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SYSTEMATIC REVIEW

Investigation of radiodermatitis in children, adolescents and young adults with cancer: A systematic review

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ABSTRACT

Background: Radiation dermatitis in children covers a wider range of symptoms and manifestations of skin toxicity after radiation therapy (RT). The rapid development of radiology in recent years has led to a significant improvement in the effectiveness of cancer treatment.

Aim: This systematic review aimed to investigate the incidence of radiodermatitis in children, adolescents, and young adults with cancer undergoing radiotherapy.

Method and Material: A systematic review of the literature was conducted from 01/01/2002 to 15/02/2022, using the keywords: radiotherapy, radiology, toxicity, dermatitis, radiodermatitis, actinodermatitis, dermatologic complications, pediatric patients, children, cancer, for articles written in the English language, in the following databases: MEDLINE (via PubMed), The Cochrane Library, CINAHL, Web of Science Collection, and Scopus. The PICOTS process (Population, Intervention, Comparator, Outcome, Timing, Setting) was used as an evaluation criterion for the induction of articles in the study. After the articles' evaluation, 16 articles emerged.

Results: The results of 16 studies in 2,818 children, adolescents, and young adults showed that dermal toxicity after radiotherapy varies not only in the frequency of occurrence but also in the severity and extent, independently of the radiotherapy method. Skin effects of radiodermatitis vary considerably in severity, course, and prognosis, and the most apparent relation of its occurrence was the higher dose of RT and the extent of skin therapy. Moreover, limited evidence indicates higher rates of radiodermatitis in smaller children compared to adolescents or young adults.

Conclusions: The incidence of radiodermatitis in children undergoing radiotherapy appears to occur quite frequently. Further research is needed to substantiate strong evidence for assessing and managing radiodermatitis.

Keywords: Radiation oncology, children, hospitalized, radiodermatitis.

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INTRODUCTION

It is the nature of pediatric cancer treatment to evolve in various ways. Combined with precision medicine evolution, new targeted anti-tumor drugs, molecular diagnosis, accurate imaging, and personalized approaches have led to combination therapies that transformed the indications and methods of radiotherapy. On the other hand, the technology improvements and innovations in radiotherapy improved its accuracy, limited its complications, and reduced late toxicities. Therefore, radiation therapy (RT) remains a critical element of therapeutic choices and its role in the era of individualized precision medicine continues to be valuable even if its implications are under continuous re-evaluation.[1]

The two predominant methods in modern pediatric oncology are photon and proton irradiation. Although produced by different means, both are provided by a bundle that comes from outside the patient and stores energy in the patient's tumor and areas at risk of tumor spread. Radiation from either photons or protons causes double-stranded DNA fragments that can affect cell division and lead to mitotic destruction.[2]

The high-energy X-rays used in modern RT produce direct and indirect ionization events that not only lead to injury to cancer cells but also pose a risk of injury to normal tissues. Most patients undergoing RT receive small, daily doses of radiation. The clinical goal is to achieve tumor death after repeated exposure while minimizing damage to healthy surrounding tissue. Consequently, a prevalent side effect of ionizing radiation is radiodermatitis, also referred to as radiation dermatitis or radiation-induced skin reaction. It is the most common adverse reaction in the sites of radiation. This is developed since a small fraction of rapidly proliferating cells in the basal layer of the skin is injured or destroyed, accelerating the decline in the population of differentiated epidermal keratinocytes. This can lead to flaking depending on the total radiation dose provided. Impaired skin barrier function carries risks of trauma formation, loss of immune function, and infection.[3] The acute phase of radiation dermatitis is often defined as the changes observed within 90 days after RT. The development of acute dermatitis from radiation follows a predictable course. In literature there are several systems for rating skin effects by RT, with the Common Terminology Criteria for Adverse Events (CTCAE) rating and Radiation Therapy Oncology Group (RTOG) scale being among the most commonly mentioned. However, independently of the rating system, the severity of radiation dermatitis ranges from mild erythema to moist desquamation and ulceration.[4]

Transient, mild erythema may occur within hours of RT, possibly due to dilation of capillaries shortly after the patient is exposed to radiation. However, RT-related erythema typically does not appear until 2-4 weeks after treatment. Hair follicles and sebaceous glands can be affected early during RT, leading to dry skin and hair loss. As the erythema develops, a sunburn-like reaction may follow, swelling, itching, tenderness, and a burning sensation. Dry flaking, which manifests as itching and flaking of the skin, can occur 3-6 weeks after the RT regimen in cumulative doses above 20Gy. With increasing amounts of radiation above 30-40Gy, patients may develop wet exfoliation, a condition characterized by tender, red skin associated with serous exudate, a bleeding crust, and the possibility of developing bulbs. Due to the breakdown of the skin barrier, this stage is generally painful. It is characterized by increased susceptibility to contact injury, especially in flexural areas prone to abrasion stress.[5]

The acute skin reaction usually peaks 1-2 weeks after RT completion. As epidermal keratinocytes proliferate and the immune response is reversed, the symptoms of acute dermatitis subside in most patients. The time to resolve any flaking, erythema, and edema is usually 2-4 weeks after the end of treatment. It is not uncommon for residual post-inflammatory hyperpigmentation to persist, but it usually subsides in the months following treatment.[6]

There is no consensus regarding the incidence of chronic radiation dermatitis since there are differences in the reported prevalence due to different assessment approaches and a broad spectrum of radiation therapy implementation with varying effects of side. In general, it is believed that even 95% of patients undergoing RT may develop some form of dermal toxicity. There is no direct relationship between the occurrence of an acute skin reaction and the further development of chronic radiation dermatitis.[7]

Both the likelihood of dermatitis from radiation and the severity of the symptoms depend on several factors. Factors associated with the highest incidence of radiation dermatitis can be divided into two groups - directly RT-dependent and non-RT-dependent. Factors that increase the risk of dermatitis and depend on RT include the proximity of the radiation target to the skin, the energy of the radiation used, the radiation dose, the fractionation schedule of the treatment, the size of the skin surface exposed to the radiation and the therapy with radiosensitizing concomitant chemotherapy (CHT) or not.[8] Factors that increase the risk of dermatitis not directly associated with RT include concomitant CHT,[9] concomitant targeted therapy[10] and connective tissue disorders.[9]

Thus, significant radiation dermatitis is more common in pediatric patients receiving treatment in areas near o the skin, such as sarcomas and skin, breast, head, and neck cancers. Thus, there is limited ability to protect the skin, especially at higher doses. Some patient-specific factors may also increase the risk and severity of radiation dermatitis. These include malnutrition, smoking, excessive skin folds, elevated body mass index, underlying vascular or connective tissue disease, and genetic factors such as inherited DNA repair deficiencies.[11]

The main aim of this systematic review was to investigate the incidence of radiodermatitis in children, adolescents, and young adults with cancer undergoing radiotherapy.

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METHODS AND MATERIAL

A systematic review of the literature was conducted for articles published from 01-01-2002 to 15-02-2022, using the following keywords: "radiotherapy, radiology, toxicity, dermatitis, radiodermatitis, actinodermatitis, dermatologic complications, pediatric patients, children, cancer" in international bibliographic databases (MEDLINE (via PubMed), The Cochrane Library, CINAHL, Web of Science Collection and Scopus) as well as synonyms and combination of terms.

The PICOTS process (Population, Intervention, Comparator, Outcome, Timing, Setting) was used as an evaluation criterion for introducing articles in the study. The criteria for including an article in the study are presented in Table 1.

The results of the article selection process are reported according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[12] The study's authors were trained in selecting titles/abstracts and examined each title and abstract in terms of suitability. After eliminating the duplicates, the eligible articles were screened based on the title and abstract; finally, the full text of the articles potentially suitable for inclusion in the systematic reviews was analyzed. Two team members independently reviewed each article and the team leader resolved any discrepancies.

After searching the databases and applying the search filters of articles of the last two decades, 40 articles emerged. After evaluating the title, the summary and/or the text of the articles, 16 articles were selected for inclusion in the study. The article selection flow chart (see Figure 1) summarizes the search strategy. The data extracted from each study were: authors, year of publication, country of origin, methodology, purpose, age of participants, sample, control group, sample selection criteria, radiodermatitis assessment tools, and results.

RESULTS

The studies included in this systematic review derive mainly from middle and high-income countries (7 studies from Europe (5 from Germany,[13-17] 1 from the Netherlands,[27] 1 from the United Kingdom[28]), 7 from the USA,[18-24] 1 from Brazil[25] and 1 from Japan[26] (see Table 2)), and half of them were published in the last five years (2 articles were published in 2021, 2 articles in 2020, 2 articles in 2018, 2 articles in 2017, 2 articles in 2016, 1 article in 2015, 1 article in 2013, 2 articles in 2009 and 2 articles in 2002). The results in these 16 published articles include data from 2,818 children, adolescents, and young adults.

The severity and the incidence of dermatitis in these studies varied significantly between the different settings, the type of radiation therapy and the patients' groups.[14-23, 25-28] Specifically, 3 studies reported that patients after RT developed grade 1 radiodermatitis,[13,16,22] 3 studies reported grade 2 radiodermatitis after RT,[14,27,28] in 6 studies there is a reference of grade 3 radiodermatitis after RT,[17-19, 21,22,25] and in 3 studies there is reference of even grade 4 radiodermatitis after RT developed.[15,20,26] In addition, there was no significant difference in skin toxicity between children undergoing scattered or pencil beam proton therapy (PRT)[24] (Table 2).

The study by Salfelder et al. (2020) reported a pretty low incidence (5.05%) of radiodermatitis with grade 3 severity after multitarget RT (mtRT) and 56% incidence of grade 1 or 2. Other common toxicities after mtRT were fatigue (72%) and nausea/vomiting (50%).[13] Häußler et al. concluded that the most common side effects related to CHT and RT included neutropenia, mucositis, nausea and vomiting, and grade 2 dermatitis, without reporting the exact incidence due to the limited sample.[14] Song et al. found no grade 4 or 5 toxicity in their study. The incidence of radiodermatitis was 5.6% for grade 3 injury complications. However, just half of them received adjuvant RT. There was no significant difference in the complication rate of grade 3 trauma in patients who received adjuvant RT or those who did not. In patients undergoing adjuvant RT, radiation dermatitis was usually self-limiting without treatment, and in the other cases, dressing were applied for wet desquamation.[18]

Lucas et al., in their study, showed that acute toxicity was mainly limited to radiation dermatitis, with 6 patients (26.1%) developing grade 3 radiation dermatitis. Late dermatological toxicity was mainly limited to grade 3 radiation dermatitis (13 patients, 56.5 %).[25] Kim et al. reported 58.8% radiodermatitis incidence, with only one patient developing > 2-grade dermatitis (5.88%), and even in that case, there was no significant complication of the injury.[19] The study by Pixberg et al. showed a high degree of acute toxicity after RT in children and adolescents (18.9% of patients), with dermatitis occurring in 7.6%.[15] Krasin et al. stated that a significant correlation was observed between the increased degree of dermal toxicity 4 between the dose ($P < 0.01$), the extent of the treated skin > 4000cGy ($P = 0.03$), the bolus administration ($P < 0.01$), Caucasian race ($P < 0.01$) & pain ($P < 0.01$).[20] Sterzing et al. showed that the acute side effects of RT were low-grade skin erythema (grade 1-2 CTC) in less than 5% of the patients.[16]

Chang et al. reported 79.9% incidence of dermatitis in their study, but in all cases, the dermatitis was grade 1-2. There were no cases of grade 3–4 skin toxicity using either

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photons or electrons.[21] Sasaki et al. studied the tumor characteristics and evaluated the efficacy of radiotherapy in thirty patients with angiosarcoma. They found that high-dose RT suppressed the onset of distant metastases (P = 0.006), the high dosages were related to the occurrence of radiodermatitis but were limited mainly in presentation as skin erythema, and only 6.7% of the patients developed grade 4 dermatitis (RTOG Grade 4).[26] In addition, Suneja et al. also found in their study with 48 children with CNS malignancies under radiation therapy that acute dermatological toxicity from RT was low-grade and treatable. The most common acute toxicities were fatigue, alopecia, and grade 3 dermatitis. The least common were insomnia and vomiting.[22] In addition, Cox et al. showed that 73% of patients developed cranial skin erythema (grade 2) with dry exfoliation (40%) or wet exfoliation limited to the dermal folds of the ear (33%) after intensity-modulated radiation therapy (IMRT).[27]

Breen et al. report that patients receiving RT 49-55 Gy were more likely to develop skin toxicity (OR: 2.18; 95% CI, 1.06-4.44; P = 0.033) than those receiving RT with less than 49 Gy, indicating the relation between RT dosage and radiodermatitis.[23] Gaito et al. investigated the incidence of acute & late skin radiation-induced toxicity in children with cancer receiving XRT or PBT in 79 children. They concluded that 77.4% of patients developed acute skin toxicity (29.0% of patients had grade 1-2 and 48.4% had grade 3 toxicity) after RT.[28] Doyen et al. reported maximum acute skin toxicity grade ≥ 2 in 49 (38.6%) patients after PRT, of whom 8 (6.3%) had grade 3 toxicity. No acute grade 4 or 5 skin toxicity was observed.[17] Laack et al. concluded that there was no difference in skin toxicity (72%, P = 0.56) between children undergoing scattered or pencil beam proton therapy (PRT).[24]

DISCUSSION

In literature, more than enough evidence supports that radiodermatitis has increased incidence in adult patients.[29,30] However, that is not the case in children. In pediatric patients, the incidence of radiation-related dermatitis varies significantly across studies, indicating a significant amount of parameters that should be investigated to reveal the contributing factors, and therefore, there is space for treatment implementation reevaluation.

In the present systematic review, we examined the incidence of radiation related dermatitis in the care of pediatric patients and young adults. Sixteen articles were analyzed through which it was found that the acute and late skin toxicity associated with RT in patients is relatively moderate or even low compared to adults.[25] However, the variance of results among the studies with children was wide. The skin effects of RT vary considerably in severity, course, and prognosis. Acute skin toxicity from RT is common, including erythema and pain, and occurs within 90 days, as observed in the studies analyzed. These results are consistent with other studies.[31,32]

In six studies, the acute side effects of RT were low-grade skin erythema (grade 1-2 CTC). These results are consistent with the study by Fogliata et al., who have compared different radiation techniques for selected pediatric patients and have stated that the underlying toxicity of radiation is dermatitis.[33] Previous studies of the effects of radiation on the postoperative environment have reported less severe toxicity. It was then observed that in 9 of 16 studies, patients had grade 3 and 4 skin erythema. Even with modern RT techniques, most patients will experience a moderate to a severe acute skin reaction in the exposed areas. This finding is consistent with that of another study.[34]

About 50% of pediatric cancer patients receive RT for their oncology management.[35] In these patients, balancing the potential for early and late toxicity with tumor control is particularly important. Radiation is used to treat a variety of malignancies and to inhibit metastatic disease. However, the development of radiation-induced skin changes is a significant negative effect of RT. Skin reactions to radiation are primarily a function of the technique, the total dose, the volume, and the treatment variants. Although advances in technology, changes in treatment regimens, and early therapeutic interventions have reduced the severity of skin reactions and associated pain, as clearly noted in this review, radiation dermatitis remains a negative side-effect of RT. Moreover, digital transformation of care helps to limit possible technical or dose errors during the various stages of radiation therapy. The implementation of a quality assurance checking system can substantially reduce these limited errors but never eliminate them.[36]

The synthesis of data in this systematic review is limited since only articles written in English and in selected international databases were examined in the present study. In addition, searching bibliographies only in international electronic databases may have introduced publication bias to our systematic review be- cause it is unlikely to detect studies that have not been published in peer-reviewed journals. Therefore, further in-depth research may be needed, mainly in clinical studies, to draw further conclusions

CONCLUSIONS

Skin toxicity after RT occurs in various degrees while its skin effects vary significantly in severity, course, and

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prognosis. Choosing the proper RT method, dosing, and fractionation technique can reduce the risk of radiation-induced dermatitis. The prevention of radiodermatitis should not affect the decision for precision radiation therapy. However, assessment of toxicity with accurate scale development, early interventions after dermatitis assessment, and quality control & audit regarding radiation services will enhance the effectiveness and quality of radiation therapy and limit skin toxicity. Further research is needed to substantiate strong evidence for assessing and managing radiodermatitis.

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ANNEX

TABLE 1: Criteria for including articles in the study

PICOTS Question: What is the incidence of radiodermatitis in children with cancer undergoing radiotherapy?

Population: Children, adolescents, or young adults (< 23 years old) with cancer (all types) undergoing RT (all methods)

Intervention: None

Comparator: Without comparison or RT method or the CHT

Outcomes: Quantitative data on the incidence of radiodermatitis in children treated for cancer under RT.

Timing: During implementation of RT.

Setting: Hospitalized patients.

Inclusion criteria	**Exclusion criteria**
Studies in children, adolescents or young adults (< 23 years) with cancer (all types) undergoing RT (all methods). Published from 2002-2022. Published in English language. Investigating the incidence of radiodermatitis in children with cancer undergoing RT. Studies that report at least one result. The study design to be quantitative study, prospective study or observational study.	Systematic reviews, meta-analyzes, letters, comments, reviews or gray literature that includes abstracts and is not peer reviewed. Studies lacking sample information for pediatric cancer patients.

CHT: concomitant chemotherapy, RT: radiation therapy

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FIGURE 1: Article selection flowchart.

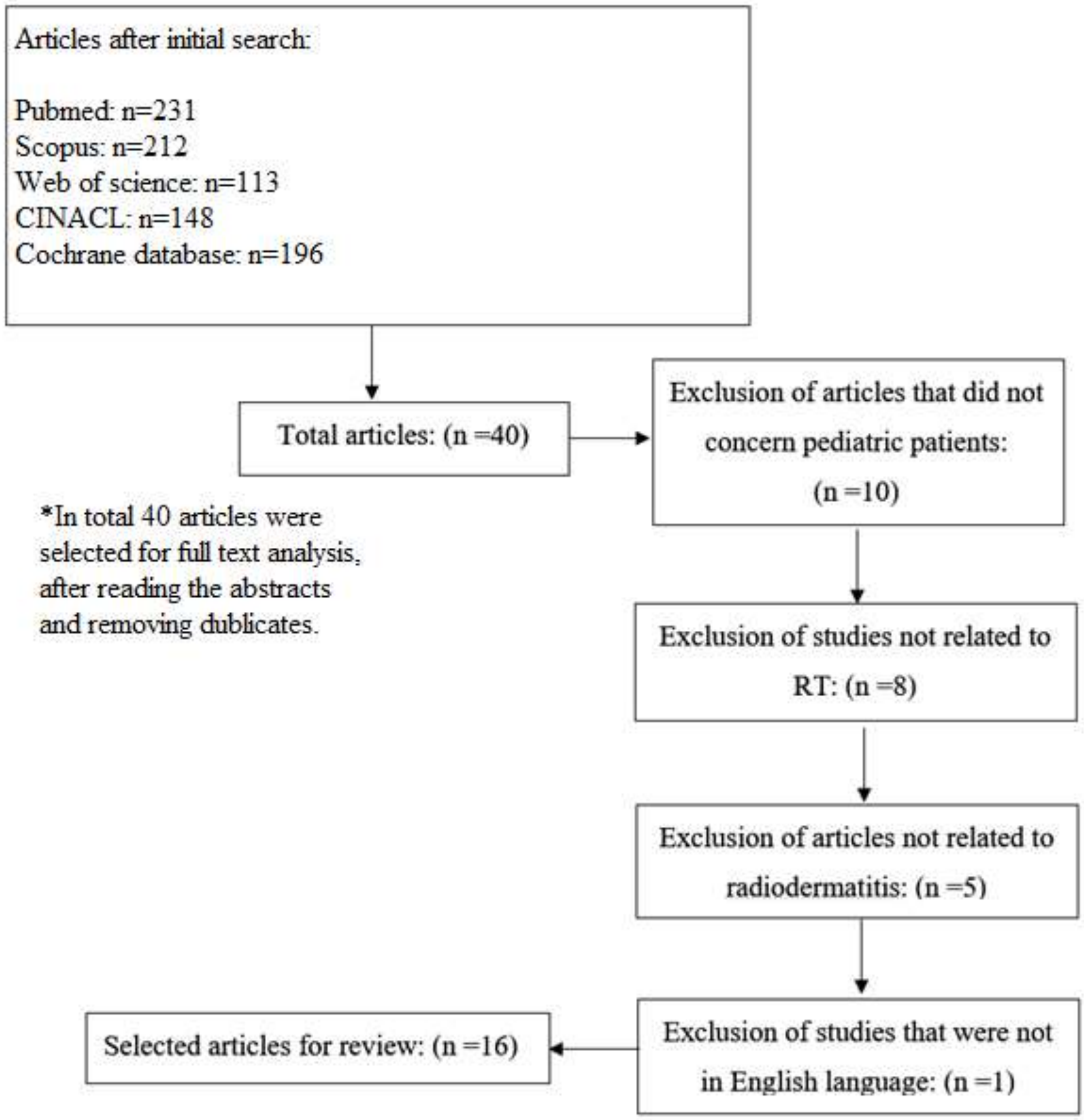

TABLE 2: Studies characteristics

Author, year, country	Methodology	Aim	Age range / mean or median	Sample	Main participation criteria	Radiodermatitis assessment	Findings
Salfelder et al., 2020, Germany	Retrospective study	Investigation of the incidence of toxicity & the outcome of mtRT in children with sarcomas	6-19 years, median 15 years	38 children	mtRT	Clinical assessment, CTCAE criteria ver 4.03	Two patients suffered from acute grade 3 radiodermatitis after mtRT. The most common grade 1 & 2 toxicities during mtRT were fatigue (72%), dermatitis (56%) & nausea / vomiting (50%).
Häußler et al., (2018)	Retrospective study	Evaluation of head & neck RMS in pediatric patients in relation to clinical image, treatment & survival.	0.1-16.0 years, mean 6.8 years	28 children	RT	Clinical assessment	The most common side effects that resulted from CHT & RT were neutropenia, mucositis, nausea & vomiting & grade 2 dermatitis.
Song et al., (2017)	Retrospective study	The effect of RT in patients with synovial sarcoma	5-72 years, median 33 years	103 patients (30% of them were <25 years old)	To 73% of patients were undergoing RT	Clinical assessment, CTCAE criteria ver 4.0	6 patients had grade III trauma complications. Three of them received adjuvant RT & 3 did not receive. There was no significant difference in the complication rate of grade 3 trauma in patients who received adjuvant RT or in those who did not (P = 0.175). In patients

							undergoing adjuvant RT, radiation dermatitis was usually self-limiting without treatment.
Lucas et al., (2017)	Prospective study	Investigation of the contribution of RT to acute and late dermal toxicity in children with thoracic wall sarcoma	3.6-20.6 years, median 12.5 years	23 children	RT	Clinical assessment, CTCAE criteria ver 3.0	Acute toxicity was mainly limited to radiation dermatitis, with 6 patients (26.1%) developing grade 3 radiation dermatitis. Late toxicities were mainly limited to grade 3 radiation dermatitis (13 patients, 56.5%).
Kim et al., (2016)	Retrospective study	Evaluation of the effect of postoperative RT on survival and its complications in patients with sarcoma	12-78 years, median 32 years	17 patients	RT	Clinical assessment, CTCAE criteria ver 4.03	Only one patient developed grade 3 radiation dermatitis & there was no significant complication of the injury.
Pixberg et al., (2016)	Retrospective study	Investigation of the incidence and reasons for the development of a high degree of acute toxicity by RT in children & adolescents with cancer	0-18 years	1,359 children & adolescents	RT	Clinical assessment, RTOG/EORTC scores for acute & late toxicities	Highly acute post-RT toxicity in children & adolescents occurs in 18.9% of patients, with dermatitis occurring in 7.6% of patients.
Krasin et al., (2009)	Prospective study	Investigation of the	1.4-22.7 years,	82 children &	RT, Children < 25	Clinical assessment, CTCAE criteria	Significant correlation of the dermal toxicity degree IV and the dose

		relationship between maximum skin toxicity, radiation dose & clinical variables in children & adolescents with bone and soft tissue sarcomas receiving RT	median 11.8 years	adolescents	years, No previous irradiation to the primary site	ver 2.0	(P < 0.01), the extent of the treated skin >4000cGy (P = 0.03), the bolus administration (P < 0.01), the Caucasian race (P < 0.01) & pain (P < 0.01).
Sterzing et al., (2009)	Retrospective study	Evaluation of IMRT use in 18 of 31 children & adolescents with cancer	1.5-20.5 years, mean 14.2 years	31 children & adolescents	IMRT	Clinical assessment, CTCAE criteria ver 2.0	The acute side effects of IMRT were low-grade skin erythema (grade 1-2 CTC) in one patient.
Chang et al., (2002)	Retrospective comparative study	Determination of the incidence of acute dermal toxicity & cessation of cranial ERT & PRT in children with cancer receiving or not receiving CHT.	0.13-18.94 years, median 8.7 years	79 patients (ERT group n = 46, PRT group n = 33)	RT	Clinical assessment, CTCAE criteria ver 4.0	Most patients developed grade 0-1 dermatitis whether or not they received CHT.
Sasaki et al., (2002)	Retrospective study	Evaluation of the efficacy of RT in patients with angiosarcoma	4-89 years, median 66 years	30 patients (4-89 years old)	RT	Clinical assessment, RTOG scores for acute & late toxicities	High-dose RT suppressed the occurrence of distant metastases (P = 0.006) while 2 patients developed grade 4

							radiodermatitis.
Suneja et al., (2013)	Retrospective study	Investigation of acute skin toxicity in children with CNS malignancies receiving PRT	1-22 years, median 10.8 years	48 children	PRT	Clinical assessment, CTCAE criteria ver 4.0	Acute toxicities were low-grade & treatable. The most common were fatigue, alopecia & grade 3 dermatitis.
Cox et al., (2015)	Prospective study	Investigation of acute dermal toxicity in children with medulloblastoma undergoing IMRT	4-16 years, median 8 years	15 children	Newly diagnosed patients, with medulloblastoma, aged 3-21, IMRT	Clinical assessment, CTCAE criteria ver 2.0	73% of patients developed mild cranial skin erythema with dry exfoliation (40%) or wet exfoliation limited to the dermal folds of the ear (33%).
Breen et al., (2021)	Prospective study	Investigation of factors associated with the development of acute skin toxicity in children with cancer receiving PRT	0.5-21.9 years, median 9.9 years	422 children	PRT	Clinical assessment	Patients receiving 49-55Gy were more likely to develop skin toxicity (OR: 2.18; 95% CI, 1.06-4.44; P = 0.033) than those receiving < 49Gy.
Gaito et al., (2021)	Retrospective comparative study	Investigation of acute & late skin radiation-induced toxicity in children with cancer	XRT group mean age 15,6 years,	79 children	XRT or PBT	Clinical assessment, RTOG scores for acute & late toxicities	48.4% of patients had acute grade 2-3 skin toxicity & 29.0% of patients had grade 1-2 skin toxicity.

		receiving XRT or PBT	PBT group mean age 9.1 years				
Doyen et al., (2021)	Retrospective study	Investigation of early dermal toxicity in cancer patients under high PRT dose	Mean age 55 years (1.6-89)	127 patients	PRT	Clinical assessment, CTCAE criteria ver 5.0	Maximum acute grade ≥ 2 skin toxicity was observed in 49 (38.6%) patients, of which 8 (6.3%) showed grade 3 toxicity. No acute grade 4 or 5 toxicity was observed.
Laack et al., (2018)	Prospective comparative study	Determination of factors associated with the development of acute toxicity in children with cancer undergoing scattered PRT or pencil beam PRT	0.5-21.9 years, median 9.9 years	422 patients	scattered PRT or pencil beam PRT	Clinical assessment	There was no difference in skin toxicity (72%, P = 0.56) between children undergoing scattered PRT or pencil beam PRT.

RT: radiation therapy, mtRT: multitarget RT, RMS: rhabdomyosarcoma, CTCAE: Common Terminology Criteria for Adverse Events, RTOG/EORTC: Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer, IMRT: intensity-modulated radiation therapy, ERT: electron radiation therapy, PRT: photon radiation therapy, RTOG: Radiation Therapy Oncology Group, PRT: proton radiation therapy, XRT: radiotherapy with X-rays, PBT: proton beam therapy, CHT: chemotherapy, CNS: central nervous system.

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