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# Abscopal effect: new perspectives in Oncothermia

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## *Abstract*

Radiotherapy has a relevant action on the tumor environment and its distant component. Abscopal effect is the bystander effect of radiotherapy observed at a site distant to the irradiated one within the same patient. Abscoopal effect even though described, is not a common clinical event. We are reporting a documented observation of an abscopal effect in one patient with lung cancer treated on target with radiotherapy and oncotehrmia. This is the first case in literature of abscopal effects in lung cancer, a synergistic action between radiotherapy and oncoteramia is suggested.


## *Introduction*

The abscopal phenomenon is the effect of radiation therapy observed as response of metastases distant from the site of irradiation. The word abscopal is derived from Latin ab means “position away from” and “scopos meaning” a target for shooting at.

There is evidence of reactions occurring outside the defined zone of radiation field. First described in 1953 by Mole (1), who called these out-of-field events “abscopal effects”, these distal effects rarely have been documented since then. It should be stressed that abscopal effects are not bystander effects in the traditional sense (2) but refer to radiation responses in areas separate from the irradiated tissue and are presumably mediated by secreted soluble factors.

In both radiotherapy patients and in external-beam-irradiated animal models, most reports on abscopal effects refer to antitumor consequences outside the radiation field (see Figure 1.). Much of the observed physiological abscopal effect has been associated with splenic irradiation (3). In the clinical setting, these include regression of hepatocellular carcinomas after radiotherapy to treat a tumor at the base of the spine and histologic changes in metastatic lymph nodes in some women treated for breast cancer but also in variety of malignancies including lymphoma, papillary adenocarcinoma, melanoma, adenocarcinoma of the esophagus, chronic lymphocytic leukemia (4-10).

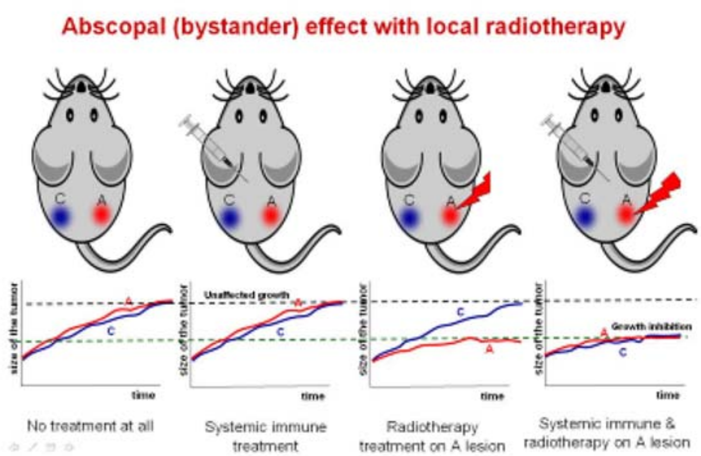


**Figure 1.** The mice have two distant tumors in left and right femoral region. The growths of the tumors are equal. When the mice were treated systemically with immune supporters, no change could be seen. When the A tumor was treated locally with radiotherapy, that tumor did not grow so quickly as the reference C. However, when we apply the systemic immune therapy and the local radiotherapy were applied for the only A-lesion, surprisingly the C lesion is also suppressed

Radiation-induced bystander effects are biologic responses in the cells that were not traversed by an ionizing radiation track and, thus, they were not subject to direct energy deposition; that is, the responses occur in nonirradiated cells. These bystander effects take place in the neighbors of irradiated cells or in other non irradiated cells that have received secreted signals from the irradiated cells. As such, bystander effects are somehow communicated from an irradiated cell to a nonirradiated bystander cell via cell-to-cell gap junctions (14) or by the secretion on shedding of soluble factors (14-16). The precise nature of factors that mediate the bystander effect is unknown, but reactive oxygen and nitrogen species and various cytokines have been implicated. Radiation-induced bystander effects have been extensively documented in several recent reviews (17-18), which have described both detrimental (e.g., DNA stand cleavage, chromosomal damage, and cytotoxicity (11) and potentially beneficial bystander effects.

Although the bystander effect is widely considered a new concept, reports that biologic entities may be inactivated equally by ionizations within the entity or in the surrounding medium have existed since the 1950s(1), and clastogenic factors in plasma from radiotherapy patiens were first observed in the 1950s. Studies have demonstrated that bystander effects induced by high linear energy transfer (LET) – but not those induced by low LET – are dependent on cellular interaction and functioning gap junctions (14-18). It is suggested that the abscopal effect relates to immune response mediated by cytokines, but the mechanism remains unclear because this phenomenon is so rare and poorly understood in clinical practice, showing many controversies also and sometimes it is used complementary to other type of local therapies including surgery, hyperthermia and immunotherapy (19-23).We report a case of Abscopal effect in lung cancer. This observation has never been reported.

## *Case presentation*

The Abscopal effect was shown in a patient, who is a 72 years old male with advanced non-small-cell lung carcinoma (classified as cT2 cN2 M0, stage IV), with metastases in sentinel and in distant lymphnodes was treated locally on the primary lung tumor. A trimodal protocol was applied. It consisted of fractional radiotherapy with 28 sessions delivering 1.7 Gy each, plus Oncothermia 6 sessions, one each week of irradiaton. As supportive treatment 250 microgram of GM-CSF (sargramostim) were given on weekly basis. Two months after treatment a Partial Remission has been observed in the primary lung tumor and evidence of Complete Remission in the distant lymphnodes metastases was reached. The patient felt increase of quality of life, and well being for prolonged time (see Figure 2).

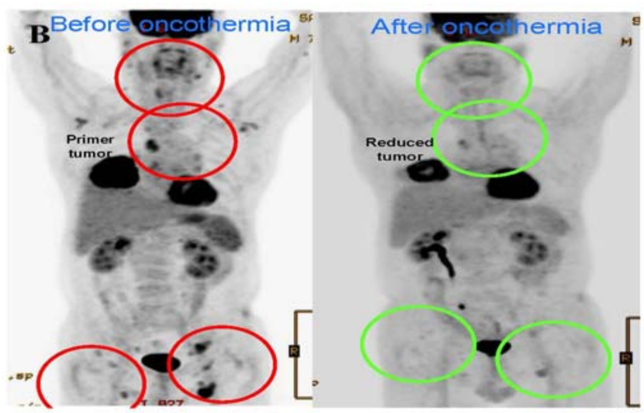


**Figure 2.** Patient with lung cancer before and after treatment: evidence of abscopal effect

## *Discussion*

Numerous studies have assessed the relative effect of radiotherapy and dose rate on tumor cells, with conflicting results that may be dependent, in part, on tumor type and experimental model or design. When the existence of an inverse dose-rate effect was reported, and these findings were initially attributed to incomplete repair of DNA damage and arrest of cells in the radiosensitive, G2 phase of the cell cycle. Since then, there have been multiple reports of an inverse dose-rate effect in a variety of tumor types, with some studies demonstrating the absence of an association between G2 arrest and radiosensitivity and implicating other mechanisms of action.

There have been two main theories proposed to explain the abscopal antitumor effect. The first applies to leukemias and lymphomas, it is hypothesized that during splenic irradiation diseased lymphocytes circulate through the irradiated volume (spleen), and as the splenic size decreases the remotely located masses also decrease in size, giving an impression of a systemic antitumor effect from local treatment. The second applies to solid tumors, it is postulated that local radiation induces a release of mitotic inhibitors (cytokines) into the circulation that mediate a systemic antitumor effect. It has been demonstrated that an elevation of circulating tumor necrosis factor after radiotherapy that coincided with the regression of a hepatocellular carcinoma situated away from the radiation field (9). Others proposed hypothesis is that the abscopal effect is mediated by the immune system. Irradiation of tumour in one site induces release of circulating tumor antigen or inflammatory factors that may then mediate an augmented immune response against non-irradiated, malignant lesions expressing similar tumor antigens (10-18). In our patient by virtue of this unusual presentation, we were able to predict and observe the rare abscopal effect in the site distant from the site of irradiation. Irradiation and oncothermia of the disease in the chest resulted in tumor mass regression in the untreated distant site. Strong synergy of heat and modulated electromagnetic field in tumor cell killing have been observed in animal models (19-21) and could be translated to humans in the routine therapy of cancer. Based on this experiemental and clinical case, we hypothesize that Abscopal effects could be observed in patients treated with radiotherapy, radiotherapy plus oncothermia or only oncothermia. Further studies are necessary.

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