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Analysis of the effectiveness of teleradiotherapy with modulation of beam intensity in the extramedullary plasmacytoma of the head and neck region: A new look at inductive systemic treatment

Analiza efektywności teleradioterapii z modulacją intensywności wiązki w pozaszpikowej postaci szpiczaka w obrębie głowy i szyi – nowe spojrzenie na indukcyjne leczenie systemowe

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Introduction: Extramedullary plasmacytoma (EMP) is a very rare malignancy. EMP is highly radiosensitive. Local disease control can be obtained by administering a dose of 45–50 Gy. Relatively rarely, in less than 20% of cases, a progression of EMP to the systemic form of multiple myeloma (MM) may be observed.

Material/Methods: This paper presents a retrospective analysis of 5 patients with EMP of the head and neck region, treated in 2009–2016 with the use of intensity modulated radiation therapy (IMRT). In three of the five patients, the tumor was located in the larynx; in one case, it was located in the nasopharynx and one in the maxillary sinus. All patients were qualified for definitive radiotherapy using the IMRT technique. Two patients with EMP located in the nasopharynx and in the maxillary sinus, with tumor sizes of 10 cm and 8 cm, respectively, received induction systemic treatment to improve the anatomical conditions for the planned radiotherapy and to reduce associated radiation doses in critical organs.

Results: The effect of radiotherapy with modulation of beam intensity on local, regional and remote control in patients with EMP of the head and neck region was analyzed. The median of the dose used was 50 Gy. During the observation period of maximum 29 months (median: 26 months), all patients (100%) remained without disease recurrence and progression to the MM.

Conclusion: IMRT leads to very good results in the form of local and regional control in patients with EMP of head and neck region. Based on the discussion, which is not a direct result of the study, in cases of extensive tumor mass or close proximity of critical organs, it seems justified to use inductive systemic treatment.

Keywords: **extramedullary plasmacytoma • multiple myeloma • intensity modulated radiation therapy • solitary extramedullary plasmacytoma • solitary bone plasmacytoma**

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Abbreviations: **CT** – computed tomography, **CTV** – clinical target volume, **DFS** – disease free survival, **EMP** – extramedullary plasmacytoma, **GTV** – gross tumor volume, **Gy** – gray, **IMRT** – intensity modulated radiation therapy, **LC** – local control, **MLS** – microlaryngeal surgery, **MM** – multiple myeloma, **MMFS** – multiple myeloma free survival, **MRI** – magnetic resonance imaging, **OS** – overall survival, **PAD** – ortezomib, doxorubicin and dexamethasone, **PS** – performance status, **PTV** – planning target volume, **RECIST 1.1** –Response Evaluation Criteria In Solid Tumors Version 1.1, **RTOG/EORTC** – Radiation Therapy Oncology Group/European Organisation for Research and Treatement of Cancer scale, **SBP** – solitary bone plasmacytoma, **SEP** – solitary extramedullary plasmacytoma, **VCD** – Velcade®, Cyclophosphamide and Dexamethasone.

INTRODUCTION

An extramedullary plasmacytoma (EMP) is a very rare malignancy. Monoclonal plasma cells may occupy a single localization as a plasmacytic tumor; however, they more often reveal their presence in the form of a systemic condition with bone marrow involvement, i.e. multiple myeloma (MM) [24, 25, 26, 34]. Isolated varieties may occur as a solitary bone plasmacytoma (SBP) or a solitary extramedullary plasmacytoma (SEP) [6, 8]. The form located in soft tissues constitutes 3% of all plasma cells tumors and men suffer from it 3 times more often than women [37]. The average age of onset is 56–59 years [10]. In order to diagnose SEP, confirmation of the presence of clonal plasmocytes in the extramedullary tumor in a single tumor tissue biopsy should be obtained [10]. It is also important to exclude MM cells infiltration of soft tissues in other locations and osteolytic bone lesions [24, 25, 26, 34]. The diagnosis is confirmed by the absence of organ-specific symptoms characteristic of MM [15, 18]. For the exclusion of MM, it is necessary to confirm the absence of bone marrow involvement by monoclonal plasma cells or to reveal their infiltration in a lesser extent than 10% of all nucleated cells in the bone marrow biopsy [9, 11, 19]. There may be M protein in serum and/or urine in SEP, but in concentrations lower than in MM [11]. The most common EMP location (approximately 80% of all cases) is the head and neck region [27]. The most frequently occupied areas are the nasal cavity, paranasal sinuses and nasopharynx [12]. According to various authors, these tumors in 10–25% also occupy the regional lymphatic system [13, 20]. The most common clinical symptoms include rhinitis, epistaxis, pain, hemoptysis, dysphonia and proptosis [22, 23]. Radiation therapy is the standard treatment or, in the case of small, resectional changes, surgical treatment. In some cases, it is reasonable to combine these methods. 50–80% of patients survive for 10 years. Negative predictors are tumor size greater than 5 cm and the involvement of the lymphatic system [32]. EMP is a highly radiosensitive neoplasm. Local disease control can be obtained by administering a dose of 45–50 Gy [35]. Relatively rarely, in less than 20% of cases, progression to the systemic form of MM occurs [9]. Prognosis in EMP is the best of all forms of plasma cells neoplasms. The only negative prognostic factor is progression to MM [38].

MATERIAL AND METHODS

A retrospective analysis was carried out of patients treated for EMP of the head and neck region with the use of intensity modulated radiation therapy (IMRT) in the years 2014–2017 in the First Radiotherapy Department, St. John's Cancer Center in Lublin, Poland. The study group consisted of three men and two women between the ages of 30 and 68 (median 59). Three patients were in very good general condition (performance status PS 0) and two in good condition (PS 1) according to the

Zubrod performance scale. In three out of five patients, the neoplasm was located in the larynx, in one case in the nasopharynx and one in the maxillary sinus. In each of the three patients with the localization of EMP in the larynx hoarseness occurred and in one case a dry cough was also observed. The patient with the infiltration localized in the nasopharynx presented diplopia, eye pain, exophthalmos and paresthesia of the cheek on the tumor's site as well as a stuffy nose. Symptoms of EMP in the maxillary sinus were the following: exophthalmos on the side of the infiltration and epistaxis.

Primary sizes of EMP assessed by MRI with contrast ranged from 1.5–10 cm (median 4 cm). Patients included in the study did not present lymph node involvement in the course of the underlying disease. One of the patients with a laryngeal tumor had microlaryngeal surgery (MLS) performed three times. The first procedure was performed

Table 1. Patient characteristics

Patient	1	2	3	4	5
Gender	female	male	male	female	Male
Age	57	65	30	68	59
Location	Larynx	Nasopharynx	Maxillary sinus	Larynx	Larynx
Signs and symptoms	Hoarseness	Diplopia, eye pain, exophthalmos, paresthesia of the cheek on the tumor's site and stuffy nose	Exophthalmos on the side of the infiltration and epistaxis	Hoarseness, dry cough	Hoarseness
Surgical treatment	MLS -2009 primary treatment -2011 treatment of relapse -2015 treatment of second relapse	None	None	None	None
Radiation therapy	IMTR postoperative organ/ space site	IMTR tumor	IMTR tumor	IMTR tumor	IMTR tumor
Dose	46Gy	54Gy	50Gy	50Gy	54Gy
Outcome according to Recist 1.1 criteria	CR	CR	CR	CR	CR
Follow-up	26 months	28 months	25 months	29 months	26 months
Primary tumor size	1.5 cm	10 cm	8 cm	3 cm	4 cm
Systemic treatment before radiation therapy	None	VCD 6 cycles every 21 days; Bortezomib 1,3 mg/m2, day 1, 4, 8, 11; Cyclophosphamide 500 mg/m2 day 1; Dexamethasone 40 mg day 1, 2, 4, 5, 8, 9, 11, 12 (cycles 1–3) and day 1, 4, 8, 11 (from 4th cycle) Recist 1.1- PR	PAD 2 cycles every 21 days; Bortezomib 1,3 mg/m2, day 1, 4, 8, 11; Doxorubicin 30 mg/m2, day 4; Dexamethasone 40 mg day 1, 2, 4, 5, 8, 9, 11, 12 Recist 1.1- PR	None	None
Systemic treatment after radiation therapy	None	None	None	None	None

MLS, microlaryngeal surgery; IMRT, intensity-modulated radiotherapy; Recist 1.1, Response Evaluation Criteria In Solid Tumors Version 1.1; CR, complete remission; PR, partial remission

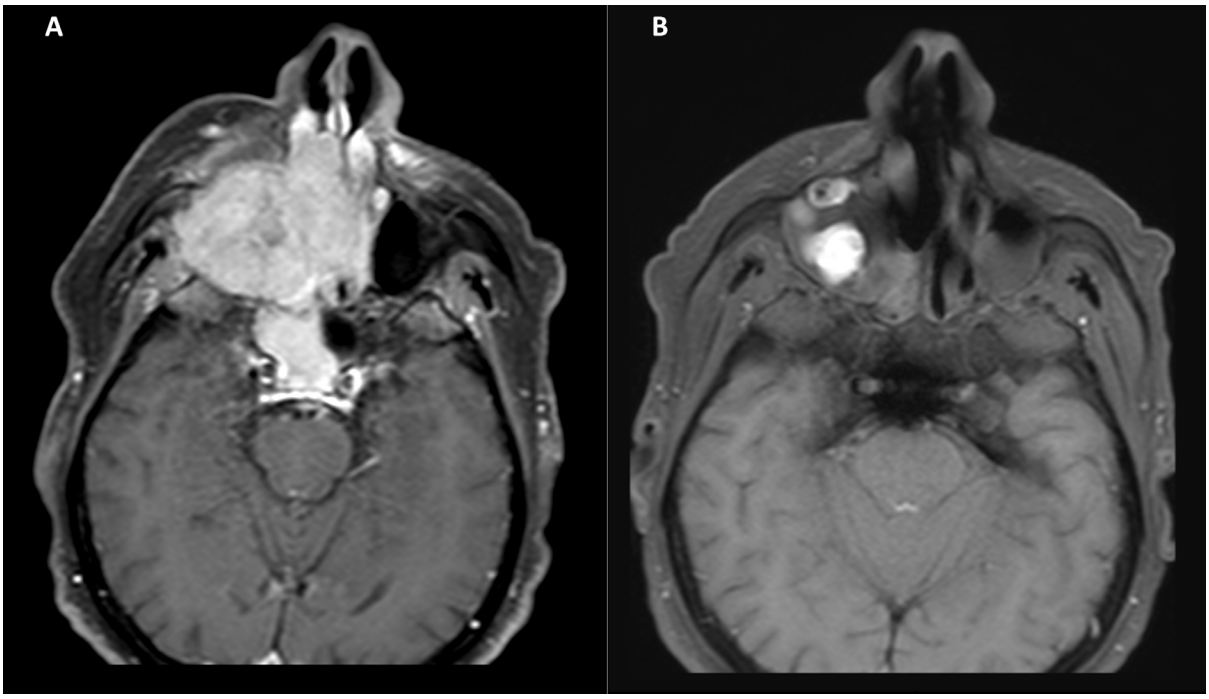

Fig. 1. MRI scan of a patient with infiltration in the maxillary sinus prior to the initiation of systemic induction treatment (1A) and after the systemic induction treatment (1B)

to remove the primary lesion and the next two due to the recurrence of the local tumor. After the last treatment, the patient was referred to radiotherapy. The other four patients were not previously operated. The detailed characteristics of the patients are presented in Table 1.

Two patients with EMP located in the nasopharynx and in the maxillary sinus, with tumor sizes of 10 cm and 8 cm, respectively, received induction systemic treatment to improve the anatomical conditions for the planned radiotherapy and to reduce associated radiation doses in critical organs. The patient with nasopharyngeal infiltration received 6 cycles of chemotherapy every 21 days according to the VCD scheme (bortezomib, cyclophosphamide and dexamethasone, Table 1). The patient with infiltration within the maxillary sinus received 2 cycles every 21 days according to the PAD scheme (bortezomib, doxorubicin and dexamethasone, Table 1). The magnetic resonance imaging (MRI) scan of this patient prior to the initiating of induction treatment is shown in Figure 1A. Figure 1B shows the same patient after the systemic treatment.

Both patients after completion of chemotherapy were qualified for radical radiotherapy using the IMRT technique, similarly to the other three patients without induction treatment.

During the planning of radiotherapy, gross tumor volume (GTV) was determined by means of a fibroscopic examination and image obtained by merging MRI with contrast with computed tomography (CT). In each case, a 2 cm margin was added to the GTV for clinical target volume (CTV). The area of CTV was reduced by natural barriers to cancer spreading, such as cartilage and bones. Next, a 5 mm radial margin was added to the CTV area to obtain planning target volume (PTV). The applied therapeutic doses ranged from 46 to 54 Gy (median 50 Gy, Table 1). Target areas and the isodose distribution of a patient with EMP located in the maxillary sinus are shown in Figure 2A and 2B.

After the end of IMRT, the following parameters were evaluated in the group of patients: disease-free survival (DFS), multiple myeloma free survival (MMFS) and local control (LC). The follow-up period ranged from 25 to 29 months after the end of IMRT (median 26 months). One month after completion of radiotherapy, patients were tested with a fibroscopic examination and laboratory tests, which were then repeated every 3 months to the 13th month after the end of IMRT, together with the MRI examination. In the second year, control tests were carried out every 4 months. The response to the treatment was assessed in MRI with contras using the Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST 1.1).

RESULTS

After induction treatment, in both cases (EMP in the nasopharynx and EMP in the maxillary sinus), partial remission (PR) of the disease in the MRI examination was obtained according to the criteria of RECIST 1.1. Four months after the end of IMRT, all 5 patients, both

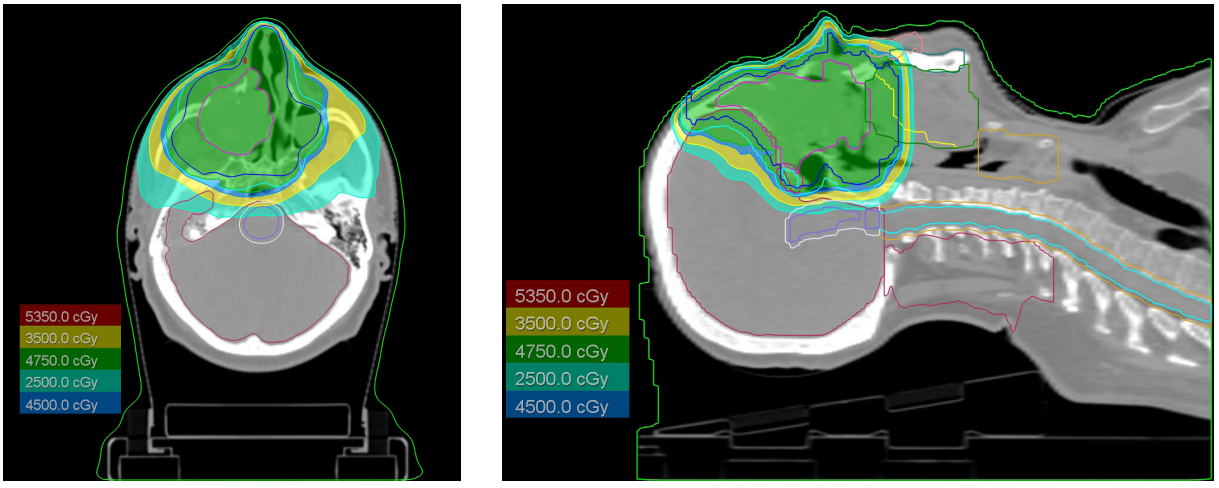

Fig. 2. Target areas and the isodose distribution of a patient with EMP located in the maxillary sinus; 2A – axial plane, 2B – mid-sagittal plane

in fiberoscopy and MRI, presented complete remission of the disease (CR) according to the criteria of RECIST 1.1. All patients are still alive and have no relapse or progression to MM (Table 1).

Radiotherapy was well tolerated. During the irradiation, two patients presented mucositis grade 2 according to the RTOG/EORTC scale (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scale), which completely resolved within 4 months after the end of radiotherapy. During the follow-up period, late side effects of IMRT were not observed.

DISCUSSION

An EMP is high radiosensitive neoplasm. LC can be achieved in 64–100% of cases. Reported radiation doses sufficient to provide LC in tumors below <5 cm range from 35–45Gy [14, 36]. However, this may not be eough to obtain satisfactory results if the tumor size is above 5 cm and when the primary site of tumor is nasopharynx. Mendenhall et al. suggested that doses higher than 40 Gy provide LC in 94% of cases. At lower doses than 40 Gy, LC was achieved only in 64% of patients [21]. Bolek et al. showed 100% LC and recommended a dose of 40 Gy using a fraction of 2 Gy [3]. The suggested final dose is in the range of 40–50 Gy; for tumors below 5 cm, it is about 40 Gy and for tumors over 5 cm it is recommended to give approximately 50 Gy [30]. In turn, reports by Skóra et al. show a 10-year LC at 90.9% with the doses of 45–70 Gy (median 56 Gy) [29]. Other analyzes suggest that in the long-term follow-up, final doses higher than 45 Gy provide a higher percentage of LC [35]. Kimberly et al. reached 100% LC using a mean dose of 50.4 Gy and also suggested doses higher than 40 Gy. These researchers also recommend including the entire nasal cavity and the paranasal sinuses in the irradiation area at this EMP location [5]. Ryohei et al. achieved a 10-year LC at 87% using doses with a median of 50 Gy. In a multicenter analysis, the authors suggested that the combination of radiotherapy and surgery brings better results in overall survival (OS) [28]. The authors of the present paper suggest the use of final doses of 46–54 Gy (median 50 Gy), using a fraction of 2 Gy, which allowed us to achieve 100% LC.

Relatively few reports refer to the use of chemotherapy in the cases of EMP, and in particular the possibilities and effects of inductive systemic treatment. The benefits of its use may be similar to those in patients with diagnosed squamous cell carcinoma of the head and neck region [16]. The results of the studies on head and neck cancers did not confirm the improvement of LC and OS; however, inductive chemotherapy in many situations is able to improve anatomical conditions, and therefore reduce tumor size and improve the possibility of better protection of critical organs during planned radiotherapy [17]. This procedure can also reduce the risk of distant metastasis.

In the case of EMP, higher chemosensitivity would be expected than in squamous cell carcinoma, so the use of induction systemic treatment could improve LC [2]. The use of such treatment could improve the OS and enable the reduction of the final doses of radiotherapy, leading to better protection of healthy tissues. The topic of future research should focus on setting the optimal inductive treatment regimen as well as on assessing the number of cycles required for administration prior to radiotherapy. Improvement of the MMFS and OS using adjuvant chemotherapy based on melphalan and prednisolone was demonstrated in a randomized trial of Aviles et al. [1]. The trend towards MMFS improvement was also observed by Suh et al. in a similar study [33]. According to the guidelines published by Soutar et al. in patients with tumors greater than 5 cm, as well as in cases of incomplete response to radiotherapy, chemotherapy should be considered [31]. In other reports, the authors did not recommend the administration of

chemotherapy as this may result in the formation of resistant clones and limit the possibility of subsequent therapy [6]. However, this data was published in 2000 and it presented the influence of older system treatment regimens. Currently, better results in the treatment of MM are achieved with newer regimens using bortezomib and thalidomide, which should suggest the use of these drugs in daily practice [4, 7, 15, 31]. It should also be remembered that there is an increased risk of secondary tumors following the use of melphalan-based chemotherapy [29]. In one of the patients analyzed by our group, the use of only 2 cycles of PAD treatment allowed us to reduce the tumor size by 60%, which suggests that the total number of cycles required for administration in induction therapy may be small. The selection of an appropriate schedule and the optimal number of cycles, as well as finding predictors of response to chemotherapy should be a stage of subsequent tests in patients with EMP. The key period from the end of treatment is the period of two years, in which recurrence and progression to the systemic form (MM) usually occurs [5].

In conclusion, radiotherapy with doses of 46–54 Gy resulted in excellent results in the treatment of patients with EMP we examined, as evidenced by the lack of recurrence and progression during the two-year follow-up period. The optimal dose of radiotherapy in SEP of the head and neck region is becoming more understood. Based on the discussion, which is not a direct result of the study, in cases of extensive tumor mass or close proximity of critical organs, it seems justified to use inductive systemic treatment.

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