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Tissue Reactions (Deterministic Effects) in Diagnostic and Interventional Radiology: An Integrative Review of Recent Literature

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Abstract: Ninety-eight percent of the global average individual dose delivered by artificial sources of ionizing radiation results from their use in medical applications, especially for diagnostic and interventional purposes. Although the benefits of radiation in medicine are widely recognized, exposure to this agent can cause harmful effects on the health of exposed individuals. Radiation applications for diagnostic purposes are generally associated with low doses, but interventional procedures may involve much higher doses. In the 2000s and 2010s, several publications described tissue reactions in patients and professionals exposed during interventional radiological procedures. This work aimed to review the literature on the most recent reports (last decade) on the occurrence of tissue reactions after diagnostic or interventional radiological procedures. The PubMed search tool was used to search and select publications on the topic. Although 826 articles were initially selected, only 5 presented relevant content for this review. The low number of articles in the final selection may be a result of the methodology we used or an actual reduction in the number of individuals presenting these effects in more recent years, due to the growing concerns about radiological protection in these practices. Among the articles analyzed, there were reports of skin lesions, as well as thinning or hair loss in patients exposed to doses (cumulative air kerma at the reference point) above 3.5 Gy. However, these reactions are rare and do not appear in most patients, even among those who received higher doses. An increased frequency of lens opacities (cataracts) has also been reported in occupationally exposed professionals. An adequate assessment of the occurrence of these effects is essential to try to understand their causes and minimize the frequency or consequences of their occurrence. Carrying out research like this can help with this task.

Keywords: tissue reaction, deterministic effect, ionizing radiation.

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Reações Teciduais (Efeitos Determinísticos) em Radiologia Diagnóstica e Intervencionista: Uma Revisão Integrativa da Literatura

Resumo: Noventa e oito por cento da dose individual média global fornecida por fontes artificiais de radiação ionizante resulta da sua utilização em aplicações médicas, especialmente para fins de diagnóstico e intervencionismo. Embora os benefícios do uso da radiação em medicina sejam amplamente reconhecidos, a exposição a este agente pode causar efeitos danosos à saúde dos indivíduos expostos. As aplicações de radiação para fins diagnósticos são geralmente associadas a doses baixas, mas procedimentos intervencionistas podem envolver doses muito mais elevadas. Nas décadas de 2000 e 2010 diversas publicações descreveram a ocorrência de reações teciduais em pacientes e profissionais expostos durante procedimentos radiológicos intervencionistas. Este trabalho teve como objetivo realizar uma revisão da literatura sobre os relatos mais recentes (última década) sobre a ocorrência de reações teciduais após procedimentos radiológicos diagnósticos ou intervencionistas. Para buscar e selecionar publicações sobre o tema foi utilizada a ferramenta de busca PubMed – com auxílio de descritores e filtros específicos. Embora inicialmente tenham sido selecionados 826 artigos, apenas 5 apresentavam conteúdo relevante para o propósito desta revisão. O baixo número de artigos na seleção final pode ser resultado da metodologia utilizada ou da própria redução do número de indivíduos que apresentam esses efeitos nos últimos anos, devido à crescente preocupação com a proteção radiológica nessas práticas. Entre os artigos analisados, há relatos de lesões cutâneas, bem como afinamento ou queda de cabelo em pacientes expostos a doses (kerma no ar acumulado no ponto de referência) acima de 3,5 Gy. Contudo, estas reações são raras e não aparecem na maioria dos pacientes, mesmo naqueles que receberam doses mais elevadas. Foi relatada também uma frequência aumentada de opacidade do cristalino (catarata) em profissionais ocupacionalmente expostos. Uma avaliação adequada da ocorrência destes efeitos é essencial para tentar compreender suas causas e minimizar a frequência ou consequências da sua ocorrência. A realização de pesquisas como esta pode ajudar nessa tarefa.
Palavras-chave: reação tecidual, efeitos determinísticos, radiação ionizante.

1. INTRODUCTION

Medical applications of ionizing radiation are the main source of artificial radiation exposure for the global population [1]. Although the benefits of the medical use of ionizing radiation are well known, exposure to this agent may cause harmful health effects on exposed individuals. Radiation applications for diagnostic purposes are generally associated with low doses, but interventional procedures may involve much higher doses and have been used with increasing frequency, variety and complexity [1]. The occurrence of tissue reactions (deterministic effects) in both patients and occupationally exposed individuals in interventional procedures has been described by several publications, mainly in the 2000s and 2010s [2, 3]. Although rare, these reactions can be severe and debilitating. The challenges of radiological protection for patients and professionals in these applications have been highlighted by the International Atomic Energy Agency (IAEA) [4, 5]. Knowledge of the main factors associated with their occurrence can help to avoid or minimize them. This work aimed to carry out an integrative review of the literature on the most recent studies (last decade) on the occurrence of tissue reactions associated with diagnostic or interventional radiology procedures.

2. MATERIALS AND METHODS

This integrative review used the PubMed search tool in the MEDLINE bibliographic database (https://pubmed.ncbi.nlm.nih.gov/) to find and select publications on tissue reactions (deterministic effects) associated with diagnostic and interventional radiology procedures. The search - carried out on September 15, 2023 - used the expression "((("deterministic effect*") OR ("tissue reaction*"))) AND (radiation)" as a descriptor.

To restrict this selection to a reasonable number of publications for the full-text analysis, some inclusion criteria were defined: date of publication (last 10 years), language (Portuguese, English, or Spanish), availability of the abstract, and whether the study was carried out in humans.

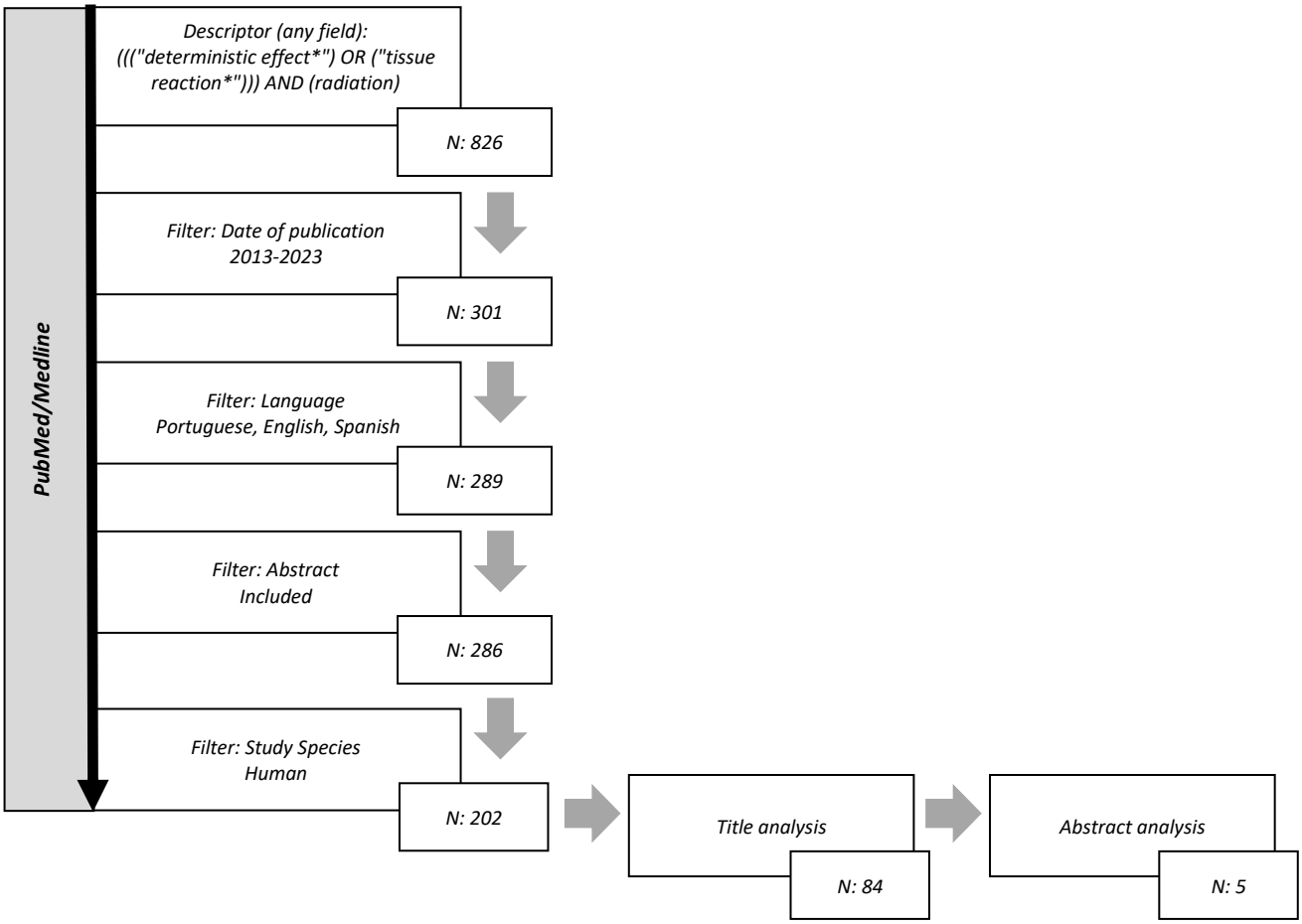
In the next phase, the adherence of the selected publications to the topic of interest was assessed by reading the article's titles and, if necessary, the abstracts. Publications whose title or abstract indicated content unrelated to the proposed topic were classified according to their main subject and excluded from subsequent analysis.

Articles that met the inclusion criteria were read in full and summarized. The type of procedure, individual (patient or professional) and affected organ or tissue, frequency of occurrence, and estimated dose were classified. Furthermore, the main information contained in each of these articles was analyzed, described, and discussed.

3. RESULTS AND DISCUSSIONS

Figure 1 shows the results of the search for publications on tissue reactions (deterministic effects) associated with ionizing radiation exposure, using the PubMed search tool and MEDLINE database, on September 15th, 2023. The initial search, using the expression "((("deterministic effect*") OR ("tissue reaction*"))) AND (radiation)" as a descriptor, in any field, resulted in the selection of 826 articles. The sequential application of the filters: publication date (last 10 years), language (Portuguese, English, or Spanish), availability of the abstract, and whether the study was carried out in humans led to the exclusion of a total of 624 publications.

Figure 1: Number of publications selected after each step of the search and selection process.



The adherence of the selected publications to the proposed theme was first evaluated by the reading of the title, leading to the exclusion of 118 articles (figure 1). Most of these publications were radiobiology studies (32), mainly reports on radiosensitivity in general and/or on the biological mechanisms of tissue reactions. Another 27 articles were related to radiotherapy, addressing mainly the biological effects associated with this type of procedure. Others were related to nuclear medicine procedures or focused on dosimetry and radiation protection, or other topics not related to tissue reactions in diagnostic and interventional procedures.

The reading of the abstracts of the 84 publications remaining led to the exclusion of 79 publications. These were mainly literature reviews (39) which, although mentioned tissue reactions

and/or diagnostic or interventional radiology in both the title and the abstract, did not provide original information on the topic of interest. The other articles excluded at this stage were evaluations of doses associated with interventional procedures which, however, did not include new reports on the identification of tissue reactions (23). Articles related to radioprotection in general (6), radiotherapy (3), or various subjects (8) were also excluded at this stage.

Thus, only 5 articles describing tissue reactions associated with diagnostic or interventional radiology procedures remained for detailed full analysis, as listed in Table 1.

Table 1: Articles selected for full and detailed analysis.

REF	TITLE	AUTHORS	YEAR	JOURNAL
[6]	Observations of tissue reactions following neuroradiology interventional procedures	Corrigall RS, *et al.*	2020	J. Radiol. Prot.
[7]	Monitoring and Follow-Up of High Radiation Dose Cases in Interventional Radiology	Perry BC, et al.	2019	Acad. Radiol
[8]	Deterministic effects after fenestrated endovascular aortic aneurysm repair	Kirkwood ML, *et al.*	2015	J. Vasc. Surg.
[9]	Radiation-induced skin injury after complex endovascular procedures	Kirkwood ML, *et al.*	2014	J. Vasc. Surg.
[10]	Prevalence of Lens Opacity in Interventional Cardiologists and Professional Working in the Hemodynamics in Brazil	Barbosa AHP, *et al.*	2019	Arq. Bras. Cardiol.

The low final number of selected articles was somehow surprising, considering that the initial search was carried out using very broad descriptors - "deterministic effect*" or "tissue reaction*" and “radiation” - in any search field. Reports on tissue reactions in diagnostic and interventional radiology may have been reduced in the last decade because of the many reports in the 1990s and 2000s on the appearance of skin lesions, hair loss, and induction of cataracts in patients and professionals in interventional procedures. As a result, there was an increase in warnings about the harmful consequences of the misuse of fluoroscopic techniques, which led to greater concern about radiological protection in these

procedures [2, 3]. This hypothesis was not evaluated in this work. The main information presented in the final selection articles is presented in Table 2.

It is important to draw attention to the fact that the best quantity to assess the risk of skin injury is peak skin dose (PSD), which is the maximum dose absorbed anywhere on the skin surface of the patient. There is no currently available real-time method to measure PSD, which must account for gantry motion, patient size, and patient location relative to the gantry. However, PSD can be estimated from dose measurements at a defined "reference point". For an iso-centric interventional fluoroscope, the reference point is located 15 cm from the isocenter toward the X-ray tube and moves with the gantry [11, 12]. Modern fluoroscopy machines indicate the "cumulative air kerma at the reference point" (Kar,c) which is a simple measurement of air kerma at the reference point. It does not include attenuation by the patient couch nor backscatter from tissues deeper within the body. If the reference point happens to be on the patient's skin, and the beam does not move during the procedure, PSD is Kar,c multiplied by a backscatter factor. However, more complex calculations are needed to account for beam motion, patient position, and field overlaps, and Kar,c may overestimates PSD in many cases. "Reference point air kerma" ($K_{a,r}$) and "Reference air kerma" (RAK) are different nomenclatures for Kar,c (https://www.iaea.org/resources/rpop/health-professionals/interventional-procedures).

Table 2: Summary of information from publications selected in the present study.

REF	Procedure type	Affected individual	Organ/tissue and effect	Frequency (%)	Estimated dose (Gy)	Observations
[6]	Interventional neuroradiology	Patient	Scalp: erythema	< 10 ~ 15	> 4.5 – 5.0[1] > 5.0 – 7.0[1]	• Follow-up of 114/124 interventional neuroradiology procedures with dose ($k_{ar,c}$) >3 Gy ▪ Hair thinning and hair loss: May occur in 50% of patients receiving dose ($k_{ar,c}$) > 4.5 Gy ▪ Multiple effects: Reported by 12.5% of the patients receiving doses (kar, c) 3.5-4.0 Gy to 60% of those receiving doses 6.0-7.0 Gy ▪ 2 patients receiving the highest doses (kar,c 9-10 Gy) did not report any effect
			Scalp: dryness and itching	< 5 12 – 30	> 3.5 – 4.0[1] > 4.0 – 7.0[1]	
			Hair: thinning	20 – 30 50 – 70	> 3.5 – 4.5[1] > 4.5 – 6.0[1]	
			Hair: hair loss	~ 10 30 – 60	> 3.5 – 4.5[1] > 4.5 – 7.0[1]	

REF	Procedure type	Affected individual	Organ/tissue and effect	Frequency (%)	Estimated dose (Gy)	Observations
[7]	Interventional radiology and neuroradiology	Patient	Hair: hair loss (temporary)	~ 8	> 5.0[2]	• Follow up of 368 fluoroscopically guided interventional radiology procedures with dose (Ka,r) > 2 Gy ▪ Ka,r > 5 Gy: 10 patients - no tissue reactions reported • Follow up of 1,025 neuro-interventional procedures with dose (Ka,r) > 2 Gy ▪ Ka,r > 5 Gy: 52 patients - 5 reported temporary skin/hair injuries
[8]	Complex endovascular procedures (CEPs)	Patient	No tissue reaction observed	---	> 5.0[3]	• Follow up 784 patients undergoing complex endovascular procedures ▪ 61 patients received dose (RAK) ≥ 5 Gy ✓ Average RAK: 8 ± 2 Gy (range: 5-17 Gy) ▪ 16 patients had multiple exposures - RAK: 12 ± 3 Gy (range 7-19 Gy)
[9]	Fenestrated endovascular aortic	Patient	No tissue reaction observed	---	> 5.0[3]	• Follow up of 61 patients undergoing complex endovascular procedures ▪ 21 patients received dose (RAK) ≥ 5 Gy ✓ Average RAK: 7.6 ± 2.0 Gy (range: 5.1 - 11.4 Gy) ▪ 11 patients had multiple exposures - RAK: 10 ± 3 Gy (range: 5.5 – 15.1 Gy)
[10]	Interventional cardiology	Professional	Eyes: posterior subcapsular cataract	13 vs 2	NE[4]	• Professionals in the field of cardiology (112 from interventional cardiology and 88 unexposed controls) ▪ Posterior subcapsular cataract is more frequent in professionals exposed to radiation (13%) than in controls (2%). ▪ No difference was found in the frequency of cortical cataract. ▪ Cataract was more frequent in the left eye of professionals. There was no eye prevalence in the control group

[1]Cumulative air kerma at the reference point (Kar,c).
[2]Reference point air kerma (Ka,r).
[3]Reference air kerma (RAK).
[4]Professionals exposed to radiation versus non exposed controls. Doses were not evaluated.

The most frequent injuries after procedures for diagnostic or interventional purposes are skin erythema, and/or thinning and hair loss, in patients, and radio-induced cataracts or skin lesions, in professionals, occurring mainly after complex interventional procedures in the areas of cardiology, neuroradiology, and endovascular, which involve prolonged exposure and consequently, high doses of radiation. It is important to note that thresholds

for tissue reactions on the skin are dependent on the type of radiation, its energy, the geometry of exposure, fractioning of the dose and length of exposure.

Corrigal and collaborators [6] evaluated 114 patients undergoing interventional radiology (neuroradiology) procedures who received cumulative scalp air kerma values above 3 Gy. Only a small proportion of these individuals reported tissue reactions, even at high-dose levels. Itching and dryness of the scalp were observed in approximately 5% of the patients who received a dose above 3.5 Gy. This proportion increased to 50-70% for doses above 4.5 Gy. These patients also presented mild erythema on the scalp. The authors also observed hair loss for doses above 3.5 Gy, with the frequency of affected patients increasing with the dose, reaching 30-60% of patients for doses above 4.5 Gy. Some patients experienced multiple effects. More serious skin injuries were not reported in this study. The observation that 2 patients who received doses above 9 Gy had no tissue reactions is noteworthy and may be a result of possible overestimation of dose.

Similarly, Perry and collaborators [7] evaluated tissue reactions in a group of 1,393 patients in interventional radiology procedures for which reference air kerma greater than 2 Gy. Most of these procedures (1,025) were interventional neuroradiology – mainly intracranial and spinal interventions, including aneurysm "coils" and tumor embolization, fistulas, or arteriovenous malformations. About 10% of patients who received estimated skin doses greater than 5 Gy in these procedures experienced (temporary) hair loss. This frequency is lower than that presented by Corrigal *et al.* (6). Skin lesions were not observed even for a patient who received the largest cumulative air kerma, approximately 19 Gy. Patients undergoing other types of interventional radiology procedures (primarily abdominal/pelvic embolization, inferior vena cava filter placement, and percutaneous nephrostomy) did not report skin lesions or hair loss.

In contrast, Kirkwood and colleagues, in two different publications [8-9], did not report radiation-induced tissue reactions in patients who underwent complex endovascular

procedures to correct aortic aneurysms, even though these procedures may have involved very high doses (above 5 Gy) and multiple exposures. First, these authors evaluated 784 patients who had done a single procedure within 30 days, among which 61 had RAK greater than 5 Gy. Only two of them showed skin lesions. However, both had other health problems, suggesting that the observed skin lesions may not have been caused by radiation [8]. In 2015, the authors published a new study [9], in which 61 patients who underwent the same type of procedure with RAK ≥5 Gy (as in the previous study) were followed over 6 months. None of these patients presented skin lesions, even with a substantial mean PSD (Peak Skin Dose) and a more comprehensive follow.

Barbosa *et al.* [10] showed a high incidence of cataracts in interventional cardiologists and other professionals occupationally exposed during hemodynamic procedures. Although individual doses were not estimated in this study, some professionals claimed to do between 50 and 100 interventional procedures per month. Cataract cases were more frequent in the left eye which seems to reflect the greater exposure of the left side of the body due to the positioning of professionals in relation to the X-ray tube during these procedures [10]. Many studies reported a high prevalence of cataracts in interventional professionals, mainly of the posterior subcapsular type which manifests itself in the back of the lens and appears earlier when compared to other types of cataracts [13-14]. The eye lens is one of the most radiosensitive organs and cataracts seem to develop at doses of 0.1-1.0 Gy. The International Commission on Radiological Protection (ICRP) reduced the annual equivalent dose limit to the lens from 150 to 20 mSv [15]. This measure aimed to reduce the incidence of cataracts induced by ionizing radiation in healthcare professionals.

In this review, no articles reporting damage to the skin of professionals occupationally exposed in diagnostic or interventional radiology procedures were found. We also did not select any publications reporting tissue reactions after unintentional (accidental) exposures in diagnostic or interventional radiology, nor reports of tissue

reactions after exposure in computed tomography (CT). However, publications on these subjects are available in the literature [16-18].

The relatively small number of articles selected in our study may be a result of the methodology we used for the search and selection of publications of interest. Alternatively, there may have been a real decrease in the frequency of these type of reports in recent years driven by the improvements in radiological protection in this field in the previous decades.

Although tissue reactions associated with diagnostic and interventional procedures are rare and generally mild and transient, serious, debilitating and/or permanent injuries, which often require intense and prolonged treatment or cause loss of quality of life, can also occur. Furthermore, the risk of developing stochastic effects, such as radio-induced cancer, is known to be greater the higher the dose. Indeed, prognosis and risk analysis after local exposure to the skin must also take into account in-depth doses (iso-doses). On the other hand, the benefits associated with procedures involving radiation exposure are widely known, allowing the diagnosis or treatment of serious and potentially deadly diseases. Interventional radiology procedures are minimally invasive, and sometimes replace open surgeries, reducing the chance of complications, hospitalization time, and cost, among other benefits. When carried out under appropriate medical indication, considering alternative interventions that do not use radiation and the condition of the individual patient, the associated risks are generally not relevant given the benefits involved.

In summary, knowledge of the causes and characteristics of tissue reactions resulting from interventional radiological exposures is important for implementing radiological protection measures to minimize the frequency and severity of these effects. This may be helped by two systems established by IAEA: SAFRAD, aimed to gather data for patients whose exposure from a fluoroscopically guided interventional procedure exceeded some defined trigger level [19] and ISEMIR-IC, a tool for data collection and analysis of occupational doses for individuals in interventional cardiology [20].

4. CONCLUSIONS

In this integrative bibliographic review, we found, analyzed, and discussed 5 recent publications reporting tissue reactions (deterministic effects) associated with interventional radiology procedures.

Recent reports on the appearance of skin lesions and/or hair loss in patients, and of radio-induced cataracts in professionals, indicate that these tissue reactions, although rare, should still be the subject of attention regarding radiological protection. Furthermore, patients undergoing complex procedures must be informed about the possible effects and how to proceed if they occur, facilitating the diagnosis and treatment of possible tissue reactions.

Diagnostic and interventional radiology procedures are sometimes essential and indispensable for the diagnosis and treatment of various health conditions, saving or improving patients' quality of life. However, adequate justification for each procedure, the use of alternative techniques that do not involve radiation exposure, the implementation of dosimetry techniques, quality control, training of professionals, and other measures that improve the safety of patients and professionals are fundamental for adequate provision of health care and reduction of the possible harmful effects of ionizing radiation.

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

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