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The role of radiotherapy in melanoma

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ABSTRACT

The role of radiotherapy (RT) in the treatment of melanoma is constantly evolving. Although melanoma is considered a radioresistant tumour with great potential for repairing sub-lethal damage, RT is an important component of treatment. Indications for sole or adjuvant radiotherapy of the primary lesion are limited and include desmoplastic melanoma, the presence of satellite lesions and/or in-transit metastases, the presence of melanoma cells in blood or lymphatic vessels, infiltration of nerve trunks, recurrence after previous surgery, and locally advanced melanomas of the head and neck region, especially inoperable. In the past, the most common indication for radiotherapy in melanoma was adjuvant treatment after lymphadenectomy in patients with risk factors for nodal recurrence (large metastasis diameter, multiple nodes involved, extracapsular extension). Adjuvant radiotherapy after lymphadenectomy has been shown to almost double the local control of the disease, but it does not affect patient survival and may also lead to significant toxicity. Nevertheless, currently the recommended approach is systemic adjuvant treatment (anti-PD-1 immunotherapy with pembrolizumab or nivolumab and, in the presence of *BRAF* mutation, BRAF/MEK inhibitors), and RT should be reserved for situations in which there are contraindications to other adjuvant treatment. Stereotactic techniques, including radiosurgery of brain metastases, are becoming more widely used. RT could be a definitive treatment for a limited number of metastases or in cases of limited progression on systemic treatment. The effectiveness of RT can be increased by combining with hyperthermia. An increasing number of reports suggest great benefit from the combination of RT with immunotherapy. At present, there is no convincing evidence supporting the combination of RT with molecularly targeted treatment, and according to emerging data on the toxicity of such a combination it should be used with caution.

Key words: melanoma, radiotherapy adjuvant, immunotherapy, radiotherapy

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Introduction

Radiotherapy (RT) is one of the three basic therapeutic modalities in oncology, and its role in the treatment of melanoma is constantly evolving. Historically, melanoma cells were considered to be radioresistant, hence the role of RT was mainly limited to the symptomatic treatment of advanced disease. In the past, RT was used in selected cases as an adjuvant treatment after surgery for primary lesion or lymph nodes, and as palliative treatment in patients with distant metastases. The rapid development of precise RT techniques, new imaging methods, and the introduction of new options of effective systemic treatments have caused the role of RT in the treatment of melanoma to change significantly, especially over the past 20 years (Table 1). In 2004 it was calculated that, according to the current state of knowledge and best clinical practice, RT should be used in as much as 23% of patients with advanced melanoma [1]. There are no such data in the literature for the last 10 years; however, due to the prolonged survival of patients and the beneficial effects of the combination of RT and immunotherapy, it can be assumed that nowadays this proportion should be even higher.

Radiobiology of melanoma

Studies on cell lines have shown that melanoma has a high ability to repair sub-lethal damage [2]. Hence, it

Table 1. Evolution of the role of radiotherapy in melanoma treatment

Radiotherapy type	Past	Present
Adjuvant after lymphadenectomy	+++	+
Palliative	+++	++*
Whole brain radiotherapy	+++	+
Adjuvant after primary tumour resection	++	+
Definitive	+	++*
Oligometastatic disease	+	++*#
Oligoprogression	–	+++*#
"Boost" during immunotherapy	–	+++?*

*Including stereotactic techniques
#Also treatment of brain metastases with radiosurgery

was concluded that higher dose per fraction is needed to achieve satisfactory local control (LC). The results of retrospective analyses of large groups of patients carried out in the 1980s confirmed the hypothesis that a higher dose per fraction is an independent factor of the effectiveness of RT. However, no significant differences were found between hypofractionated RT regimens [3]. Further studies questioned the benefit of hypofractionation over conventional RT regimens [4]. The results of a large international prospective randomised clinical trial by the Radiation Therapy Oncology Group (RTOG 83-05) showed no significant difference in LC between 8 Gy per fraction administered four times over 21 days and 2.5 Gy per fraction administered five days a week for four weeks. In clinical practice, when calculating the biological effective dose or equivalent dose to a 2 Gy fraction dose, it should be assumed that the alpha/beta ratio of melanoma is lower than 3 Gy [5].

Primary lesion treatment — skin melanomas

Wide local excision is the primary method of melanoma treatment. Definitive RT is reserved only for patients who cannot undergo surgery (e.g. locally advanced disease, disability, comorbidities, lack of patient consent). RT may be an alternative to surgical treatment of *lentigo maligna* (extensive facial lesions) in selected groups of patients. The regimen consists of a total dose of 50–52 Gy in 2 Gy fractions using superficial RT (kilovolt radiation). RT of *lentigo maligna* — definitive or adjuvant to non-radical surgery — provides LC of 83–97% [6].

Desmoplastic melanoma is a subtype of melanoma in which adjuvant RT is used. Because of the tropism to nerve cells (spreading along nerve trunks), wide local excision may not be sufficient to achieve satisfactory LC. Analysis of large groups of patients with neurotropic melanomas supported the use of adjuvant RT in this clinical situation. For microscopic margins smaller than 8 mm, adjuvant RT reduced the risk of local recurrence by approximately 50% [7, 8].

In some clinical situations, RT may improve the LC after surgical treatment. Adjuvant RT after primary tumour resection should be considered for high-risk local recurrence factors, which include the following [9]:
— desmoplastic subtype with lesion thickness according to Breslow > 4 mm;
— extensive macroscopic ulceration;
— presence of satellite lesions and/or in-transit metastases;
— presence of melanoma cells in blood or lymphatic vessels;
— infiltration of nerve trunks (regardless of subtype);
— recurrence after surgery of the primary tumour;
— locally advanced melanomas of the head and neck area.

The advantage of a specific fractionation regimen over the others was not demonstrated. One of the most commonly used is the administration of 30 Gy in five fractions of 6 Gy during 2.5 weeks [10].

Due to the growing evidence supporting the use of neoadjuvant or adjuvant immunotherapy and molecularly targeted treatment in patients with locally advanced melanomas, definitive RT can also be a consolidation treatment after achieving a response to systemic therapy. Such management is not yet supported with scientific evidence, and all decisions should be made individually after discussing the clinical situation at a multidisciplinary meeting.

Primary lesion treatment — mucosal melanomas

Mucosal melanomas account for about 1% of all melanomas [11]. Most often they affect the head and neck region, perianal area, rectum, and genitourinary tract. The treatment of choice is surgery. RT can be

a adjuvant treatment after non-radical surgery or definitive therapy of inoperable lesions. Most reports of the effectiveness of sole RT in the treatment of mucosal melanomas relate to the head and neck region, in particular paranasal sinuses. Definitive RT allows a three-year LC of 50–85%. Due to the increasing role of systemic therapy in locally advanced melanomas and the potential immunosensitization by RT, concomitant definitive radioimmunotherapy might be considered. Such treatment should be carried out within clinical trials or in tertiary centres with experience in the treatment of melanomas.

Postoperative RT of mucosal melanomas improves LC but has no effect on patient survival [12, 13]. In some centres, adjuvant RT of mucosal melanomas is used routinely because recurrence in these sites is usually unresectable and is associated with a dramatic deterioration of patients' quality of life. Due to the lack of recommendations, the management should be individual and include evaluation of:

— performance status;
— risk factors for recurrence;
— potential RT toxicity and proximity of organs at risk;
— the possibility of other adjuvant treatment (systemic therapy).

In some locations, the use of proton therapy may benefit, allowing greater protection for radiosensitive organs at risk such as central nervous system (CNS) structures and sense organs. In Poland in 2019, proton therapy is reimbursed in cases of inoperable melanoma of paranasal sinuses or as a adjuvant treatment after its non-radical resection.

Adjuvant RT after lymphadenectomy

In the past the most common indication for RT in melanoma patients was macroscopic lymph node metastasis. The role of RT in this setting significantly decreased after the introduction of effective systemic therapies such as immunotherapy or molecularly targeted treatment (BRAF and MEK inhibitors). At present, US NCCN recommendations give adjuvant RT category 2B, while adjuvant systemic treatment has the highest level of recommendation (category 1). Adjuvant RT after lymphadenectomy almost doubles LC but has no effect on patient survival [14, 15]. In the ANZMTG 01.02/TROG 02.01 randomised clinical trial, 250 patients with stage III melanoma were randomly assigned for adjuvant RT (48 Gy in 20 fractions) or observation after lymphadenectomy.

Patients in the RT arm had a significantly lower percentage of nodal recurrences compared to non-irradiated patients (21 *vs.* 36%, hazard ratio 0.52, 95% CI 0.31–0.88), but relapse-free survival and overall survival

did not differ significantly between the groups. Furthermore, RT often led to late toxicity. Low-grade toxicity, such as chronic pain and fibrosis of skin and subcutaneous tissue, were common. In 22% of irradiated patients, serious toxicity (CTCAE grade 3 and 4) occurred, mainly affecting the skin (10%) and subcutaneous tissue (7%). Five years after treatment completion a significantly larger lower limb volume was observed in the irradiated group than in patients undergoing surgery alone. The risk of lymphoedema was highest for groin irradiation, medium for axillary irradiation, and relatively low for irradiation of lymph nodes of the head and neck region (Fig. 1). On the other hand, nodal relapses may be associated with symptoms worsening the patient's quality of life, such as ulceration, bleeding, pain, and lymphoedema. In turn, RT for large lymphatic area is also associated with the risk of significant toxicity in the form of persistent lymphoedema, fistulas, fibrosis, ulceration, and symptoms associated with particular anatomical regions. Hence, the decision to use RT after lymphadenectomy should be made taking into account the risk-benefit balance and availability of alternative treatments. The preferred RT regimen is 48 Gy in 20 fractions of 2.4 Gy.

Risk factors for nodal recurrence after lymphadenectomy that may be indications for adjuvant radiotherapy include:

— extracapsular extension of nodal melanoma metastases;
— metastases to multiple lymph nodes (any number of parotid nodes, two or more cervical or axillary nodes, three or more inguinal nodes);
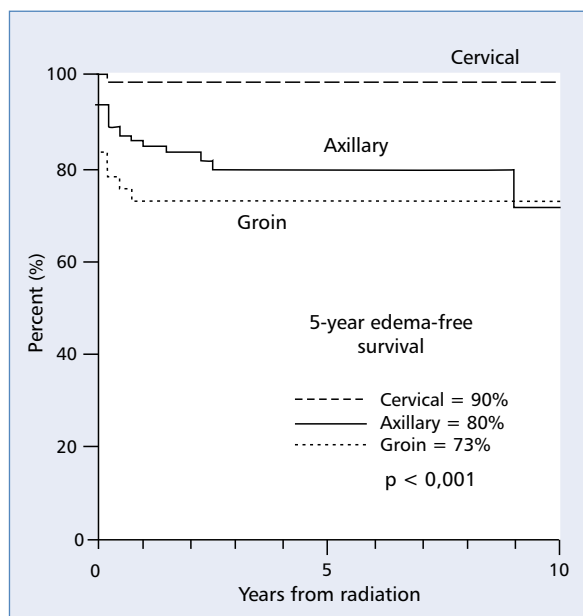

Figure 1. The risk of lymphoedema following surgery and radiotherapy of large nodal areas [42]

— large metastasis diameter (three or more centimetres for cervical lymph nodes, four or more centimetres for axillary and inguinal nodes);

— non-radical resection;

— recurrence after previous lymphadenectomy.

Nevertheless, the recommended approach is to qualify the patient for systemic adjuvant treatment (currently available options include anti-PD-1 immunotherapy with pembrolizumab or nivolumab and additionally, in the case of *BRAF* mutations, BRAF/MEK inhibitors: dabrafenib with trametinib), preferably within controlled clinical trials if available. RT should be considered in clinical situations in which neither immunotherapy (e.g. active severe autoimmune disease) nor molecularly targeted therapy (lack of *BRAF* mutation) can be used, or as a rescue treatment after resection of locoregional recur-

rence after adjuvant treatment. An alternative approach is frequent follow-up and treatment (surgery ± RT ± systemic treatment) in the case of locoregional recurrence. The algorithm presented in Figure 2.

Patients with skin melanoma of the head and neck region with lymph node metastases constitute a particular group. Cervical lymphadenectomy with adjuvant therapy (RT, immunotherapy, and BRAF and MEK inhibitors) is the preferred management; however, sole radiotherapy can be an alternative to surgery. In an American study, a small group of patients (n = 36) with skin melanoma of the head and neck region underwent dissection of macroscopically suspicious lymph nodes followed by RT of lymphatics using 6 Gy twice a week for a total dose of 30 Gy [16]. Five-year LC was higher than 90%, and the rate of late toxicities did not exceed 10%.
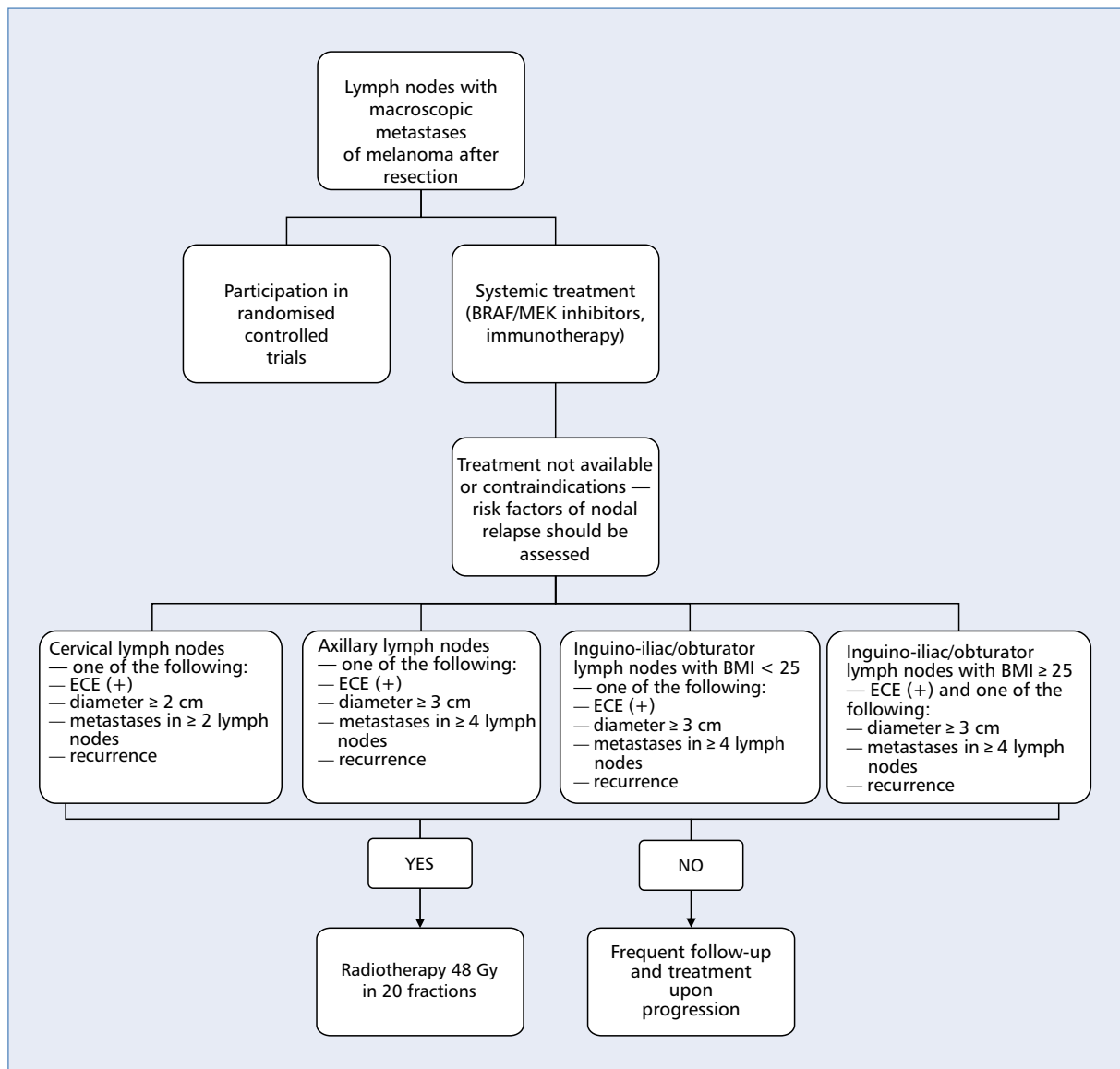

Figure 2. Algorithm of management after lymphadenectomy due to macroscopic melanoma metastases to lymph nodes

Stereotactic RT and radiosurgery

Stereotactic body radiotherapy (SBRT) is a RT method that involves delivering a high fraction dose to a small volume of a macroscopically visible tumour, sparing surrounding healthy tissues (without elective volume). Its particular type is stereotactic radiosurgery (SRS), in which the prescribed dose is delivered in one fraction. It is mainly used in irradiation of tumours of the CNS. SBRT and SRS are increasingly used in the treatment of melanoma patients. Indications may include:
— inoperable primary lesions, e.g. limited-volume mucosal melanomas;
— inoperable recurrent melanoma with limited volume;
— brain metastases;
— oligoprogression during systemic treatment;
— oligometastatic disease;
— single spinal or other bones metastases.

Fractionation regmens should be appropriate to the anatomical site, taking into account the tolerance of organs at risk. It should be noted that there are currently no recommendations as to optimal fraction and total doses for SBRT and SRS in melanoma patients. In order to apply optimal RT regimen and dose constraints for organs at risk, protocols of ongoing clinical trials in oligometastatic disease such as NRG-BR001 can be used.

RT as a treatment of limited progression

RT may play a role in local definitive treatment of metastases that has progressed during a currently effective systemic treatment. Oligoprogression occurs when, in a single or several metastatic lesions, molecular changes develop that determine resistance to treatment. An effective method of local treatment extends the time of use of systemic therapy, which provides benefit to patients [17]. SBRT seems to play a special role because it provides very good LC with minimal toxicity. In some cases, the combination of RT and immunotherapy may enhance effectiveness of systemic treatment, which is described later in this article.

RT in combination with hyperthermia

Hyperthermia is a method of temporarily increasing the temperature within a tumour to increase the effect of RT or chemotherapy. The mechanism of heat efficacy in the treatment of cancer has not been fully explained, but the effectiveness of such a combination of methods has been demonstrated in a randomised clinical trial: combining local hyperthermia with RT in patients with advanced melanomas led to a significantly increased LC (sole radiotherapy 28%, radiotherapy with hyperther-

mia 46%) [18]. Hyperthermia was very well tolerated. However, the results of the study should be interpreted with caution due to the low percentage of patients who completed the treatment according to the protocol (14%). Most reports on the role of hyperthermia in melanoma are from the 1980s and 1990s, and hence do not take into account the contemporary systemic treatments that might be combined with RT. The use of hyperthermia during RT may allow for a better response by increasing tumour perfusion and oxygenation, inhibiting DNA repair mechanisms, cell death, and extensive immune modulation, including increased expression of immunogenic surface receptors such as MHC-1 and heat shock protein secretion, which activate NK cells and antigen-presenting cells, thereby intensifying immune responses mediated by CD8+ cells [19].

It seems necessary to conduct prospective clinical trials. The data available so far allow the routine use of hyperthermia in combination with RT in the treatment of advanced melanomas; however, in the case of concomitant use of immunotherapy or targeted therapy, qualification should be careful.

Palliative RT

RT can be an effective symptomatic treatment of melanoma metastases to the bone, brain, soft tissues, and lungs and a emergency therapy in case of developing spinal cord compression or superior vena cava syndrome. Additionally, RT is also one of the options for achieving LC in patients with numerous unresectable in-transit metastases of melanoma. Doses higher than 4 Gy per fraction are preferred because of the higher probability of achieving a response (82% at doses > 4 Gy vs. 44% at ≤ 4 Gy) [20]. The RT regimen should be adapted to the patient's performance status, cancer stage, and possibilities of systemic treatment.

The management of brain metastases is a separate issue. The role of whole brain RT decreased in the last years due to low efficacy of such treatment and its severe toxicity. If possible, the treatment of choice should be surgery or SRS. The issue is discussed in detail in the Polish guidelines for the management of brain melanoma metastases [21].

A particularly challenging clinical situation is the presence of melanoma metastases to the spine (bones or soft tissues), due to the risk of fracture or the spinal cord compression with neurological deficits and severe pain. The combination of immunotherapy with RT and local neurosurgical interventions often gives satisfactory LC in this group of patients. The best results were obtained when SRS or SBRT was applied to residual tumour volume after surgical spinal cord decompression, where the one-year local recurrence rate did not exceed 10% [22, 23]. The alternative may be a sole SRS/SBRT — some

studies indicate that the LC rate of such treatment is higher than 90% [24]. At present, there are no data on the effectiveness of combining immunotherapy with SRS/SBRT in the treatment of melanoma metastases to the spine.

RT in combination with molecularly targeted therapy

Data regarding the sense of combining BRAF inhibitors with simultaneous RT are contradictory, and the use of such a combination requires caution. Some reports suggest an advantage of using the described combination in sensitising melanoma cells to RT after the administration of BRAF inhibitors [25].

Targeted therapy can reduce the size and number of metastases in CNS and thus in some cases allow the use of SRS instead of whole brain RT. However, there is no clear biological explanation for the potential synergy of RT and BRAF/MEK inhibitors, as in the case of immunotherapy, except for the immunological impact of BRAF-targeted therapy. However, recent studies indicated that the combination of targeted therapy with SRS, similarly to immunotherapy, seems to improve overall survival [26]. An ongoing, prospective, open-label, phase II study (NCT01721603) will assess the effect of dabrafenib in combination with SRS on the six-month brain metastasis-free survival rate compared to historical control (SRS alone). In this study, all patients will receive dabrafenib 150 mg twice daily (continuous dosing) and trametinib at an initial dose of 2 mg once daily, starting from cycle 3 on day 1. Treatment continues until disease progression, consent withdrawal, or development of intolerable treatment-related toxicity. MRI is performed after 28 days of dabrafenib treatment. Patients with complete response (regression of all brain lesions) will continue to receive dabrafenib and trametinib during the study but will not be qualified for SRS. For patients with disease stabilisation or partial response to treatment, SRS will be performed in cycle 2 ($\pm$ 3 days, 28-day cycle). The first data from interim analysis showed that one-year overall survival (64.3 *vs.* 40.4%, p = 0.205), local progression rate (3.3 *vs.* 9.6%, p = 0.423), and distant intracranial progression rate (63.9 *vs.* 65.1%, p = 0.450) were not statistically different between the SRS + BRAF inhibitors and SRS alone groups. Patients in the group receiving both SRS and BRAF inhibitors had higher rates of radiation necrosis (RN) (22.2 *vs.* 11.0% after one year, p < 0.001) and symptomatic radiation necrosis (SRN) (28.2 *vs.* 11.1% after one year, p < 0.001) than patients who received only BRAF inhibitors. Multivariate analysis showed that treatment with BRAF inhibitors implies an increased risk of both RN and SRN compared to SRS alone [27]. RN usually develops seven to 12 months after therapy and may be associated with the onset of neurological disorders, including convulsions, speech disorders, psychomotor retardation, and sensory-motor deficiency [28]. Final analysis and publication of the results of NCT01721603 study is awaited.

Increasing number of publications raise the issue of potential enhancement of side effects. There are many case reports in the literature regarding increased skin toxicity when BRAF inhibitors are used concomitantly with RT. RT while receiving BRAF inhibitors increases the risk of RTOG grade 2 and 3 dermatitis and other rare skin complications (e.g. cutis verticis gyrata when combined with whole brain RT). This effect is probably dose-dependent; therefore, doses $\geq$ 4 Gy are not recommended for conventional radiotherapy in patients taking BRAF inhibitors. No similar side effects have been reported in the literature for MEK inhibitors. The guidelines of the Eastern Cooperative Oncology Group recommend discontinuation of BRAF and MEK inhibitors at least three days before the start of RT and the re-use of these drugs at the earliest three days after its completion or one day before and one day after CNS SRS. However, it should be emphasised that these recommendations are not based on strong scientific evidence. The decision to temporarily withdraw targeted therapy during RT should be individualised after comprehensive analysis of the patient's clinical situation by a clinical oncologist and a radiation oncologist, because discontinuation of targeted therapy may lead to rapid disease progression [29].

RT in combination with immunotherapy

Available data suggest a beneficial effect of combining RT with immunotherapy. This is confirmed by increased frequency of an extremely rare phenomenon known as the abscopal effect (response of untreated lesions as consequence of local treatment of another lesion) with simultaneous use of RT with immunotherapy [30]. The benefits of combining the described methods may result from the so-called antigenic effect, when RT breaks down affected melanoma cells and releases antigens into the blood, which stimulates dendritic cells and lymphocytes, and thus enhances the effect of immunotherapy (Fig. 3, Fig. 4).

Preclinical studies have shown that the combination of RT and anti-PD-1/PD-L1 immunotherapy activates cytotoxic T cells, reduces levels of bone marrow suppressor cells, and induces a response of non-irradiated lesion to RT of another lesion [31]. RT results in increased antigen presentation and CD8+ T-cell infiltration, stimulation of tumour-specific cytotoxic T lymphocytes in many metastatic lesions, which can lead to abscopal
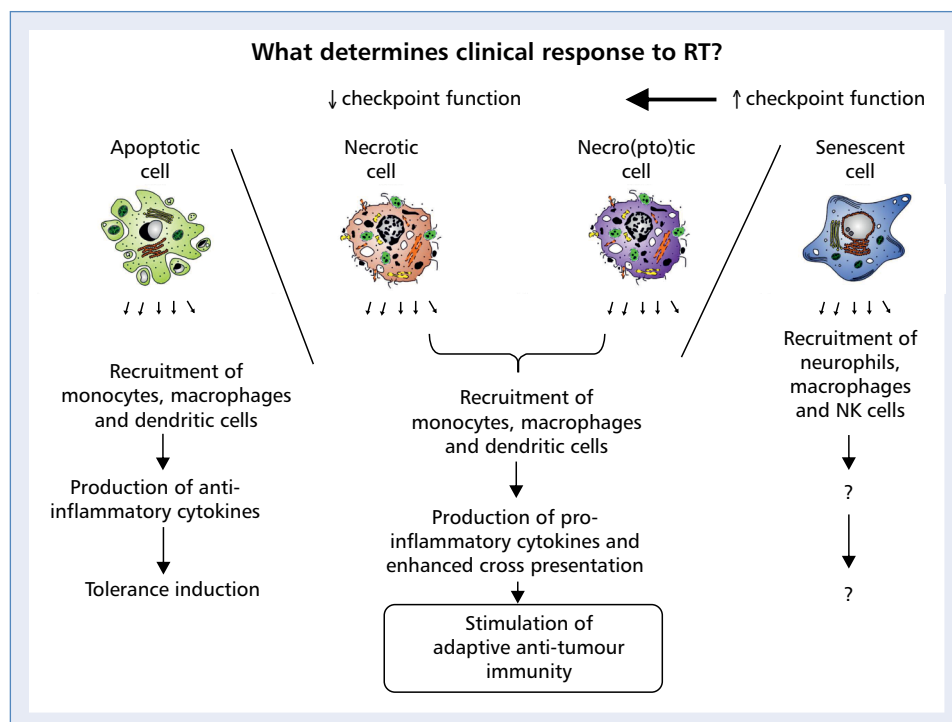
Figure 3. Immunological factors determing response to radiotherapy [43]
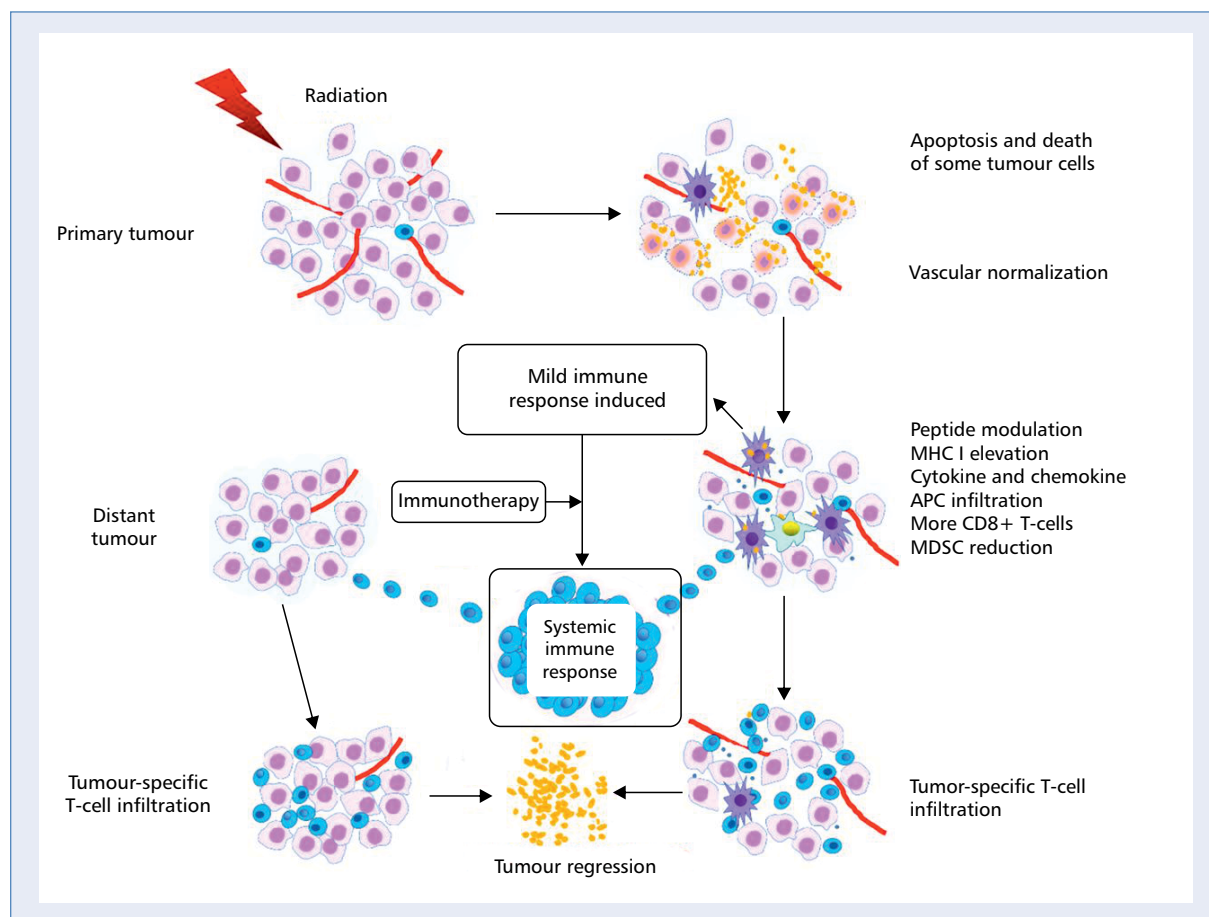

Figure 4. Mechanism of radiotherapy and immunotherapy synergy [44]

effect during immunotherapy. An example of this effect was described in NEJM in 2013 [32]. In a melanoma patient during treatment with ipilimumab, the progression occurred in a form of constantly-growing metastatic lesions within the pleura and new spleen lesions. She received palliative RT for the paravertebral conglomerate metastases using 28.5 Gy in three fractions. Response was seen in lesions that were outside target volume.

In one prospective clinical trial, 22 patients underwent RT for a single lesion five days after receiving the first dose of ipilimumab [33]. Six patients achieved objective responses, including three partial regressions and three complete responses. Similarly, another study showed that adding ipilimumab to RT significantly prolongs the survival of patients with brain melanoma metastases compared to RT alone (median overall survival: 18.3 months *vs.* 5.3 months) [34]. Oncologists from Penn University analysed a group of 22 patients with stage IV melanoma in a phase I study receiving SBRT (2–3 fractions of 6–8 Gy), and after five days four cycles of ipilimumab [35]. In the study, 8/22 (36%) patients achieved complete or partial response to the treatment. At the same time, using the mouse model, they described a number of molecular relationships, including the observation that RT increased the presentation of tumour cell antigens for T cells, administration of anti-CTLA-4 treatment promotes T-cell expansion, and anti-PD1 drugs reverse T-cell depletion. A team from the Dana-Farber Institute described a group of 47 patients with stage IV melanoma, who received RT after ipilimumab treatment [36]. In this group, 53% of patients were irradiated within three months of ipilimumab treatment. The most frequent types of RT were: 34% = brain SRS, 19% = whole brain RT, and 17% = RT for soft tissue metastases. In total 11% of lesions responded after treatment with ipilimumab alone as compared to 25% of responses after adding ipilimumab to RT. RT was also associated with faster response. *BRAF* mutation status, total dose and target volume localisation, and time of ipilimumab administration did not affect response to treatment. Lower fraction doses (≤ 3 Gy) were the only factor that positively correlated with an increased response rate. The study from the University of Cologne included 127 patients with stage IV melanoma, 82 of which received ipilimumab alone and 45 received local treatment, and 40 patients received both ipilimumab and RT [37]. 17/45 (38%) obtained objective responses in the group of patients treated with ipilimumab and RT compared to 12/82 (15%) of those receiving only ipilimumab. The median overall survival was 93 weeks in the RT and immunotherapy group *vs.* 42 weeks in the group receiving radiotherapy alone; the difference was statistically significant (p = 0.003). Koller et al. evaluated a cohort of patients with advanced melanoma treated with ipilimumab with or without RT

[38]. Median overall survival, objective response rate, overall response rate, and median progression-free survival significantly improved in the ipilimumab and RT group. In addition, no increase in toxicity was seen in the group receiving combination treatments compared to ipilimumab alone. We are currently awaiting the results of the phase II clinical trial NCT01970527 RADVAX, in which the effects of combining SBRT with ipilimumab will be assessed. The results of the phase I clinical trial NCT01996202 have not yet been published; in this study a combination of ipilimumab and RT was used as neoadjuvant or adjuvant therapy in melanoma patients with poor prognosis. This group included patients with mucosal melanomas, desmoplastic melanomas, melanomas of the head and neck region, and melanomas from outside this area, but with macroscopic lymph node involvement and the presence of previously described risk factors being the indications for RT.

In the study with RT combined with anti-PD-1 immunotherapy the response rate of non-irradiated lesions was 46% [39]. Interesting observations also come from analyses of effects of combining immunotherapy with RT in melanoma patients with brain metastases. The results of the retrospective analysis from 2016 confirm the effectiveness of this combination with good toxicity profile. A group of 26 melanoma patients with brain metastases who received nivolumab in the last six months before, during, or after RT underwent SRS of metastatic CNS lesions [26]. LC after six and 12 months was 91% and 85%, respectively. Similar results were obtained using pembrolizumab with RT. The results of a retrospective study assessing the effectiveness of SRS and pembrolizumab in patients with diagnosed brain melanoma metastases support the hypothesis of the benefits of combining these methods. SRS with concurrent administration of pembrolizumab results in significantly better responses (8/23 complete responses, 8/23 partial responses, 16/23 in total) than SRS without concurrent immunotherapy (5/23). On the other hand, it should be remembered that not only BRAF inhibitors increase the toxicity of RT, but also immunotherapy can be a factor associated with the development of RN [27]. Other observations, including data from the MD Anderson Cancer Centre, do not support this hypothesis [40].

The optimal timing to start RT remains an open question. Available data suggest that RT is most beneficial when used concurrently with immunotherapy [39]. The optimal RT dose regimen during immunotherapy is unknown. At present, many clinical studies are ongoing with the combination of RT and immunotherapy in the treatment of advanced melanomas, and their results will provide valuable data on the optimal combination of RT with immune checkpoint inhibitors [41]. Particularly interesting will be the results of the NCT03850691 study. This is a phase II clinical trial that aims to evaluate the

combination of nivolumab immunotherapy and aldesleukin (IL-2) therapy after receiving standard palliative RT for the treatment of inoperable metastatic melanoma. Patients with a diagnosis of cutaneous melanoma who have at least three (preferably > 5) measurable > 1.5 cm lesions and have already received systemic treatment in the form of immunotherapy, BRAF/MEK inhibitors, and/or chemotherapy are eligible for the study.

Conclusions

RT has an important role in the treatment of patients with melanoma; however, the indications for RT in melanoma have changed significantly over the past few years. Indications for palliative RT remain unchanged. Adjuvant RT after lymphadenectomy is not recommended because more effective adjuvant treatments are available. RT is increasingly used to enhance the effectiveness of immunotherapy and targeted therapy, as well as to delay the withdrawal of effective systemic therapy in the case of oligoprogression. This topic requires new prospective clinical trials; however, emerging data justify the use of RT in the described clinical situations. Since the response to RT is partly dependent on CD8+ T-cells, developing future strategies to increase T-cell infiltration may improve the effectiveness of RT in melanoma patients.

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