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Melanoma: Last call for radiotherapy

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ABSTRACT

Melanoma is traditionally considered to be a radioresistant tumor. However, radiotherapy and immunotherapy latest developments might upset this radiobiological dogma. Stereotactic radiotherapy allows high dose per fraction delivery, with high dose rate. More DNA lethal damages, less sublethal damages reparation, endothelial cell apoptosis, and finally clonogenic cell dysfunction are produced, resulting in improved local control. Radiotherapy can also enhance immune responses, inducing neoantigens formation, tumor antigen presentation, and cytokines release. A synergic effect of radiotherapy with immunotherapy is expected, and might lead to abscopal effects. If hadrontherapy biological properties seem able to suppress hypoxia-induced radioresistance and increase biological efficacy, ballistic advantages over photon radiations might also improve radiotherapy outcomes on usually poor prognosis locations. The present review addresses biological and clinical effects of high fraction dose, bystander effect, abscopal effect, and hadrontherapy features in melanoma. Clinical trials results are warranted to establish indications of innovative radiotherapy in melanoma.

1. Introduction

Malignant melanoma's incidence ranges from 3 to 25/100 000/years in european countries, with a steadily increasing incidence and mortality over the past decades (Dummer et al., 2015; Garbe et al., 2012; Hollestein et al., 2012; Markovic et al., 2007; Siegel et al., 2012). Prognostic and treatment depend on

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melanoma's stage (Garbe et al., 2012; Siegel et al., 2012). Stages I and II (*i.e.* localized melanomas) are treated with surgery (wide excision with safety margins)(Hayes et al., 2016), associated to adjuvant immunotherapy (alpha interferon) if melanoma is thicker than 1.5 mm. Stages III (*i.e.* locally advanced melanomas) are treated with surgery. Adjuvant immunotherapy (alpha interferon) can be associated in stages III-N1a (micrometastases) without primary ulcerated melanomas. Stages IV (metastatic diseases) are treated with immunotherapy or kinase inhibitors, before chemotherapy (Fort et al., 2016; Garbe et al., 2012; Siegel et al., 2012). The 5-year relative survival rates are about 98.2% for stages I/II, 61.7% for stages III and 15.2% for stages IV (Siegel et al., 2012).

If stage IV melanoma still has a dismal prognosis, the recent development of immunotherapy improved overall survival of metastatic patients, giving grounds for hope (Mahadevan et al., 2015).

Indications of radiotherapy are currently reduced, since melanoma is traditionally considered to be a radioresistant tumor (Mahadevan et al., 2015). In pre-clinical studies, a solid rationale can explain poor clinical outcomes to conventional radiation therapy treatment. Low sensitivity to conventional fractionation radiations (1.8–3 Gy) was demonstrated *in vitro* in melanoma cells. However, this radiobiological impasse might be upset by radiation therapy modern developments, allowing high dose per fraction with high dose rate delivery. Hadrontherapy (*i.e.* radiotherapy using carbon ions or protons instead of photons) might also be an ideal technique in melanoma, with an increased ballistic precision and a greater relative biologic effectiveness (RBE). Finally, immunotherapy might also revolutionized the place and role of radiation therapy, since radiotherapy following immunotherapy has been suggested to induce abscopal effect, increasing overall survival of patients (Gorayski et al., 2015).

The aim of the present study was to clarify the place and role of radiotherapy in melanoma, through an exhaustive literature review, addressing biological and clinical effects of high fraction dose and hadrontherapy, bystander and abscopal effects, and the possible combinations with immunotherapy.

2. Search strategy and selection criteria

Requests were performed in the Medline database (*via* PubMed) to identify all publications studying radiation therapy in melanoma. The latest update was performed in January 2016, using the following MESH terms: "melanoma, radiotherapy", "melanoma, adjuvant radiotherapy", "metastatic melanoma, radiotherapy", "melanoma, radioresistance", "melanoma, stereotactic", "melanoma, endothelial apoptosis", "melanoma, bystander effect", "melanoma, abscopal effect", "melanoma, lymphocytes", "melanoma, hadrontherapy", as keywords and "English" as limit. A request was also performed on ClinicalTrials.gov using the terms "melanoma, radiotherapy". Currently recruiting trials studying melanoma, immunotherapy, and radiotherapy are summarized in Table 1.

3. Indications

Current indications of radiation therapy in melanoma have been recently stated by international scientific societies, and are summarized hereafter.

Primary exclusive radiotherapy should be considered when the wide excision of the primary site is not possible [3,8,9]. Superficial lentigo maligna, lentigo maligna melanoma, and mucosal melanoma may also be successfully treated with radiotherapy (Fort et al., 2016; Mahadevan et al., 2015). Finally, the last indication of primary exclusive radiotherapy is intraocular melanomas, in order to preserve eyesight.

Adjuvant radiotherapy has shown to improve local control of the primary site in case of high recurrence risk after surgery: Breslow thickness >4 mm, ulceration, satellitosis or angiolymphatic invasion, narrow or positive resection margins, desmoplastic melanoma (particularly with neurotropic features), mucosal or head and neck melanoma (Fort et al., 2016; Gorayski et al., 2015). Some retrospective studies and one randomised controlled trial suggested that radiotherapy of the regional nodal basin could be performed after node dissection in order to improve regional control in case of multiple positive nodes (>3), bulky nodes (>3 cm), extracapsular extension or regional recurrent disease (Fort et al., 2016; Gorayski et al., 2015; Henderson et al., 2015; Mahadevan et al., 2015). Palliative radiotherapy should always be considered in case of metastases-induced symptoms, with adapted fractionation (Garbe et al., 2012; Jochemsen, 2014; Mahadevan et al., 2015). Doses per fraction higher than or equal to 4 Gy are recommended on cutaneous, lymph node, and visceral metastases, but seem to bring no benefit in case of skeletal metastases. In case of brain oligometastases and controlled systemic disease, stereotactic radiosurgery and stereotactic radiotherapy have proved interesting efficacy in patients with Karnofsky performance score higher than 70% (Garbe et al., 2012; Jochemsen, 2014; Mahadevan et al., 2015).

4. Radioresistance dogma

Melanoma is considered to be radioresistant based on *in vitro* studies of clonogenic cell death assay (Barranco et al., 1971; Rofstad, 1992). Efficacy of conventional fractionated radiation therapy based on photons (1.8–3 Gy) could be estimated using the "linear quadratic" mathematic model. This approximation method depicts tumor cell survival curves and gives information on cell reaction to radiation, through the calculation of two variables (alpha and beta) and their ratio. Alpha depicts the probability of lethal damage induced by radiation (DNA double-strand breaks, locally multiple damaged sites). Beta depicts the probability of lethal damage due to accumulated sublethal lesions. The alpha/beta ratio depends on DNA repair cells ability. A broad shoulder in melanoma cell survival curves was clearly established, reflecting an increased sensitivity to high doses per fraction, with an alpha/bêta ratio of about 4.8 Gy (Jochemsen, 2014; Mahadevan et al., 2015; Malaise et al., 1986). Melanoma cells feature high repair capacity due to efficient enzymatic system, high proliferation capacity, poor cell differentiation, and hypoxic cell pools including radioresistant cancer stem cells (Rofstad, 1992; Yu et al., 2012; Zabierowski and Herlyn, 2008). Abnormal apoptosis was also described in melanoma cell and is probably one more reason to melanoma radio-resistance. Apoptosis is indeed a major way of radiation-induced death, involving p53 and caspases pathways (effector of apoptosis). If it was shown that p53 mutation is rare in melanoma, the functional attenuation is common, since it is needed for tumor development through an overexpression of p53 inhibitors such as Mdmx, TA-p53 or iASPP (Jochemsen, 2014).

However, it was proved that extrinsic radiosensitizing factors (such as ionizing radiation characteristics) could influence *in vitro* melanoma cell survivals. Radiosensitivity could be clearly improved by high dose and high dose rate, short overall treatment time, radiosensitizers, tumor reoxygenation induced by fractioned radiotherapy (Rofstad, 1992), high linear energy transfer (LET) and high RBE technologies (Suchowerska et al., 2010). Featuring all these properties, hadrontherapy could be an ideal candidate in order to overcome radio-resistance of melanoma.