

RESEARCH

Open Access



# Targeted RT study: results on early toxicity of targeted therapies and radiotherapy

Dinah Konnerth<sup>1\*</sup>, Aurelie Gaasch<sup>1</sup>, C. Benedikt Westphalen<sup>2,3,4</sup>, Kathrin Heinrich<sup>2,3</sup>, Maximilian Niyazi<sup>1,5</sup>, Chukwuka Eze<sup>1</sup>, Paul Rogowski<sup>1</sup>, Sebastian Marschner<sup>1,2</sup>, Annemarie Zinn<sup>1</sup>, Claus Belka<sup>1,2,6</sup>, Stefanie Corradini<sup>1</sup> and Stephan Schönecker<sup>1</sup>

## Abstract

**Purpose/objective** Currently, there are few prospective data on the tolerability of combining targeted therapies (TT) with radiation therapy (RT). The objective of this prospective study was to assess the feasibility and toxicity of pairing RT with concurrent TT in cancer patients. The aim was to enhance the existing evidence base for the simultaneous administration of targeted substances together with radiotherapy.

**Methods** Prospective study enrollment was conducted at a single institution between March 1, 2020, and December 31, 2021, for all patients diagnosed with histologically confirmed cancer who underwent external beam radiotherapy in combination with targeted therapy. The study, known as the “targeted RT study,” was registered in the German Clinical Trials Register under DRKS00026193. Systematic documentation of the toxicity profiles of different targeted therapies was performed, and the assessment of acute toxicity followed the guidelines of the National Cancer Institute Common Terminology Criteria for Adverse Events Version v5.0.

**Results** A total of 334 patients underwent 683 radiation therapy series. During the course of RT, 51 different TT substances were concurrently administered. External beam radiotherapy was employed for various anatomical sites. The combination of RT and concurrent TT administration was generally well tolerated, with no instances of severe acute toxicity observed. The most commonly reported toxicity was fatigue, ranging from mild to moderate Common Terminology Criteria for Adverse Events (CTCAE) °I-°III. Other frequently observed toxicities included dermatitis, dyspnea, dysphagia, and dry cough. No toxicity greater than moderate severity was recorded at any point. In only 32 patients (4.7% of evaluated RT series), the concurrent substance administration was discontinued due to side effects. However, these side effects did not exceed mild severity according to CTCAE, suggesting that discontinuation was a precautionary measure. Only one patient receiving Imatinib treatment experienced a severe CTCAE °III side effect, leading to discontinuation of the concurrent substance due to the sudden occurrence of melaena during RT.

**Conclusion** In conclusion, the current study did not demonstrate a significant increase or additional toxicity when combining radiotherapy and concurrent targeted therapy. However, additional research is required to explore the specific toxicity profiles of the various substances that can be utilized in this context.

**Trial registration number** DRKS00026193. Date of registration 12/27/2022 (retrospectively registered).

\*Correspondence:

Dinah Konnerth  
dinah.konnerth@med.uni-muenchen.de

Full list of author information is available at the end of the article



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

## Introduction

Targeted therapies (TT) and radiation therapy (RT) are currently utilized in the treatment of various cancers, including common types like breast, lung, and colon cancer [1–4]. These therapies specifically target molecules or pathways involved in cancer cell growth and spread, inhibiting their progression. Targeted therapies can be used alone or in combination with chemotherapy and radiation therapy [5–7]. Examples of targeted therapies include monoclonal antibodies, kinase inhibitors, and signal transduction inhibitors [8].

Although targeted therapies are relatively new compared to other cancer treatment modalities, they have already demonstrated significant success. For example, locally advanced lung cancer was previously treated with radiation therapy and chemotherapy. However, the advent of targeted therapies has led to the examination of tumors using molecular genetic methods to identify potential targets for personalized treatment [9–11]. Nowadays, there is a wide range of specifically targetable structures, and research is progressing towards histology-agnostic therapies that focus on genomic alterations regardless of the primary tumor type [12].

Combining targeted therapies with radiation therapy has become increasingly prevalent in multimodal cancer treatment [13–15]. Examples of successful multimodal treatments include the Pacific Trial, where locally advanced lung carcinomas received chemoradiation followed by maintenance therapy with the monoclonal antibody durvalumab (anti-PD-L1), leading to improved overall survival [16]. Another notable study is the Checkmate 577, which extended the standard therapy for locally advanced esophageal cancer by incorporating maintenance therapy with the monoclonal antibody nivolumab (anti-PD-1), resulting in improved disease-free survival [17]. These findings have had a significant impact on clinical practice and were practice-changing.

However, both targeted therapies and radiation therapy can cause side effects such as fatigue, nausea, and skin irritation. When combined, these therapies may have additive or even synergistic side effects. For example, targeted therapies that inhibit specific proteins can lead to skin rashes or diarrhea [18, 19], while radiation therapy may cause skin irritation or diarrhea if the intestines are affected by radiation [20, 21]. Consequently, the combination of targeted therapies and radiation therapy and its impact on side effects are areas of active research in cancer treatment [22–24].

To date, there is limited prospective data on the tolerability of combining targeted therapies and radiation therapy. Therefore, the aim of this prospective study was to assess the feasibility and toxicity of combining concurrent targeted therapy with radiotherapy in cancer patients, with the goal of enhancing the evidence base for

the simultaneous administration of targeted substances alongside radiation therapy. Although this approach has shown promise in many cases, further data on its effectiveness and safety are still required.

## Methods

Data for this prospective study were collected at LMU University Hospital from March 1, 2020, to December 31, 2021. The targeted RT study, was registered in the German Clinical Trials Register under DRKS00026193. The study enrolled all patients with histologically confirmed cancer who underwent both radiotherapy and concurrent targeted therapy. Informed consent was obtained from all participants. Data were extracted from medical records. The toxicity profiles of different targeted therapies were systematically documented at the time of first irradiation as baseline, the final irradiation, and during follow-up visits at our institution. The assessment of toxicity followed the guidelines of the National Cancer Institute Common Terminology Criteria for Adverse Events Version v5.0 [25].

Comprehensive demographic data and treatment characteristics were recorded, encompassing age, sex, Karnofsky Performance Status Scale, diagnosis according to International Statistical Classification of Diseases and Related Health Problems 10 (ICD-10), survival status, follow-up information, and timing of irradiation. Additionally, entity-specific toxicities that may have been present at baseline were documented to facilitate a thorough comparison between the beginning and end of the RT treatment. The specific anatomic region subjected to irradiation was recorded along with the determination of the target volume size (planning target volume, PTV). Furthermore, the fraction dose, total dose, and number of fractions administered in each RT series were evaluated, considering the employed techniques such as volumetric intensity-modulated arc therapy (VMAT), 3-dimensional radiation therapy (3D-RT), stereotactic body radiation therapy (SBRT), dynamic multileaf collimator radiation therapy (dMLC-RT), intensity-modulated radiation therapy (IMRT), brachytherapy, or electrons, as well as the intent of irradiation (definitive, adjuvant, neo-adjuvant, local-ablative, palliative, consolidative, prophylactic). The occurrence of previous in-field RT was also documented, as this information is essential for assessing toxicities during the course of irradiation.

The dataset also encompassed comprehensive information regarding systemic therapies. The primary focus was on targeted substances, specifying the substance used and the number of targeted substances administered concurrently to RT. Additionally, information was collected on whether chemotherapy was administered simultaneously or in close temporal relation to irradiation, along with the specific substances involved. For

targeted substances, the timing of their application was documented, as well as whether they were paused during radiation. If paused, the duration of the break ( $<$  or  $\geq$  than one week) was noted to ensure satisfactory assessment of toxicities relative to the time interval before irradiation. A break shorter than one week before the start of irradiation treatment was considered simultaneous application. For patients receiving cerebral irradiation, the use of dexamethasone during irradiation was also recorded.

Toxicities were evaluated taking into account the specific tumor entity and the anatomical region undergoing radiotherapy, covering a wide range of 54 different items of toxicities across all tumor types. Whenever feasible, an attempt was made to discern whether a particular toxicity was associated with the irradiation or could be attributed to the targeted therapy being administered. The ASENS database [26] was employed as the data collection tool, enabling the generation and customization of data forms tailored to the specific requirements of the study. Data extraction from ASENS was conducted, and the extracted data were further analyzed using Excel.

## Results

A total of 334 patients underwent 683 radiation therapy series and the administration of 51 different targeted therapy substances. A comprehensive overview of the administered TT substances is provided in Table 1, which includes various classes such as protein kinase inhibitors (including serine/threonine kinase inhibitors, tyrosine kinase inhibitors, and multikinase inhibitors), selective estrogen receptor degraders, CDK4/6 inhibitors, PARP inhibitors, mTOR inhibitors, proteasome inhibitors, Bcl-2 inhibitors, and bispecific gp100 peptide-HLA-directed CD3 T cell engagers. Among the 683 RT series, 314 (46%) did not have targeted therapy paused or had a pause duration of less than one week before initiating irradiation treatment. Moreover, in 106 RT series (16%) chemotherapy was applied simultaneously to TT.

The RT treatments were performed across various anatomic sites, including the head and neck region (6%), central nervous system (25%), thoracic (32%), breast (8%), abdominal/pelvic region (24%), and extremities (4%). Additionally, in 1% RT was administered to overlapping regions i.e. the RT fields extended over more than one anatomical region (e.g. in the case of RT of extensive bone metastases by way of example RT from T10 to L2 includes the thoracic and the abdominal regions). Treatment intent varied, with the most common indications being local-ablative (37%) and palliative (37%). However, adjuvant, definitive, consolidating, prophylactic, and neoadjuvant treatments were also performed. A prior irradiation was present in 169 out of the total 334 patients, accounting for 51% of the cases. Some of these series involved field overlaps in the low dose range and

8% of irradiation series even involved true re-irradiation or overlap in the high dose range.

There were varying numbers of fractionation regimens administered in the irradiation series. A detailed overview is given in Fig. 1. The most frequent were single fraction (134/683), 5 fractions (184/683) and 10 fraction regimens (112/683). In total, 5998 fractions were applied. The single dose varied considerably depending on treatment intention, localization, and tumor entity and ranged from 2 Gy to local ablative single fraction irradiations with a single dose of 28 Gy.

In 32 RT series (4.7%) TT was discontinued due to side effects not tolerated by the patient or on the advice of the treating physician. Table 2 summarizes the patient characteristics and treatment details.

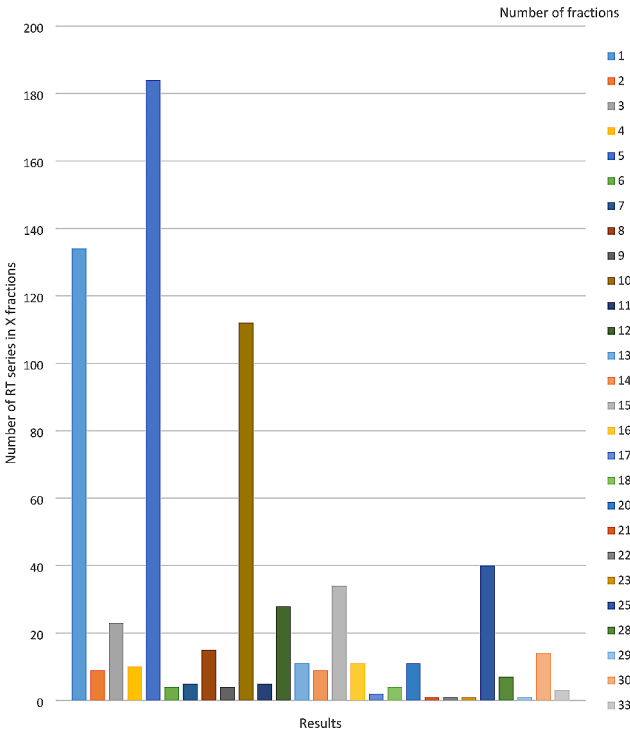
The following table (Table 3) provides an overview of the recorded toxicities at the three time points “baseline”, “end of irradiation” and “follow-up”. Owing to the limited number of events recorded, a shift to a descriptive evaluation approach was warranted, underlining the challenge posed by low event rates in achieving statistical significance for discerning differences in side effect profiles.

The most frequently observed side effect across all time points was fatigue. It also increased steadily at all evaluation time points. Baseline observations also revealed skin side effects, attributed to patients undergoing repeated series of irradiation within the same field. At the end of irradiation of course, there was an upward trend in side effects. A trend was identified by analyzing the data for a consistent increase in the frequency of side effects over a specified period of time. This involved looking at the side effects data points across different time intervals and observing a general pattern (e.g. from baseline to end of irradiation, see Table 3). In particular, the side effects concerning the skin, as well as the ear, nose and throat (ENT) side effects showed an upward trend. The first follow-up was performed after an average of about 3 months. The timing of further follow-ups depended on the tumor entity. Some follow-up visits continued to take place every three months, while subsequent follow-up visits varied based on tumor entity, with some maintaining a quarterly schedule, while others deferred the second radiotherapy follow-up for a year. The mean of all recorded follow-up visits was 6.3 months (SD=4.2 months) after the end of radiotherapy. To account for varying follow-up intervals, the subsequent table provides an inclusive view of toxicities across all follow-up periods, assessing regression, exacerbation, or the emergence of new toxicities post-radiotherapy.

The follow-up again showed a downward trend in acute skin as well as in dysphagia side effects, but an upward trend in late side effects such as hyperpigmentation. A downward trend was also observed in ENT side effects. When addressing side effects after central nervous system

**Table 1** Targeted therapy substances administered

| TT (In alphabetical order)       | Type of TT (Target in parentheses)                       |
|----------------------------------|----------------------------------------------------------|
| Abemaciclib                      | CDK4/6 inhibitor                                         |
| Adalimumab                       | monoclonal antibody (TNF alpha)                          |
| Afatinib                         | TKI (EGFR)                                               |
| Alectinib                        | TKI (ALK/RET)                                            |
| Atezolizumab                     | monoclonal antibody (PD-L1)                              |
| Axitinib                         | TKI (VEGFR)                                              |
| Bevacizumab                      | monoclonal antibody (VEGF-A)                             |
| Binimetinib                      | protein kinase inhibitor (MEK)                           |
| Bortezomib                       | proteasome inhibitor                                     |
| Cabozantinib                     | multikinase inhibitor                                    |
| Cetuximab                        | monoclonal antibody (EGFR)                               |
| Crizotinib                       | TKI (ALK/ROS1)                                           |
| Dabrafenib                       | protein kinase inhibitor (B-Raf)                         |
| Daratumumab                      | monoclonal antibody (CD-38)                              |
| Denosumab                        | monoclonal antibody (RANKL)                              |
| Durvalumab                       | monoclonal antibody (PD-L1)                              |
| Encorafenib                      | protein kinase inhibitor (B-Raf)                         |
| Erlotinib                        | TKI (EGFR)                                               |
| Everolimus                       | protein kinase inhibitor (mTOR)                          |
| Fulvestrant                      | SERD                                                     |
| Gefitinib                        | TKI (EGFR)                                               |
| Ibrutinib                        | TKI (BTK)                                                |
| Imatinib                         | TKI (multiple tyrosine kinases)                          |
| Ipilimumab                       | monoclonal antibody (CTLA-4)                             |
| Ixazomib                         | proteasome inhibitor                                     |
| Lenalidomide                     | immunomodulatory drug                                    |
| Lenvatinib                       | multi kinase inhibitor                                   |
| Lorlatinib                       | TKI (ALK/ROS1)                                           |
| Nintedanib                       | TKI (VEGFR, FGF, PDGF)                                   |
| Niraparib                        | PARP inhibitor                                           |
| Nivolumab                        | monoclonal antibody (PD-1)                               |
| Obinutuzumab                     | monoclonal antibody (CD-20)                              |
| Olaparib                         | PARP inhibitor                                           |
| Osimertinib                      | TKI (EGFR)                                               |
| Palbociclib                      | CDK4/6 inhibitor                                         |
| Panitumumab                      | monoclonal antibody (EGFR)                               |
| Pembrolizumab                    | monoclonal antibody (PD-1)                               |
| Pertuzumab                       | monoclonal antibody (Her2)                               |
| Polatuzumab                      | monoclonal antibody (CD79B)                              |
| Ponatinib                        | TKI (multiple tyrosine kinases)                          |
| Ramucirumab                      | monoclonal antibody (VEGFR2)                             |
| Ribociclib                       | CDK4/6 inhibitor                                         |
| Rituximab                        | monoclonal antibody (CD 20)                              |
| Sorafenib                        | multi kinase inhibitor                                   |
| Sunitinib                        | TKI (multiple tyrosine kinases)                          |
| Tafasitamab                      | monoclonal antibody (CD 19)                              |
| Tebentafusp                      | bispecific gp100 peptide-HLA-directed CD3 T cell engager |
| Tivozanib                        | TKI (VEGFR)                                              |
| Trametinib                       | protein kinase inhibitor (MEK)                           |
| Trastuzumab                      | monoclonal antibody (Her2)                               |
| Venetoclax                       | Bcl-2 inhibitor                                          |
| Total of 51 different substances |                                                          |



**Fig. 1** Number of fractions and amount of RT series with corresponding fractionation

(CNS) irradiation, a subtle inclination towards increased adverse events was apparent during the follow-up.

The additional surveyed toxicities are excluded from this report since they were observed even in CTCAE °I in less than 5 radiation series and exhibited minimal or negligible shifts from baseline to end of irradiation and to follow-up. Overall, no fourth- or fifth degree toxicity was observed.

**Discussion**

Overall, our dataset shows a favorable toxicity profile, across all irradiated regions and across all targeted therapies. There was no type of TT, in which particularly pronounced side effects could be observed. It is noteworthy that despite half of the patients having received more than one irradiation series, which inherently complicates toxicity assessment, and considering the elevated risk associated with re-irradiation, toxicity beyond grade 3 has remained conspicuously absent. While thorax irradiation accounted for the highest overall toxicity rates, these levels remain within an acceptable range, and are most likely reversible in the longer follow-up and/or with treatment. Expectedly, fatigue was the predominant toxicity, followed by dyspnea and dry cough.

Smets et al.'s investigation on the relationship between radiotherapy and fatigue revealed that fatigue scores post-treatment were slightly elevated compared to pre-treatment levels, and 46% of their study participants

**Table 2** Patient characteristics and treatment details of the entire cohort (334 patients and 683 radiation therapy series)

| Patient characteristics and treatment details | Characteristic                                           | n (%)         |
|-----------------------------------------------|----------------------------------------------------------|---------------|
| Gender                                        | male                                                     | = 149 (44.6%) |
|                                               | female                                                   | = 185 (55.4%) |
| Treatment intent                              | palliative                                               | = 252 (37%)   |
|                                               | local-ablative                                           | = 253 (37%)   |
|                                               | adjuvant                                                 | = 104 (15%)   |
|                                               | definitive                                               | = 49 (7%)     |
|                                               | consolidating                                            | = 17 (3%)     |
|                                               | neoadjuvant                                              | = 6 (1%)      |
|                                               | prophylactic                                             | = 2 (0%)      |
|                                               | overlapping regions                                      | = 7 (1%)      |
| Irradiated region                             | thoracic                                                 | = 219 (32%)   |
|                                               | CNS (brain)                                              | = 169 (25%)   |
|                                               | abdominal/pelvic                                         | = 162 (24%)   |
|                                               | breast                                                   | = 55 (8%)     |
|                                               | head & neck                                              | = 44 (6%)     |
|                                               | extremities                                              | = 27 (4%)     |
|                                               | see Fig. 1                                               |               |
|                                               |                                                          |               |
| Number of RT fractions                        | yes                                                      | = 55 (8%)     |
|                                               | no                                                       | = 628 (92%)   |
| Re-RT                                         | monoclonal antibody                                      | = 511 (75%)   |
|                                               | protein kinase inhibitor                                 | = 100 (15%)   |
|                                               | CDK4/6 inhibitor                                         | = 35 (5%)     |
|                                               | proteasome inhibitor                                     | = 11 (2%)     |
|                                               | PARP inhibitor                                           | = 8 (1%)      |
|                                               | immunomodulatory drug                                    | = 8 (1%)      |
|                                               | SERD                                                     | = 6 (1%)      |
|                                               | Bcl-2 inhibitor                                          | = 3 (0%)      |
| Type of TT                                    | bispecific gp100 peptide-HLA-directed CD3 T cell engager | = 1 (0%)      |
|                                               |                                                          |               |
| TT paused                                     | yes                                                      | = 369 (54%)   |
|                                               | no                                                       | = 314 (46%)   |
| Simultaneous chemotherapy                     | yes                                                      | = 106 (16%)   |
|                                               | no                                                       | = 577 (84%)   |

reported fatigue after irradiation treatment [27]. Their subsequent follow-up analysis indicated that 39% still experienced relevant fatigue symptoms nine months post-treatment [28]. Therefore, one might conclude, that fatigue is in general a very common symptom and is not enhanced due to simultaneous TT especially since fatigue values in our study population were much lower than that with around 13%.

Similarly the second and third most reported toxicities, dyspnea and dry cough, are also side effects that are related to radiotherapy - even without additional systemic therapy [29]. A study by Tsoutsou et al. showed that thorough assessment indicates that 50–90% of patients receiving thoracic irradiation develop irregularities that are evident both radiographically and in pulmonary function tests [30]. Remarkably, no excessive accumulation of these side effects that would make themselves felt via dyspnea and dry cough, was detected within our cohort, aligning with empirical values from our institution (e.g. clinical records, follow-up data and patient surveys).

Those side effects commonly follow a distinctive trajectory, often intensifying subsequent to radiotherapy. The emergence of pneumonitis aligns with this pattern, becoming evident around one to three months after the completion of radiotherapy [31]. This temporal connection is reflected in an increase in dyspnea and dry cough in our follow-up examinations as well.

Combining targeted therapies with radiation therapy can be an effective way to treat cancer. Nevertheless, informed decision-making necessitates a balanced consideration of potential advantages and disadvantages. A primary asset of combining radiation therapy with targeted medication is the precise targeting of cancer cell growth and proliferation pathways, conferring greater efficacy compared to conventional chemotherapy [5].

This amalgamation holds promise for improved outcomes by targeting specific molecular pathways crucial for cancer cell survival, while radiation therapy imparts cytotoxic damage or death to cancer cells through ionizing radiation [32–34]. Moreover, targeted therapies can

**Table 3** Overall toxicities and corresponding increasing or decreasing trends recorded during different time points of the treatment and during follow-up

| Toxicity               | CTCAE degree | Baseline frequency<br>(Number of patients) | End of irradiation frequency<br>(Number of patients) | Trend | Follow-up frequency<br>(Number of patients) | Trend |
|------------------------|--------------|--------------------------------------------|------------------------------------------------------|-------|---------------------------------------------|-------|
| Alopecia               | °I           | 4                                          | 10                                                   | ↑     | 14                                          | ↑     |
|                        | °II          | 1                                          | 2                                                    | ↑     | 15                                          | ↑     |
|                        | °III         | 0                                          | 0                                                    | →     | 2                                           | ↑     |
| Impaired Concentration | °I           | 9                                          | 15                                                   | ↑     | 16                                          | ↑     |
|                        | °II          | 2                                          | 1                                                    | ↓     | 3                                           | ↑     |
|                        | °III         | 0                                          | 0                                                    | →     | 0                                           | →     |
| Impaired Memory        | °I           | 10                                         | 7                                                    | ↓     | 15                                          | ↑     |
|                        | °II          | 1                                          | 1                                                    | →     | 2                                           | ↑     |
|                        | °III         | 0                                          | 0                                                    | →     | 0                                           | →     |
| Vertigo                | °I           | 11                                         | 8                                                    | ↓     | 17                                          | ↑     |
|                        | °II          | 0                                          | 0                                                    | →     | 1                                           | ↑     |
|                        | °III         | 0                                          | 0                                                    | →     | 0                                           | →     |
| Fatigue                | °I           | 65                                         | 75                                                   | ↑     | 79                                          | ↑     |
|                        | °II          | 11                                         | 16                                                   | ↑     | 11                                          | ↓     |
|                        | °III         | 1                                          | 1                                                    | →     | 0                                           | ↓     |
| Dysphagia              | °I           | 16                                         | 20                                                   | ↑     | 12                                          | ↓     |
|                        | °II          | 1                                          | 4                                                    | ↑     | 1                                           | ↓     |
|                        | °III         | 1                                          | 3                                                    | ↑     | 2                                           | ↓     |
| Mucositis              | °I           | 0                                          | 5                                                    | ↑     | 0                                           | ↓     |
|                        | °II          | 0                                          | 1                                                    | ↑     | 1                                           | →     |
|                        | °III         | 0                                          | 0                                                    | →     | 0                                           | →     |
| Xerostomia             | °I           | 1                                          | 5                                                    | ↑     | 7                                           | ↑     |
|                        | °II          | 0                                          | 1                                                    | ↑     | 0                                           | ↓     |
|                        | °III         | 0                                          | 0                                                    | →     | 0                                           | →     |
| Hyperpigmentation      | °I           | 5                                          | 7                                                    | ↑     | 9                                           | ↑     |
|                        | °II          | 0                                          | 1                                                    | ↑     | 0                                           | ↓     |
|                        | °III         | 0                                          | 0                                                    | →     | 0                                           | →     |
| Radiogenic Dermatitis  | °I           | 11                                         | 34                                                   | ↑     | 9                                           | ↓     |
|                        | °II          | 1                                          | 11                                                   | ↑     | 0                                           | ↓     |
|                        | °III         | 0                                          | 2                                                    | ↑     | 0                                           | ↓     |
| Fibrosis               | °I           | 5                                          | 7                                                    | ↑     | 14                                          | ↑     |
|                        | °II          | 0                                          | 0                                                    | →     | 1                                           | ↑     |
|                        | °III         | 0                                          | 0                                                    | →     | 0                                           | →     |
| Breast edema           | °I           | 0                                          | 4                                                    | ↑     | 4                                           | →     |
|                        | °II          | 0                                          | 0                                                    | →     | 0                                           | →     |
|                        | °III         | 0                                          | 0                                                    | →     | 0                                           | →     |
| Dyspnea                | °I           | 32                                         | 22                                                   | ↓     | 35                                          | ↑     |
|                        | °II          | 1                                          | 0                                                    | ↓     | 7                                           | ↑     |
|                        | °III         | 1                                          | 1                                                    | →     | 0                                           | ↓     |
| Dry Cough              | °I           | 23                                         | 24                                                   | ↑     | 36                                          | ↑     |
|                        | °II          | 3                                          | 1                                                    | ↓     | 1                                           | →     |
|                        | °III         | 0                                          | 0                                                    | →     | 0                                           | →     |
| Nausea                 | °I           | 1                                          | 4                                                    | ↑     | 2                                           | ↓     |
|                        | °II          | 0                                          | 0                                                    | →     | 0                                           | →     |
|                        | °III         | 0                                          | 0                                                    | →     | 0                                           | →     |
| Pain                   | °I           | 2                                          | 6                                                    | ↑     | 6                                           | →     |
|                        | °II          | 2                                          | 2                                                    | →     | 0                                           | ↓     |
|                        | °III         | 0                                          | 0                                                    | →     | 0                                           | →     |
| Dysuria                | °I           | 1                                          | 1                                                    | →     | 1                                           | →     |
|                        | °II          | 0                                          | 0                                                    | →     | 0                                           | →     |
|                        | °III         | 0                                          | 0                                                    | →     | 0                                           | →     |
| Urinary Incontinence   | °I           | 1                                          | 1                                                    | →     | 1                                           | →     |

**Table 3** (continued)

| Toxicity | CTCAE degree | Baseline frequency<br>(Number of patients) | End of irradiation frequency<br>(Number of patients) | Trend | Follow-up frequency<br>(Number of patients) | Trend |
|----------|--------------|--------------------------------------------|------------------------------------------------------|-------|---------------------------------------------|-------|
| Nycturia | °            | 0                                          | 0                                                    | →     | 0                                           | →     |
|          | °            | 0                                          | 0                                                    | →     | 0                                           | →     |
|          | °            | 3                                          | 3                                                    | →     | 5                                           | ↑     |
|          | °            | 0                                          | 1                                                    | ↑     | 0                                           | ↓     |
|          | °            | 0                                          | 0                                                    | →     | 0                                           | →     |

sensitize tumors to radiation, augmenting radiotherapy’s potency [35, 36].

Targeted therapies may be less toxic and may have fewer side effects than traditional chemotherapy, making them a good option for patients who are unable to tolerate potential side effects of chemotherapy [37]. Additionally, the prospect of reduced radiation doses through combination therapy has the potential to mitigate side effects and long-term complications [38]. In their consensus recommendations, the EORTC–ESTRO OligoCare consortium identified a clinically significant increase in SBRT-induced thoracic and abdominal toxicity when SBRT was combined with certain monoclonal antibodies or kinase inhibitors, including ipilimumab, nivolumab, bevacizumab, and sorafenib. Conversely, combining EGFR, ALK, and mTOR inhibitors with metastases-directed SBRT did not show increased toxicity rates. Regarding the same-day administration of targeted therapies and SBRT, consensus was reached for only some substances. Similarly, consensus on the duration of interruption before and after SBRT was also achieved for only some targeted therapies. The authors acknowledge that the limited data available made it challenging to reach a consensus on the simultaneous application for all substances and the appropriate duration of treatment interruption [39].

The integration of chemotherapy and radiotherapy has already been established as a well-acknowledged therapeutic modality within the landscape of cancer treatment. In the context of this study, a subset of our patient cohort underwent concurrent administration of chemotherapy and radiotherapy (16%). It is noteworthy that this proportion might initially appear moderate; however, this observation can be attributed to the fact that this study included patients who were concurrently undergoing targeted therapy at the time of radiotherapeutic intervention. As of now, targeted therapeutic approaches typically assume a secondary role in the therapeutic hierarchy, reserved for advanced cancer stages after the depletion of conventional treatment modalities, which predominantly encompass chemotherapy. Along with this, in this study population, the percentage of palliative intended radiotherapy (also rather a treatment for advanced stages) is quite high (37%).

Decisions regarding the continuity or interruption of targeted therapy during the course of radiotherapy were contingent upon multifaceted considerations. Initially, our determinations were underpinned by the guidance furnished by the Radiation Safety Commission (Strahlenschutzkommission [40]). Nevertheless, it is imperative to acknowledge that the aforementioned regulatory source does not comprehensively encompass the entire gamut of current targeted agents. Consequently, a broader spectrum of determinants, encompassing the patient’s overall medical condition and the tolerability of the targeted therapeutic regimen leading up to the radiotherapeutic intervention, were influential in the decision-making process.

Furthermore, it merits attention that a considerable proportion of targeted therapeutic agents are administered in temporal intervals spanning 3 to 4 weeks. Even in instances where the targeted regimen was not deliberately halted, meticulous consideration was exercised to avert any precise overlap between individual radiotherapy sessions and the administration of the therapeutic agent. This practice, however, encountered exceptions, notably in the context of orally administered agents such as CDK4/6 inhibitors that necessitate daily consumption, whereupon radiation therapy and targeted therapy coincided exactly.

Instances wherein the targeted therapeutic regimen required interruption were infrequent (4.7%). Such decisions predominantly emanated from a precautionary standpoint, owing to the prevailing dearth of robust empirical evidence substantiating the concurrent utilization of these therapeutic modalities. The rationale behind discontinuation encompassed a spectrum of factors, inclusive of a general decline in overall health status, fatigue or cutaneous reactions. However, it remains uncertain, whether these occurrences should be solely attributed to the combined therapeutic approach. Of particular significance is a solitary case wherein a patient afflicted with a gastrointestinal stromal tumor (GIST) was treated with imatinib—a protein kinase inhibitor—and concurrently received palliative radiotherapy at our institution. In this patient, a notable adverse effect, specifically melaena, manifested, necessitating the suspension of the targeted therapeutic regimen. Nevertheless, it is reasonable to infer that this phenomenon is unlikely to

be causally related to the parallel administration of palliative radiotherapy [41].

In spite of diligent efforts invested in conducting this study, it is essential to acknowledge the presence of limitations that warrant thoughtful consideration. One of the main reasons was the COVID pandemic. Due to the COVID restrictions imposed in Germany, some follow-ups during the period in which this study was conducted were done by telephone if possible. Thus, it is of course significantly more difficult to assess the side effects adequately, one has to rely to a large extent on the assessment of the patient. It might be the case that patients do not report side effects or do not recognize a side effect as such [42]. There may also be disincentives for reporting side effects, such as fear of treatment discontinuation possibly leading to a worse oncological outcome. In addition, while the evaluation of toxicities by means of CTCAE is a very good tool which tries to give objective criteria to the evaluator, there is always a risk for interobserver variability. In our facility, patients in this study were seen and assessed by many different physicians, so these differences in assessment may play a role after all [43–45]. Other limitations could be the unawareness of the complete spectrum of potential side effects linked to specific therapies. This can include a lack of reporting from healthcare providers, who sometimes might not be aware of the full range of potential side effects for a particular therapy and as a result may not report all of the side effects that they observe in their patients.

Moreover, inpatient care is available in our facility for cases where outpatient radiation is unfeasible due to deteriorated health. Timely inpatient admission, already at the onset of radiation induced side effects and treatment by specialized medical and nursing staff, effectively prevents the development of severe side effects and contributes to our favorable results. These limitations might underscore the complexity of the clinical landscape and the necessity for cautious interpretation of our findings.

Despite potential data limitations, our current findings affirm the safe administration of targeted therapies combined with radiation therapy. Although every medical treatment bears potential for side effects, our study witnessed scarce high-grade side effects in patients undergoing this combination, suggesting a low risk of severe complications. It is essential to note that effective side effect management in Germany contributes to this outcome, with early intervention preventing the escalation of toxicities. These combined therapies exhibit promising results across various cancer types, and the continual emergence of novel targeted therapies further underscores the importance of investigating combination therapy safety. Utilized in conjunction with radiation therapy, targeted therapies hold the potential to amplify treatment effectiveness while potentially reducing radiation dosage.

It is important to note that our data may not be comprehensive and there may be other factors that could affect the safety of this treatment combination. Further research is needed to fully understand the long-term effects of targeted therapies in combination with radiation therapy. However, our present data supports the safe application of this combined modality in clinical practice. Future research should persist in exploring the long-term tolerability of radiation and targeted therapy combinations, including a focus on potential changes in laboratory values as well as in exploring the efficacy of this combination treatment.

In summary, the combination of targeted therapies and radiation therapy emerges as a safe approach in cancer treatment. However, each patient's individualized treatment plan must meticulously weigh the potential benefits and drawbacks. Collaborative interdisciplinary decision-making is paramount in optimizing patient outcomes.

#### Author contributions

D. K.: conceptualization, data collection, data analysis and interpretation, manuscript writing, literature review, figure and table creation. A. G.: patient recruitment, collecting clinical data. C. B. W.: review and editing. K. H.: review and editing. M. N.: project supervision. C. E.: patient recruitment, collecting clinical data. P. R.: patient recruitment, collecting clinical data. S. M.: patient recruitment, collecting clinical data. A. Z.: patient recruitment, collecting clinical data. C. B.: project supervision. S. C.: conceptualization, review and editing, grant acquisition. S. S.: methodology development, data analysis, review and editing. All authors reviewed the manuscript.

#### Funding

This work was partly supported by the Friedrich-Baur-Stiftung under Grant Number: 76/18.

Open Access funding enabled and organized by Projekt DEAL.

#### Data availability

No datasets were generated or analysed during the current study.

#### Declarations

##### Ethics approval

Approval was obtained from the local ethics committee: "Ethikkommission bei der LMU München", project number 19–470.

##### Consent to participate

Informed consent was obtained from all individual participants included in the study.

##### Competing interests

The authors declare no competing interests.

#### Author details

<sup>1</sup>Department of Radiation Oncology, University Hospital, LMU Munich, Munich, Germany

<sup>2</sup>Partner Site Munich, German Cancer Consortium (DKTK), Munich, Germany

<sup>3</sup>Department of Medicine III, University Hospital, LMU Munich, Munich, Germany

<sup>4</sup>Comprehensive Cancer Center (CCC Munich LMU), University Hospital, LMU Munich, Munich, Germany

<sup>5</sup>Department of Radiation Oncology, University Hospital Tübingen, Tübingen, Germany

<sup>6</sup>Bavarian Cancer Research Center (BZKF), Munich, Germany

Received: 13 April 2024 / Accepted: 22 July 2024

Published online: 29 August 2024

## References

- Vanneman M, Dranoff G. Combining immunotherapy and targeted therapies in cancer treatment. *Nat Reviews Cancer* 2012. 2012;12:4. <https://doi.org/10.1038/nrc3237>.
- Nelson VM, Benson AB. Status of targeted therapies in the adjuvant treatment of colon cancer. *J Gastrointest Oncol*. 2013;4:245. <https://doi.org/10.3978/j.issn.2078-6891.2013.035>.
- Yuan M, Huang LL, Chen JH, Wu J, Xu Q. The emerging treatment landscape of targeted therapy in non-small-cell lung cancer. *Signal Transduct Target Therapy* 2019. 2019;4:1. <https://doi.org/10.1038/s41392-019-0099-9>.
- Higgins MJ, Baselga J. Targeted therapies for breast cancer. *J Clin Invest*. 2011;121:3797–803. <https://doi.org/10.1172/JCI57152>.
- Bagnyukova T, Serebriiskii IG, Zhou Y, Hopper-Borge EA, Golemis EA, Astsaturou I. Chemotherapy, and signaling. 2010;10:839–53. <https://doi.org/10.4161/CBT.10.9.13738>.
- Bosacki C, Boulefour W, Sotton S, Vallard A, Daguenet E, Ouaz H, et al. CDK 4/6 inhibitors combined with radiotherapy: a review of literature. *Clin Translational Radiation Oncol*. 2020;26:79–85. <https://doi.org/10.1016/j.ctro.2020.11.010>.
- Becherini C, Visani L, Cainsi S, Bhattacharya IS, Kirby AM, Nader Marta G, et al. Safety profile of cyclin-dependent kinase (CDK) 4/6 inhibitors with concurrent radiation therapy: a systematic review and meta-analysis. *Cancer Treat Rev*. 2023;119. <https://doi.org/10.1016/j.ctrv.2023.102586>.
- Targeted Therapy for Cancer. - NCI n.d. <https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies> (accessed January 15, 2023).
- Tsao AS, Scagliotti GV, Bunn PA, Carbone DP, Warren GW, Bai C, et al. STATE OF THE ART: CONCISE REVIEW scientific advances in Lung Cancer 2015. *J Thorac Oncol*. 2016;11:613–38. <https://doi.org/10.1016/j.jtho.2016.03.012>.
- Tsimberidou AM. Targeted therapy in cancer. *Cancer Chemother Pharmacol*. 2015;76:1113–32. <https://doi.org/10.1007/S00280-015-2861-1/METRICS>.
- Xie YH, Chen YX, Fang JY. Comprehensive review of targeted therapy for colorectal cancer. *Signal Transduction and targeted therapy* 2020 5:1 2020;5:1–30. <https://doi.org/10.1038/s41392-020-0116-z>.
- Mateo J, Steuten L, Aftimos P, André F, Davies M, Garralda E, et al. Delivering precision oncology to patients with cancer. *Nat Med* 2022. 2022;28:4. <https://doi.org/10.1038/s41591-022-01717-2>.
- Mirreştan CC, Iancu RI, Iancu DT. Immunotherapy and Radiotherapy as an Antitumoral Long-Range Weapon-A Partnership with Unsolved challenges: Dose, Fractionation, volumes, therapeutic sequence. *Curr Oncol (Toronto Ont)*. 2022;29:7388–95. <https://doi.org/10.3390/CURRONCOL29100580>.
- Eckert F. [Multimodal treatment concepts of local radiation therapy with immunotherapy: Rationale for combination therapy and possible clinical treatment strategies]. *Urologie (Heidelberg Germany)*. 2022;61:1324–31. <https://doi.org/10.1007/S00120-022-01966-6>.
- Fleischmann M, Glatzer M, Rödel C, Tselis N. Radioimmunotherapy: future prospects from the perspective of brachytherapy. *J Contemp Brachytherapy*. 2021;13:458–67. <https://doi.org/10.5114/JCB.2021.108601>.
- Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares L, et al. Five-year survival outcomes from the PACIFIC Trial: Durvalumab after Chemoradiotherapy in Stage III Non-small-cell Lung Cancer. *J Clin Oncology: Official J Am Soc Clin Oncol*. 2022;40:1301–11. <https://doi.org/10.1200/JCO.21.01308>.
- Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, et al. Adjuvant nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N Engl J Med*. 2021;384:1191–203. <https://doi.org/10.1056/NEJMOA2032125>.
- Lacouture M, Sibaud V. Toxic side effects of targeted therapies and immunotherapies affecting the skin, oral mucosa, hair, and nails. *Am J Clin Dermatol*. 2018;19:31–9. <https://doi.org/10.1007/S40257-018-0384-3/FIGURES/4>.
- Pessi MA, Zilembo N, Haspinger ER, Molino L, Di Cosimo S, Garassino M, et al. Targeted therapy-induced diarrhea: a review of the literature. *Crit Rev Oncol Hematol*. 2014;90:165–79. <https://doi.org/10.1016/j.critrevonc.2013.11.008>.
- Hegedus F, Mathew LM, Schwartz RA. Radiation dermatitis: an overview. *Int J Dermatol*. 2017;56:909–14. <https://doi.org/10.1111/IJD.13371>.
- Claßen J, Belka C, Paulsen F, Budach W, Hoffmann W, Bamberg M. Radiation-induced gastrointestinal toxicity. Pathophysiology, approaches to treatment and prophylaxis. *Strahlentherapie Und Onkologie: Organ Der Deutschen Röntgengesellschaft [et Al]*. 1998;174(Suppl 3):82–4.
- Anscher MS, Arora S, Weinstock C, Amatya A, Bandaru P, Tang C, et al. Association of Radiation Therapy with risk of adverse events in patients receiving immunotherapy: a pooled analysis of trials in the US Food and Drug Administration Database. *JAMA Oncol*. 2022;8:232–40. <https://doi.org/10.1001/JAMAONCOL.2021.6439>.
- Kroeze SGC, Fritz C, Hoyer M, Lo SS, Ricardi U, Sahgal A, et al. Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: a systematic review. *Cancer Treat Rev*. 2017;53:25–37. <https://doi.org/10.1016/j.ctrv.2016.11.013>.
- Kroeze SGC, Fritz C, Schaule J, Blanck O, Kahl KH, Kaul D et al. Continued versus interrupted targeted therapy during Metastasis-Directed Stereotactic Radiotherapy: a retrospective Multi-center Safety and Efficacy Analysis. *Cancers* 2021;13. <https://doi.org/10.3390/CANCERS13194780>.
- Cancer Institute N. Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 2017.
- LoeScap - Everything. Online PACS n.d. [https://www.loescap.com/produkt\\_asena.html](https://www.loescap.com/produkt_asena.html) (accessed January 15, 2023).
- Smets EMA, Visser MRM, Willems-Groot AFMN, Garssen B, Oldenburger F, Van Tienhoven G, et al. Fatigue and radiotherapy: (A) experience in patients undergoing treatment. *Br J Cancer*. 1998;78:899–906. <https://doi.org/10.1038/bjc.1998.599>.
- Smets EMA, Visser MRM, Willems-Groot AFMN, Garssen B, Schuster-Uitterhoeve ALJ, De Haes JCM. Fatigue and radiotherapy: (B) experience in patients 9 months following treatment. *Br J Cancer*. 1998;78:907–12. <https://doi.org/10.1038/bjc.1998.600>.
- Benveniste MF, Gomez D, Carter BW, Betancourt Cuellar SL, Shroff GS, Benveniste APA, et al. Recognizing radiation therapy-related complications in the chest. *Radiographics*. 2019;39:344–66. <https://doi.org/10.1148/rq.2019180061>.
- Tsoutsou PG, Koukourakis MI. Radiation pneumonitis and fibrosis: mechanisms underlying its pathogenesis and implications for future research. *Int J Radiation Oncology\*Biophysics*. 2006;66:1281–93. <https://doi.org/10.1016/j.jrobp.2006.08.058>.
- BERKEY FJ. Managing the adverse effects of Radiation Therapy. *Am Family Phys*. 2010;82:381–8.
- Khalifa J, Amini A, Popat S, Gaspar LE, Faivre-Finn C. Brain metastases from NSCLC: Radiation therapy in the era of targeted therapies. *J Thorac Oncol*. 2016;11:1627–43. <https://doi.org/10.1016/j.jtho.2016.06.002>.
- Wargo JA, Reuben A, Cooper ZA, Oh KS, Sullivan RJ. Immune effects of Chemorapy, Radiation, and targeted rapy and opportunities for Combination with Immunorapy. *Semin Oncol*. 2015;42:601–16. <https://doi.org/10.1053/j.seminoncol.2015.05.007>.
- Simone CB, Burri SH, Heinzerling JH. Novel radiotherapy approaches for lung cancer: combining radiation therapy with targeted and immunotherapies. *Translational Lung Cancer Res*. 2015;4:545–52. <https://doi.org/10.3978/j.issn.2218-6751.2015.10.05>.
- Wang H, Mu X, He H, Zhang XD. Cancer Radiosensitizers. *Trends Pharmacol Sci*. 2018;39:24–48. <https://doi.org/10.1016/j.tips.2017.11.003>.
- Karelitis G, Tremi I, Kaitatzi M, Drakaki E, Serafetinides AA, Makropoulou M et al. Combined radiation strategies for novel and enhanced cancer treatment. *Int J Radiat Biol* 2020:1087–103. <https://doi.org/10.1080/09553002.2020.1787544>.
- GERBER DE. Targeted therapies: a New Generation of Cancer treatments. *Am Family Phys*. 2008;77:311–9.
- Xing DT, Khor R, Gan H, Wada M, Ermongkonchai T, Ng SP. Recent research on combination of Radiotherapy with targeted therapy or immunotherapy in Head and Neck Squamous Cell Carcinoma: a review for Radiation oncologists. *Cancers* 2021. Page 5716 2021;13:13:5716. <https://doi.org/10.3390/CANCERS13225716>.
- Kroeze SGC, Pavic M, Stellamans K, Lievens Y, Becherini C, Scorsetti M, et al. Metastases-directed stereotactic body radiotherapy in combination with targeted therapy or immunotherapy: systematic review and consensus recommendations by the EORTC-ESTRO OligoCare consortium. *Lancet Oncol*. 2023;24:e121–32. [https://doi.org/10.1016/S1470-2045\(22\)00752-5](https://doi.org/10.1016/S1470-2045(22)00752-5).
- Strahlenschutzkommission. Kombinationswirkungen Strahlentherapie/medikamentöse Tumorthherapie n.d.
- El Hajj II, Chehal A, El Saghir NS. Recurrent GI bleeding and surgery following the initial response to Imatinib Therapy in GIST of the stomach. *Dig Dis Sci*. 2005;50:65–9. <https://doi.org/10.1007/s10620-005-1279-8>.
- Rabinowitz T, Peirson R. Nothing is wrong, doctor: understanding and managing denial in patients with cancer. *Cancer Invest*. 2006;24:68–76. <https://doi.org/10.1080/07357900500449678>.
- Fairchild AT, Tanksley JP, Tenenbaum JD, Palta M, Hong JC. Interrater reliability in toxicity identification: limitations of current standards. *Int J Radiation*

Oncology\*Biography\*Physics. 2020;107:996–1000. <https://doi.org/10.1016/j.ijrobp.2020.04.040>.

44. Nelson JC, Pepe MS. Statistical description of interrater variability in ordinal ratings. <http://dx.doi.org/10.1177/096228020000900505>. 2000;9:475–96. <https://doi.org/10.1177/096228020000900505>.
45. Tuijn S, Janssens F, Robben P, Van Den Bergh H. Reducing interrater variability and improving health care: a meta-analytical review. *J Eval Clin Pract*. 2012;18:887–95. <https://doi.org/10.1111/j.1365-2753.2011.01705.x>.

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.