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Abscopal effect and interventional oncology: state of art and future perspectives

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Abstract. – OBJECTIVE: The concept of abscopal effect is currently gaining importance in modern oncology, as the link between localized irradiation and triggering of immuno-mediated systemic antitumor effects is getting clearer. An increasing number of reports documented abscopal effect mainly after external beam irradiation. Interventional radiotherapy (IR) may be used with sealed radioactive sources as brachytherapy (BT) or with unsealed radioactive sources as transarterial radioembolization (TARE). The aim of this paper is to review the existing clinical IR data and discuss the mechanisms of the abscopal effect.

MATERIALS AND METHODS: A systematic research of the main bibliographic databases (PubMed, WOS, Scopus, and Google Scholar) from the earliest possible date through August 2019 was performed. The search strategy was based on the terms "abscopal effect", "interventional radiotherapy", "brachytherapy" and "TARE".

RESULTS: Thirteen titles were identified. Three papers met inclusion criteria and were included in the review. All of them were case reports.

CONCLUSIONS: Even though there are still scarce data in literature regarding the association of locoregional interventional treatments with the abscopal effect, this review demonstrates that the immunomodulatory theories, which have been widely used so far for external beam radiotherapy (EBRT), may be actually considered valid also in the contest of IR.

Key Words:
Abscopal, Interventional oncology, Brachytherapy.

Introduction

The term "abscopal" derives from Latin with the meaning of "away from target".

It was firstly used in 1953, to identify "an action at a distance from the irradiated volume but within the same organism"[1]. The concept of abscopal effect is currently gaining importance in modern oncology, as the link between localized irradiation and triggering of immuno-mediated systemic antitumor effects is getting clearer[2]. Interventional oncology is a group of interventional techniques, which consists of four sectors: interventional radiotherapy, interventional radiology, interventional chemotherapy and interventional endoscopy[3]. Interventional radiotherapy (IR) in particular may be used with sealed radioactive sources (brachytherapy, BT) or with unsealed radioactive sources (transarterial radioembolization, TARE)[4,5]. Aim of this paper is to review the existing clinical IR data and discuss the mechanisms of the abscopal effect.

Materials and Methods

A systematic research of the main bibliographic databases (PubMed, WOS, Scopus, and Google Scholar) from the earliest possible date through August 2019 was performed. The search strategy was based on the terms "abscopal effect", "interventional radiotherapy", "brachytherapy" and "TARE". Papers of any design (i.e., randomized, prospective, retrospective studies and case reports) involving humans were considered eligible for this review. Only papers dealing with BT or TARE administered either to the primary tumor or to distant metastases were evaluated. Primary outcome of our review was clinical or radiological evidence of abscopal effect. To ensure the quality

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assessment of study selection, two independent radiation oncologists (BF, LB) screened all the collected references at abstract level. Potentially eligible papers were then retrieved for full review. Disagreements were solved by other three board components (MM, ND, RI).

The following information from each paper was reported: author, publication year, number of patients, study population, IR technique (including used isotope and dose rate), delivered dose, previous use of immunotherapy, primary tumor and site of intervention.

Finally, two expert senior radiation oncologists (LT, VV) performed a final revision.

Results

Thirteen titles were identified. Eight papers were excluded, as they did not report abscopal effect evidence. After full text review of the remaining papers, one was excluded as it implied the use of EBRT and another for being a murine model. The remaining three papers were thus included in the review (Table I)[6,7]. All of them were case reports. Detailed search results are reported in Figure 1.

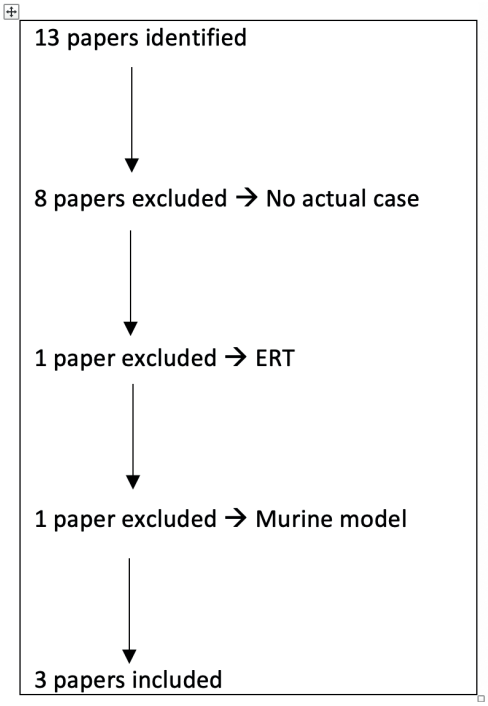

Figure 1. Search strategy.

In the first report, Deipolyi et al[6] described the case of a 44 year-old woman affected by nodal, lung, bone, brain, and liver metastases from breast cancer. After undergoing immunotherapy with Pembrolizumab and receiving 2 doses of the agonistic anti-OX40 monoclonal antibody MEDI6469, the patient was referred for TARE. After a right-lobar TARE with SIR-Spheres (administered activity: 39 mCi), the patient showed complete response in liver and extrahepatic disease with a response enduring for more than 4 months and documented with a positron emission tomography scan with 18F-FDG. Ghodadra et al[8] reported the case of a 80 year-old male affected by squamous cell carcinoma of the lung and numerous liver metastases. The patient underwent right hepatic radioembolization with SIR-Spheres (dose: 1.24 GBq). The restaging magnetic resonance scan showed partial response of the targeted lesions and the complete regression of the non-targeted hepatic lesions. More recently, Doggett et al[7] reported the case of a 20-year-old female patient affected by disseminated, bilateral lung metastases from parotid adenoid cystic carcinoma who underwent Pd-103 seeds implant into six separate right sided and four left sided lesions, after immunotherapy with anti-GITR/Pembrolizumab. The restaging thoracic computed tomo-

Table I. Results of papers included in the review.

Author	Year	No. of patients	Type of paper	Type of intervention	Isotope used	Primary tumor	Site of intervention
Doggett et al[7]	2018	1	Case report	Low dose brachytherapy (LDR)	Palladium-103 seeds	Parotid	Lung metastases
Deipolyi et al[6]	2018	1	Case report	Trans-arterial radioembolization (TARE)	SIR-Spheres (Yttrium-90)	Breast	Liver metastases
Ghodadra et al[8]	2016	1	Case report	Trans-arterial radioembolization (TARE)	SIR-Spheres (Yttrium-90)	Lung	Liver metastases

graphy performed after 6 months, demonstrated a dramatic regression of both the implanted and unimplanted lesions.

Discussion

A large number of laboratory findings confirmed that ionizing radiations, inflammation, oxidative stress with consequential DNA damage and cancer cell biology are strongly related[9].

Starting from biomolecular and immunological mechanisms of action, helps to understand the potential implication of the association of IR and abscopal effect, especially considering the use of new-targeted drugs[10]. One of the principal explanations of the abscopal effect is the release of various molecules: their complex crosstalk with growth factors, activated and sustained by high doses of radiations, may account for both acute and late effects[11,12].

More specifically, *in vitro* studies demonstrated that tumors are capable of downregulating tumor-directed immune response[13] with VEGF, IL-10, and TGF-β inhibiting the maturation of dendritic cells into effective antigen-presenting cells[14].

Interestingly, Kubo et al[15] collected the peripheral blood samples of 36 patients treated for prostate cancer with I-125 seeds. No radiological abscopal effect was showed in this case series, since all patients had localized disease. Nevertheless, the authors confirmed in clinical setting that BT is associated with a peripheral increase of activated T cell subsets, which are considered involved in abscopal effect. Indeed the immunological recognition of the tumor through cellular stress signals, termed "danger signals", can have obvious implications in terms of tumor response, mediated by the subsequent activation of the adaptive immune system[16]. Furthermore, it has been shown that fewer large fractions may elicit a more effective response from the immune system, observing the maximum immunomodulatory effect: from this perspective, IR may turn out extremely useful also for dosimetric reasons[17].

The use of IR large databases will surely enhance the evidence of this uncommon phenomenon[18].

Conclusions

Even though there are still few data in literature regarding the association of locoregional interventional treatments with the abscopal effect, this review demonstrates that the immunomodulatory theories, which have been widely used so far for EBRT, may be actually considered to be valid also in the contest of interventional oncology and open new perspectives to innovative personalized therapeutic paradigms.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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