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REVIEW

The role of radiotherapy in the treatment of ewing sarcoma of bone

Predrag Filipović[1], Marija Popović-Vuković[1], Marina Nikitović[1,2]

[1]Institute for Oncology and Radiology of Serbia, Belgrade, Serbia
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

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Correspondence to:
Predrag Filipović
Institut za onkologiju i radiologiju Srbije
Paterova 14, 11000 Beograd
+381117350683
predrag.filipovic@ncrc.as.rs

Summary

Ewing sarcoma (ES) is the second most common primary bone malignancy after osteosarcoma. The disease most often occurs in adolescence, with peak incidence around the age of fourteen. The most common primary location of the tumor is the bones of the pelvis, followed by the ribs, spine and long bones of the extremities such as the tibia and the fibula. ES shows a tendency towards hematogenous dissemination, primarily in the lungs and bones, much less often lymphogenously. One third of patients have distant metastases present at initial diagnosis, which is why ES is considered a systemic disease.

The treatment of Ewing sarcoma is based on a multimodal approach that includes the use of chemotherapy, surgery and/or radiotherapy. The identification of prognostic parameters enabled the individual treatment of patients based on the assessed risk group. With the application of modern therapeutic protocols, five-year survival for patients with localized disease lies between 60% and 68%, while for patients with metastatic disease, five-year survival is still unsatisfactory and is around 17%.

ES belongs to the group of radiosensitive tumors, and radiotherapy plays a very important role in the local control of the disease, in combination with surgical treatment or independently, and can be applied as radical, preoperative or postoperative radiation therapy. Also, radiation therapy has a role in the palliative approach to the treatment of lung metastases and other metastatic sites.

Considering that the modern multimodal treatment of Ewing sarcoma leads to long-term survival, it is necessary to take into account the expected side effects of the therapy that can reduce the quality of life of treated patients.

Modern radiotherapy techniques such as three-dimensional conformal radiation therapy (3D CRT), intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT) enable precise delivery of the prescribed dose of radiation to target volumes with better sparing of surrounding normal tissues and organs, which leads to a lower incidence of late sequelae of radiation therapy and enables the preservation of the quality of life of treated patients.

Key words: Ewing sarcoma, radiotherapy, radiotherapy techniques

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INTRODUCTION

Epidemiology and etiology of Ewing's sarcoma

After osteosarcoma, Ewing's sarcoma is the most common bone malignancy. The disease can occur in any age group, but it most often occurs in adolescence and young adulthood, and about 86% of tumors occur before the age of forty (1). The incidence of this tumor is estimated at 2.93/1,000,000 per year in the white population and has not changed significantly in the past 30 years (2).

The etiology of this disease has not been fully elucidated, but numerous studies that could clarify the molecular-genetic pathways crucial in the pathogenesis of Ewing's sarcoma are underway.

Pathohistology and genetics

Pathohistologically, Ewing's sarcoma is a tumor of small round blue cells that is often PAS, vimentin and cytokeratin positive (6). Tumors of the Ewing sarcoma family are thought to share a common precursor cell that is of neuroectodermal origin (5). Cytogenetic analyzes showed a certain number of translocations in Ewing's sarcoma cells, which probably have an impact on the tumorigenesis of this disease.

The characteristic translocation for Ewing sarcoma is t(11;22) (q24;q12). This translocation leads to the fusion of the EWS and FL1 genes, which results in the formation of an aberrant protein that plays the role of an oncogenic transcription factor. More recently, new translocations that do not involve the EWS gene, such as BCOR-CCNB3 and CIC-DUX4 fusions (8-9) have been discovered, which do not currently have a clear clinical significance. In addition to gene aberrations, epigenetic changes such as DNA methylation and their possible influence on the pathogenesis of Ewing sarcoma have recently been increasingly studied. Some of the genes that are hypermethylated in Ewing sarcoma cell lines are MGMT, HIC1, CDH1, p16 and p15. (10-11). So far, the only gene whose methylation is associated with a worse prognosis is RASSF1A (12).

Natural History

The disease is most often presented by pain and palpable swelling of the region affected by the tumor. The primary localization of Ewing sarcoma is most often on the bones of the pelvis and then in the region of the ribs, spine and long bones of the extremities such as the tibia and the fibula (4). In about a quarter of patients there is limited mobility of the extremities (13). In the case of localization in the chest area or pelvic localization that accompanies intracavitary tumor growth, it may take a long time for the first symptoms to appear (5). If it is a primary tumor, or if metastatic lesions are localized in the spinal region, in addition to pain, paresthesias may also occur if the tumor compresses the nerve roots (14). As Ewing's sarcoma occurs in adolescence, the pain caused by the tumor is often attributed to "growing pains" which prolongs the time from symptom onset to diagnosis. The time to diagnosis (TtD) in Ewing's sarcoma is 3-6 months and it is the longest TtD in the population of pediatric tumors (15).

Ewing's sarcoma most often metastasizes hematogenously to the lungs and bones, while lymphogenic spread and the affection of regional lymphatics are rare. About 30% of patients have metastatic disease at initial diagnosis (3).

Diagnostics

The first and most common diagnostic method is radiography of the affected region. A radiograph can show tumor osteolysis of bone (aggressive bone osteolysis), lifting of the periosteum by the tumor (Codman's triangle) as well as the extension of calcified spicules into the soft tissue.

The gold standard in diagnostics is magnetic resonance imaging (MR) of the primarily affected region, which must be performed before the biopsy of the tumor and obtaining a pathohistological diagnosis. MR examination enables precise determination of the size of the initial tumor, which is one of the most important prognostic parameters and is necessary in case of later planning of radiotherapy. It is necessary to include the entire bone in the examination due to the possible presence of metastases in the affected bone, which can occur in 14% of cases (16). The tumor shows a signal intensity that is hypointense on T1W sequences, and hyperintense on T2W sequences, in 96% of cases the presence of an extraosseous component of the tumor is characteristic, which shows a significant enhancement of the post-contrast signal enhancement (17).

In order to complete the staging of the disease, it is necessary to perform a computerised tomography (CT) of the thorax and scintigraphy of the skeleton in order to detect possible metastases in the lungs and bones.

Positron emission tomography (PET CT) with Fluorine F 18-fludoxyglucose (18F-FDG PET) is an optional modality for determining disease stage, which has shown high sensitivity and specificity for ES. This method has an increasing role in the detection of skeletal metastases, but due to its poorer resolution, it has a lower sensitivity compared to chest CT in the case of lung metastases (5).

Standard diagnostic methods include bone marrow aspiration and biopsy.

Prognostic parameters and prognostic groups

The most significant prognostic parameter is the presence of metastatic changes at diagnosis. In patients with metastatic disease, the five-year survival rate is less than

30%. An exception are the patients with isolated metastases in the lungs, whose five-year survival is about 50% (18). In the case of localized disease, a favorable prognostic factor is primary localization on the extremity, tumor volume less than 100ml (or in some works below 200ml), and age below 15 years at diagnosis (4). Numerous molecular parameters such as alterations of P53, p16, as well as the presence of vascular endothelial growth factor (VEGF) and CCN3 proteins are associated with an unfavorable prognosis (19-21).

The grouping of the aforementioned prognostic factors is very important for determining the therapy. According to the Euro Ewing protocol, after the sixth cycle of induction chemotherapy, patients are grouped into three therapeutic groups (R1, R2 and R3). In the case when after induction chemotherapy and after surgery, patients have a good histopathological response to chemotherapy and in the case when the tumor volume is below 200 ml, patients are classified in the R1 group. Patients who have a poor histopathological response to chemotherapy, a tumor volume of 200 ml or the presence of lung metastases belong to group R2. Group R3 includes patients who initially had metastatic disease (e.g metastases in the bones and bone marrow). Stratification into the mentioned groups enables adequate prescribing of adjuvant therapy. (23).

TREATMENT OF EWING'S SARCOMA OF BONE

A modern approach to the treatment of Ewing's sarcoma, both localized and metastatic, involves the use of a multimodal approach that includes the use of chemotherapy, surgical treatment and/or the use of radiotherapy. Using modern therapeutic protocols, five-year survival for patients with localized disease is 60% - 68%, while for patients with metastatic disease, five-year survival is still unsatisfactory and is around 17%. (5.3)

Ewing's sarcoma is a systemic disease, and the treatment according to protocols begins with induction chemotherapy, followed by local treatment. The use of induction therapy significantly prolongs the survival time of patients with a localized tumor (22). Also, given that the tumor volume is reduced, optimization of local treatment is possible: the possibility of total resection is improved, and in case of radiotherapy, it leads to a reduction of the radiation volume, which reduces the toxicity of the therapy.

In Europe, in case of a localized tumor, the Euro Ewing protocol is most often applied, which involves the application of induction polychemotherapy with six cycles of vincristine, ifosfamide, doxorubicin and etoposide (VIDE regimen). After four cycles of therapy, the therapeutic response is evaluated and a decision is made about local treatment, which can be in the form of surgical treatment, radiotherapy or a combination of these two modalities. After the local treatment, treatment continues with consolidation chemotherapy (seven cycles of chemotherapy according to the vincristine, dactinomycin, ifofosfamide/cyclophosphamide regimen). (23)

Planning optimal local therapy requires a multidisciplinary approach that involves the participation of experts from these fields. Surgical treatment is carried out with the aim of wide resection of the tumor with confirmation of negative margins of the tumor borders and with acceptable morbidity. If it is not possible to achieve this goal, surgical resection can be marginal or intralesional, or even radical in the form of amputation.

In the case of a metastatic tumor with the presence of lung metastases, the Euro Ewing protocol involves the application of induction therapy according to the VIDE protocol with radiotherapy of the lungs and the primary site of the disease and then consolidation chemotherapy according to the vincristine, dactinomycin ifofosfamide protocol (VAI). An alternative option is high-dose chemotherapy with busulfan and melphalan with autologous blood stem cell transplantation. (23).

RADIOTHERAPY IN THE TREATMENT OF EWING'S SARCOMA

Ewing's sarcoma belongs to the group of radiosensitive tumors, so radiotherapy plays a significant role in its treatment and can be applied in the definitive, preoperative, postoperative and palliative approach.

Definitive radiotherapy

Definitive radiotherapy involves the application of radiotherapy as the only type of local therapy when surgical treatment is not possible. These are most often patients with large tumors that are localized in places unfavorable for adequate surgery, such as tumors on the spinal vertebrae or the pelvis.

When planning radiation therapy, it is important to define the following target volumes: the tumor volume (Gross Tumor Volume - GTV) which includes the tumor visible on CT or MR imaging, the clinical target volume (Clinical Target Volume - CTV) which includes the zone of probable microscopic spread diseases around the GTV, and the planned target volume (Planning Target Volume - PTV) by contouring the margin around the CTV, which, with its width, includes possible inaccuracies in repositioning the patient during the performance of fractionated radiation.

Tumor volume (GTV) is determined based on the initial disease (before induction chemotherapy). In patients who have a tumor that initially protrudes into the chest or abdomen ("pushing" the lung parenchyma and bowel), and is reduced after administration of induction chemotherapy, the GTV is modified to reduce lung or bowel irradiation. CTV includes all possible places of microscopic extension of the disease (scar, biopsy tracks) and is mainly formed by the expansion of GTV by 1.5cm-

2cm radially (which depends on the anatomical localization of the tumor). The CTV must respect anatomical boundaries such as fascial barriers and bone. The PTV is defined by the margin around the CTV. Depending on the localization and immobilization of the patient, it is 0.5 cm to 1 cm. (40).

The dose applied in case of macroscopic disease is from 55.8Gy to 60Gy in daily fractions of 1.8Gy/2Gy (24). If a dose of less than 40Gy is used, local control is worse even for lesions that are below 8cm (25). According to the current EuroEwing protocol, the dose for defintive radiotherapy is 54 Gy with the possibility of a "boost" dose of 5.4 Gy (40).

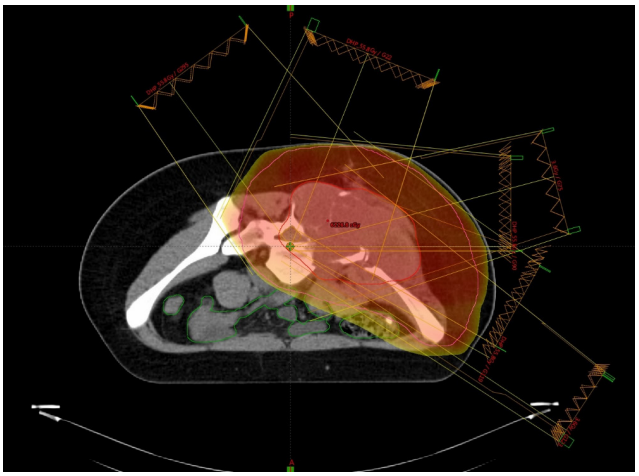

Figure 1. Definitive radiotherapy of a pelvic tumor (Institute for oncology and radiology of Serbia)

Postoperative radiotherapy

Postoperative (adjuvant) radiotherapy involves the application of radiotherapy after surgical treatment in patients with residual microscopic disease, inadequate margins or in patients who have a poor histopathological response to preoperative chemotherapy, i.e. have viable tumor cells >10%. It must be performed in cases of intralesional surgery.

Postoperative radiotherapy improves local control after surgical treatment (26). It is particularly effective in case of marginal or intralesional surgical resection (frequency of local recurrence 5% with and 12% without radiotherapy) (27). In case of wide resection but poor histological response to induction chemotherapy, the frequency of local recurrence is 12% without and 6% with adjuvant radiotherapy (28). The observational analysis of the EURO EWING group study showed (median follow-up was 6 years) that the frequency of local recurrence was 11.9%. It has also been shown that the addition of radiotherapy significantly reduces the frequency of recurrence compared to surgical treatment alone. Of all the groups, the greatest benefit in reducing local recurrence was experienced by patients who had a tumor volume of less than 200 ml and a good response to induction chemotherapy (29).

When planning postoperative radiation therapy, by definition, there is no GTV, but it is useful to delineate the preoperative GTV based on preoperative/prechemotherapy diagnostics in order to facilitate the formation of the CTV. Primarily, on the basis of the preoperative GTV, CTV1 is formed, which should include all places of potential microscopic spread, including prostheses, drainage lines, and the surgical scar. Depending on the anatomical localization, CTV1 is formed as GTV + 1.5cm to 2cm radially. Anatomical barriers to tumor spread must be taken into account. In case when the inclusion of the entire surgical scar implies the formation of a large radiation volume that will cause significant morbidity, only a part of the scar can be included. The second part of radiation therapy includes CTV2, which is formed by the expansion of the GTV by 1-2 cm (depending on the anatomical localization). The formation of PTV is equal to the formation in the planning of preoperative and definitive radiotherapy.

Adequate immobilization, which enables adequate reproducibility of the therapeutic position, is extremely important for extremity tumors. The CTV includes 2 cm from the GTV of the tumor in the bone and another 2 cm craniocaudal to the pre-chemotherapy extraosseous tumor mass. It is preferable to spare the joints and epiphyseal plates. It is also necessary to spare part of the circumference of the entire extremity in order to preserve adequate lymphatic drainage and reduce the incidence of lymphedema. It is considered necessary to preserve at least 10% of the limb circumference on each axial section of the therapeutic CT.

In tumors of the cervical spine and skull, GTV - CTV margins can be below 1.5 cm and can be corrected based on anatomical sections and to spare critical structures such as the spinal cord or optic chiasm.

Pelvic tumors often initially have a large volume that protrudes into the pelvic and abdominal cavity. Often, after induction chemotherapy, the tumor shrinks and normal tissues such as the intestines return to their normal position. The CTV needs to be adjusted so that the intrapelvic and intraabdominal organs are not unnecessarily in the air field.

In chest wall tumors, the formation of the CTV is similar to the formation of the CTV in case of pelvic tumors (post-chemotherapy tumor reduction, correction of the CTV to avoid unnecessary irradiation of the heart and lungs.). In the event that the tumor involves the pleura with the presence of pleural effusion, it is necessary to irradiate the entire hemithorax with a "boost" to the primary site of the disease.

In case of spinal and paraspinal tumors, it is necessary that the GTV includes the entire tumor as well as the extraosseous extension. CTV should include the vertebra above and the vertebra below the involved vertebra as well as the surgical scar and surgical endoprostheses (in case of previous surgical intervention). (23).

According to the EuroEwing 2012 protocol, the dose for postoperative radiotherapy is 54 Gy, where 45 Gy is

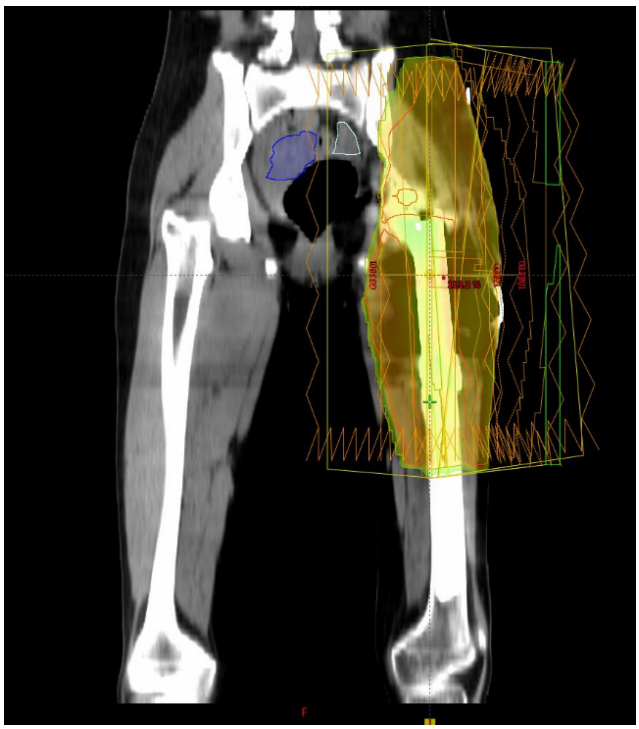

Figure 2. Postoperative radiotherapy of Ewing's sarcoma of the extremity (Institute for oncology and radiology of Serbia)

prescribed for a larger radiation volume with an additional "boost" dose of 9 Gy for a reduced radiation volume (40).

Preoperative radiotherapy

Preoperative radiotherapy is indicated in cases where tumor progression occurs during induction therapy, as well as when adequate reduction of the tumor do not occur after induction therapy and positive margins are expected during surgical treatment.

Preoperative (non-adjuvant) radiotherapy was first incorporated into the EISECC 92 protocol with the idea of reducing iatrogenic tumor dissemination during surgery and in cases where positive or "narrow" (<1mm) resection margins are expected after chemotherapy (30). The use of non-adjuvant radiotherapy has no effect on the event-free survival, while local control is satisfactory and amounts to 6% after five years. (30).

The delineation of target volumes when planning neoadjuvant therapy is identical to the delineation of volumes for definitive radiotherapy.

According to the current EURO EWING protocol, the dose for preoperative radiotherapy is 50.4 Gy in 28 radiation fractions. In case of an extremely large radiation volume that endangers the surrounding normal organs and tissues, the dose can be reduced to 45 Gy in 25 fractions (40.)

Palliative radiation therapy

Palliative radiation therapy in Ewing's sarcoma plays a significant role in the treatment of lung, bone and endocranial metastases, as well as in rapidly progressing primary tumors.

In case of lung metastases, whole lung irradiation (WLI) is used. For patients with isolated lung metastases, the analysis of the EISECC study showed the benefit of whole lung radiotherapy (four-year EFS was 40%) (31). The clinical target volume includes the pleural cavity of the surfaces of both lungs. The PTV margin is 1 cm and it is preferable to use respiratory gating. (36). According to the current EuroEwing protocol, the dose used during WLI is 15Gy in 10 fractions for patients below 14 years of age, while the dose for patients aged 14 years and older is 18Gy in 12 fractions (36).

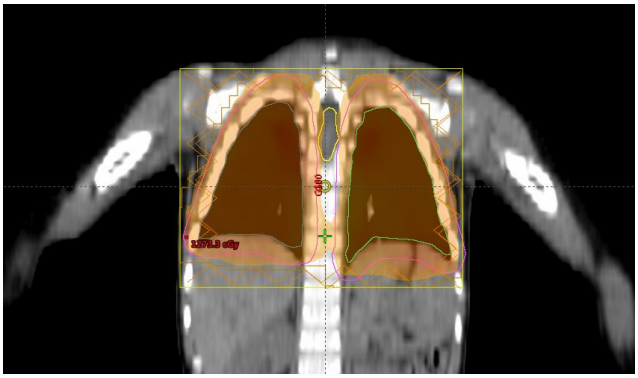

Figure 3. Whole lung radiotherapy (Institute for oncology and radiology of Serbia)

In the presence of extrapulmonary metastases, it is important to undergo a local treatment of both the primary tumor and metastases (the three-year disease-free period in case of local treatment of metastases and primary tumor is 39%, while in case of local treatment of only the primary tumor or only metastases is 17%)(32). When it comes to bone metastases, definitive radiation therapy (radical dose) can be applied to all bone metastases and the primary tumor simultaneously. When delineating bone metastases, it is important to create a smaller radiation volume so that less than 50% of the bone marrow is included in the total radiation volume. Irradiation of more than 50% of the bone marrow can lead to a significant myelosuppressive effect that may preclude the use of systemic therapy. In case of numerous bone metastases that cannot be irradiated at the same time as the primary lesion, the radiotherapy of the metastases is carried out after the radiotherapy of the primary tumor. Nowadays, stereotactic radiotherapy is increasingly used in the treatment of bone metastases. With this technique, a dose of 35-40 Gy in 5 fractions can be administered to bone metastases smaller than 5 cm (33).

In the case of the presence of endocranial metastases, stereotaxic radiotherapy is recommended if there are adequate indications. In other cases, irradiation of the entire endocranium (Whole Brain Radiotherapy - WBRT) is carried out with a dose of 30 Gy in 15 fractions (23).

If there is a rapidly progressive tumor, it is possible to perform palliative radiation therapy with TD 36Gy in 12 sessions (23).

RADIOTHERAPY TECHNIQUES IN THE TREATMENT OF EWING SARCOMA

Technological advances in radiotherapy (modern linear accelerators with multi-lamellar collimators), improved immobilization systems, as well as new knowledge in the fields of radiobiology and physics have enabled the application of conformal techniques, which involve the modulation of beams so that the planned target volume and dose distribution correspond to the irregular shape of the tumor. The high degree of conformality also allows reduced high-dose irradiation of the surrounding healthy tissues. (32). Conformal techniques include: three-dimensional conformal radiotherapy (3D CRT), intensity modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT) (34).

IMRT is a form of modern 3D conformal radiotherapy that enables high conformation of the radiation volume (especially concave tumor volumes that are near the organs at risk). Radiation volumes of a complex shape can be achieved by dividing the beam into smaller beams that can have different intensities and treat small volumes within the target volume, which enables the application of a higher radiation dose to the target volume. In addition to the above, the presence of multi-lamellar collimators allows shaping the beam to the shape of the tumor (35).

A study by Mounessi et al. comparing 3D CRT and IMRT technique in the treatment of pelvic tumor localization showed that IMRT has significant advantages over 3D CRT. Primarily, the IMRT technique makes it possible to achieve a better conformation of the radiation volume. Also, by using the IMRT technique, better protection of the small intestine is achieved (the volume of the small intestine that receives doses from 2Gy to 60Gy is lower when using the IMRT technique). In case of the bladder and rectum, there are no differences in the mean dose that these organs receive, but the volumes that receive 30Gy, 40Gy, 45Gy and 50Gy are smaller in case of the IMRT technique (36).

The VMAT technique also represents a modern form of conformal radiotherapy, which owes its high conformality to the continuous delivery of the dose, which is achieved by arcing the head of the apparatus, as well as to the continuous corrections of the beam using a multi-lamellar collimator located in the head of the apparatus. Using the VMAT technique, it is possible to achieve even a higher degree of conformality than with the IMRT technique, but at the cost of irradiating a large volume of surrounding healthy tissue with low doses.

Radiotherapy of Ewing's sarcoma is challenging because the pediatric population has a higher sensitivity and lower tolerance to radiation therapy compared to adults. The application of proton radiotherapy in the treatment of Ewing's sarcoma is being increasingly examined. In case of Ewing's sarcoma of the spinal column, proton therapy has an advantage over IMRT in terms of an improved index of conformality and homogeneity, significantly lower doses to the lungs, heart and liver, as well as reduced integral doses to the whole body (37-38).

ADVERSE EFFECTS OF RADIOTHERAPY

Unwanted effects of radiotherapy can be divided into early and late.

Early side effects of radiotherapy occur during radiation therapy and can last up to several weeks upon the end of radiotherapy treatment. These side effects are usually reversible. They are most often manifested by the presence of skin changes in the form of radiodermatitis (erythema of the skin, dry or wet desquamation), as well as by a myelosuppressive effect, which is most often manifested by leukopenia and neutropenia. The degree of myelosuppressive effect depends on the volume of active bone marrow that is included in the radiation volume.

Late complications occur in a period of time from several months to several years after the treatment and are irreversible in their nature. The severity and type of late complications depend on the localization of the irradiated region as well as the radiation dose.

About 41% of patients treated for Ewing's sarcoma have no late complications from combined therapy after 5 years (41).

The most common late complications of radiation therapy are abnormalities in bone growth, fracture of the irradiated bone, chronic lymphedema, chronic pain, fibrosis of the treated extremity, and limited range of motion.

A retrospective study investigating long-term treatment complications in a population of 101 patients showed that the most common chronic complications are related to the musculoskeletal system. Most of the mentioned patients were treated with multimodal therapy. 12 patients had asymmetry of bone growth, 12 patients had shortening of the length of the treated limb, 2 patients had chronic lymphedema, 3 patients reported the presence of chronic pain. Less frequent complications were problems with dentition and speech in patients irradiated to the head and neck region (42). Considering the fact that irradiation of epiphyseal plates stops bone growth, the most common late skeletal complications of radiotherapy represent abnormalities in the growth of the treated bone. The degree of bone growth abnormalities depends on the localization of the irradiated epiphyseal plate, the patient's age and the total radiotherapy dose (5).

Bone fractures can be a late complication of Ewing's sarcoma. Based on a retrospective study of 93 patients, it was shown that the most common fracture site is the proximal femur. From the mentioned cohort, 9 patients had a pathological fracture after radiotherapy. Of those 9 patients, in 3 patients the cause of the fracture was active recurrent disease or secondary malignancy. All patients

who had a bone fracture after radiotherapy that was not related to recurrent disease or secondary malignancy were irradiated with doses higher than 40Gy (43).

A significant late complication of radiotherapy is the appearance of tumors induced by radiotherapy. These tumors appear within the limits of the radiation volume after a latent period of more than four years. Also, the histopathological type of the tumor differs from the type of the primary tumor (44).

It is considered that the pediatric population has a tenfold risk for the development of induced malignancy than the adult population. Considering the long-term survival of patients treated for Ewing's sarcoma, frequent check-ups are necessary and should be carried out over a longer period of time (45).

CONCLUSION

Radiotherapy has an important role in the treatment of Ewing's sarcoma of the bone. The biggest benefit of radiotherapy is the improvement of local disease control both in the postoperative and in the definitive approach. Even in metastatic disease, radiation therapy plays a significant role, especially in the treatment of lung metastases. The application of modern conformal radiotherapy techniques enables a better conformation of the beam volume to the shape of the tumor and a better sparing of healthy tissues, which results in a lower incidence of late complications of radiotherapy. Modern techniques also allow escalation of the dose to the primary tumor, which theoretically can lead to an even better degree of local control.

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ULOGA RADIOTERAPIJE U LEČENJU EWING SARKOMA KOSTIJU

Predrag Filipović[1], Marija Popović-Vuković[1], Marina Nikitović[1,2]

Sažetak

Ewingov sarkom (ES) predstavlja drugi najčešći primarni malignitet kostiju nakon osteosarkoma. Bolest se najčešće javlja u adolescentnom dobu, sa pikom incidencije oko četrnaeste godine. Najćešću primarnu lokalizaciju tumora predstavljaju kosti karlice a potom rebra, kičma i duge kosti ekstremiteta kao što su tibija i fibula. ES pokazuje tendenciju ka hematogenoj diseminaciji, pre svega u pluća i kosti, znatno ređe limfogeno. Jedna trećina pacijenata ima prisutne udaljene metastaze prilikom incijalne dijagnoze, zbog čega se ES smatra sistemskom bolešću.

Lečenje Ewing sarkoma se zasniva na multimodalnom pristupu koji obuhvata primenu hemioterapije, hirurgije i/ili radioterapije. Definisanje prognostičkih parametara omogućava svrstavanje pacijenata u rizične grupe prema kojima se određuje plan lečenja. Primenom savremenih terapijskih protokola petogodišnje preživljavanje za pacijente sa lokalizovanom bolešću iznosi između 60% - 68% dok je kod pacijenata sa metastatskom bolešću petogodišnje preživljavanje i dalje nezadovoljavajuće i iznosi oko 17%.

ES spada u grupu radiosenzitivnih tumora, te radioterapija ima veoma značajnu ulogu u lokalnoj kontroli bolesti, u kombinaciji sa hirurškim lečenjem ili samostalno i može se primeniti kao radikalna, preoperativna ili postoperativna zračna terapija. Takođe, zračna terapija ima ulogu u palijativnom pristupu u tretmanu plućnih metastaza i drugih metastatskih mesta.

S obzirom na to da lečenje Ewing sarkoma dovodi do dugogodišnjeg preživljavanja, neophodno je voditi računa o očekivanim neželjenim efektima terapije koje mogu umanjiti kvalitet života lečenih pacijenata.

Savremene radioterapijske tehnike kao što su trodimenzionalna konformalna zračna terapija (3D-CRT), intezitetom modulisana zračna terapija (IMRT) i volumetrijski modulisana lučna terapija (VMAT) omogućavaju preciznu isporuku propisane doze zračenja na ciljne volumene uz bolju poštedu okolnih normalnih tkiva i organa, što dovodi do niže učestalosti pojave kasnih sekvela zračne terapije i omogućava očuvanje kvaliteta života lečenih pacijenata.

Ključne reči: Ewing sarkom, radioterapija, radioterapijske tehnike

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