sarcoma alone does not at all argue against a curative treatment approach for a later, secondary osseous malignancy.

Conflicts of Interest

Stefan Bielack reports personal fees from Boehringer Ingelheim, EISAI, Hoffmann LaRoche, MAP Biopharma, and Y-mAbs, all outside the submitted work. Stefanie Hecker-Nolting reports grants from EISAI, grants from St. Anna Kinderkrebsforschung GmbH as coordinating institution of ERN PaedCan, personal fees from Universitätsspital Basel, outside the submitted work, and Pediatric Cancer Data Commons, Chicago, USA - Co-Chair HIBISCus consortium, and Pediatric Cancer FOSTER Consortium–Co-chair Work Package 3–unpaid. Claudia Blattmann, Wolf Hassenpflug, Leo Kager, Thomas Kühne, Matthias Kevric, Paul-Gerhardt Schlegel, Vanessa Mettmann, and Benjamin Sorg report nothing to disclose.

Authors' Contributions

Stefan S. Bielack: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing–original draft; Writing–review & editing. Claudia Blattmann: Data curation; Funding acquisition; Resources; Software; Supervision; Writing–review & editing. Wolf Hassenpflug, Leo Kager, Thomas Kühne, Paul-Gerhardt Schlegel: Data curation; Writing–review & editing. Matthias Kevric: Data curation; Formal analysis; Writing–review & editing. Vanessa Mettmann: Data curation; Formal analysis; Validation; Writing–review & editing. Benjamin Sorg: Data curation; Formal analysis; Writing–review & editing. Stefanie Hecker-Nolting: Data curation; Investigation; Validation; Writing–review & editing.

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