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CURRENT TOPIC / АКТУЕЛНА ТЕМА

Radiotherapy and COVID-19 pandemic – a review of the current recommendations

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SUMMARY
Cancer patients are at high risk for developing severe symptoms with a high mortality rate due to infection of COVID-19. Radiation therapy is one of the main treatment modalities of central nervous system tumors and lung cancer. Radiotherapy is often delivered in a number of fractions, which implies many visits to the radiotherapy center and thus possibly more exposure to the COVID-19. The convenient compromise between the exposure of the patients to the SARS-CoV-2 virus and the optimal treatment is questionable. The most used measures in radiotherapy centers are classification of patients into priority groups and frequent use of hypofractionation. From the beginning of the COVID-19 outbreak, only a few expert group consensuses of radiotherapy treatment are published. In this paper we briefly review available practical recommendations of the expert groups for radiation therapy and oncology as well as the expert opinions for radiotherapy of the central nervous system tumors and lung cancer during the COVID-19 pandemic.
Keywords: COVID-19; radiotherapy; brain tumors; lung cancer

INTRODUCTION

A novel RNA virus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first described in Wuhan City, Hubei Province, China in December 2019 [1]. Coronavirus disease 2019 (COVID-19) pandemic has affected all the aspects of the public health, but also treatment processes, as well as the treatment of cancer patients [2].

Radiation therapy (RT) firmly stands as one of the most used modality of cancer treatment since the discovery of the X-rays and radium. External beam radiation therapy (EBRT) is used in 52.3% cancer patient [3].

The important question in patients with aggressive cancers and short overall survival is how and whether to make a compromise between the treatment and the reduced exposure to COVID-19.

The most used measures in RT centers are classification of patients into urgency groups and treatment with hypofractionation schedules [2]. Hypofractionation schedules provide a reduced number of visits to the RT centers and thus reduce exposure to the virus [4].

To date, there are a few published guidelines and RT schemes for cancer patients in the era of the COVID-19 pandemic. In this paper we are primarily focused on brain tumors and lung cancer RT treatment, with a critical review of the guidelines.

RADIATION THERAPY OF BRAIN TUMORS IN THE ERA OF COVID-19

Brain tumors and nervous system tumors make up 2.5% of cancer deaths [5]. The last revised classification of brain tumors was introduced in 2016 by the World Health Organization (WHO) [6]. RT is often one of the key modalities of the treatment of brain tumors (Figure 1).

European Society for Medical Oncology (ESMO) divided priorities for RT during COVID-19 pandemic into high, medium, and low priority [7]. ESMO high priority group for RT

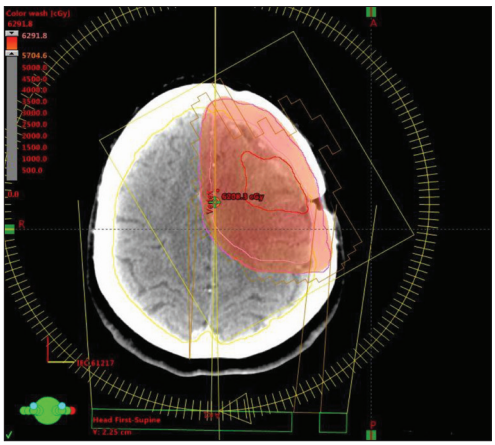

Figure 1. Example of postoperative radiotherapy plan in a patient with glioblastoma planned with volumetric modulated arc therapy technique and standard fractionation scheme treated at the Institute for Oncology and Radiology of Serbia during the pandemic of COVID-19; the dose prescribed to the planning target volume is 60 Gy; planning target volume (purple contour and color wash) is encompassed by the 95% isodose; the volumetric modulated arc therapy field arrangements are represented with yellow arcs

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includes newly diagnosed glioblastoma, isocitrate dehydrogenase (IDH) wild-type, the lower WHO grade gliomas, IDH-mutant with relevant clinical manifestations, as well as the adult medulloblastoma [7].

Standard radiation scheme for younger or fit patients with glioblastoma is 60 Gy in 2 Gy daily fractions with concomitant temozolomide (TMZ) [8]. Others with poor performance status (PS) and older than 70 years are suitable for hypofractionation with 40 Gy in 15 daily fractions as well as 34 Gy in 10 fractions [8].

In the literature, the data of the overall survival (OS) among elderly patients who were treated with standard and hypofractionated RT are different. Mak et al. [9] found that patients treated with hypofractionation RT had poorer OS than others with standard course RT. In contrast, Roa et al. [10] found no differences in OS among the groups. The addition of the oral TMZ to hypofractionation RT of glioblastoma may improve survival more than RT alone [11].

Recommendations of the hypofractionated schemes for older patients and patients with poor PS with glioblastoma is reasonable with or without pandemic of COVID-19. However, there is a lack of data about safety of hypofractionated regimens in younger patients with good PS. A Meta-analysis by Liao et al. [12] showed that hypofractionated RT is efficacious for patients older than 70 years, while in younger patients and others with good prognostic factors it is yet to be determined. Balakrishnan et al. [13] proposed treatment options for brain tumors during the COVID-19 pandemic. Among other authors' recommendations, for younger fit patients they recommended hypofractionated RT with 60 Gy in 20 fractions, with simultaneous integrated boost (SIB) technique and with concomitant TMZ. From a radiation oncologist's point of view, radiation with the SIB technique may produce toxicity different than with standard fractionation, which is important in young patients. However, Zhong et al. [14] reported mild acute and late toxicities in patients with glioblastoma treated with SIB intensity-modulated RT (IMRT) and TMZ.

According to ESMO, the high priority group for RT includes lower WHO grade gliomas, IDH-mutant with relevant clinical manifestations [7]. Medium priority for RT of gliomas is lower WHO grade gliomas, IDH-mutant [7]. For low grade gliomas, Balakrishnan et al. [13] suggested delaying RT or offering RT at progression. Mohile et al. [15] proposed to delay diagnostic surgeries and adjuvant therapy during the COVID-19 pandemic in stable patients and if the adjournment will not compromise further complete resection. For low-grade astrocytomas and 1p/19q co-deleted tumors, delay of all therapies in asymptomatic patients should be considered [15]. Yang et al. [16] found that patients treated with chemotherapy four weeks before the onset of COVID-19 symptoms were related to an increased risk of mortality. In general, hematological toxicities as well as the opportunistic infections are observed in patients with oral TMZ [17]. Patients with O^6-methylguanine DNA methyltransferase unmethylated promotor may have little or no benefits from oral TMZ, while there is the risk of hematological and other toxicities. Along with toxicities and the immunosuppressive condition, patients with cancer are at a greater risk for severe COVID-19 manifestations [17].

For medulloblastoma, Balakrishnan et al. [13] suggested the beginning of the treatment within 4-6 weeks after surgery with a possible start of the posterior fossa boost, followed by craniospinal RT with IMRT or volumetric modulated arc therapy (VMAT) [13]. Also, they proposed treatment for other brain tumors, mostly regarding treatment postponement or hypofractionation regimens.

Pediatric brain tumors are often different from adult brain tumors [18, 19]. In accordance with that, pediatric brain tumors will not be discussed here.

RADIATION THERAPY OF LUNG CANCER IN THE ERA OF COVID-19

Lung cancer is the main cause of cancer death in men, while in women it is breast cancer and colorectal cancer [5].

Expert groups for lung cancer RT as well as single institutions gave their opinions on susceptible changes in RT during the COVID-19 outbreak. The European Society for Radiotherapy and Oncology (ESTRO) and American Society for Radiation Oncology (ASTRO) made a consensus statement with recommendations for lung cancer radiation considering risk reduction and reduced RT administration [20].

An ESTRO-ASTRO statement presented by Guckenberger et al. [20] revealed as a strong consensus that in terms of risk reduction the curative treatment for stage III non-small cell lung cancer (NSCLC), as well as for limited stage small cell lung cancer (SCLC) and palliative NSCLC, should not be delayed. In the phase of the risk reduction, they were in consensus on the need not to change standard RT regimens in favor of more hypofractionated schemes. However, hypofractionated RT may be changed to more hypofractionated schemes in palliative NSCLC [20]. When concurrent radiochemotherapy is planned for stage III NSCLC, hypofractionated RT should not be applied [20]. Some of the expert participants of the ASTRO-ESTRO consensus who support hypofractionation in concurrent radiochemotherapy strategy for stage III NSCLC suggested RT regimens of 60–66 Gy in 22–30 fractions and 50 Gy in 20 fractions [20].

ESMO consider three groups of priority for lung cancer RT to be the high, medium, and low priority group [21]. The high priority group for RT comprises inoperable stage II-III NSCLC and limited stage SCLC in concurrent or sequential approach with chemotherapy as well as conditions suitable for palliative radiation such as spinal cord compression or superior vena cava obstruction [21].

An example of definitive RT planned during the COVID-19 pandemic for stage III NSCLC is presented in Figure 2.

Faivre-Finn et al. [22] proposed stereotactic ablative RT (SABR) for early stage NSCLC but with other specific limitations regarding the tumor size and the distance from the chest wall. Fractionation and dose schedules vary from 30–34 Gy in one fraction to 48–54 Gy in three fractions

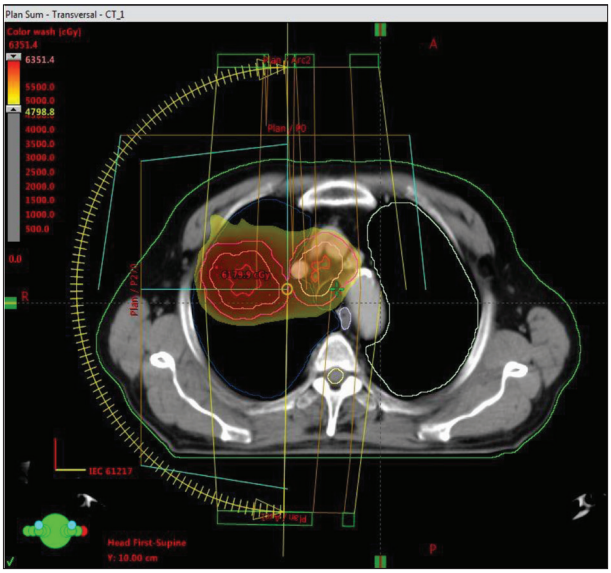

Figure 2. Example of dose distribution in volumetric modulated arc therapy plan for definitive radiotherapy in a patient with stage III non-small cell lung cancer treated at the Institute for Oncology and Radiology of Serbia during the pandemic of COVID-19; the dose prescribed to the primary planning target volume (purple contour) is 50 Gy with a sequential boost of 10 Gy to the secondary planning target volume (light pink contour) conventionally fractionated; the volumetric modulated arc therapy field arrangements are represented with yellow arcs

[22]. For central tumors, hypofractionated regimen is considered with a dose of 50–60 Gy in 15 fractions [22].

Not only for inoperable early stage NSCLC but also for operable NSCLC, stereotactic body RT (SBRT) may be a solution for the treatment in the era of COVID-19 [4]. Aside from having a better outcome with surgical resection, Moore et al. [23] concluded that definitive RT may be a feasible curative approach for stage II NSCLC.

Radiation pneumonitis (RP) is one of the toxicities that is observed in patients with lung cancer treated with RT. The mechanism of RP is correlated with treatment factors as radiation dosimetry, irradiated lung volume, radiation treatment technique, as well as with patient characteristics [24]. Considering α/β ratio of normal lung parenchyma, a question about safety of hypofractionation and therefore possible toxicity is posed. Barriger et al. [25] reported 9.4% of RP in patients treated with SBRT. Lung volume that received 20 Gy (V20) was a predictor of toxicity rather than gross tumor volume or planning tumor volume. Moreover, Jin et al. [26] reported that hypofractionation may be a better option for smaller tumor volumes. It should be kept in mind that many patients have concurrent or sequential chemotherapy or immunotherapy and their synergistic effect with radiation may increase the risk of pneumonitis. Palma et al. [27] showed that elderly patients treated with concurrent chemoradiation with carboplatin-paclitaxel chemotherapy are at the highest risk for symptomatic pneumonitis. Similarity between symptoms of RP and SARS-CoV-2 may be fatal if it remains unrecognized. Shaverdian et al. [28] suggested that patients with RP symptoms should be tested for COVID-19 infection, regarding different treatments for these conditions.

CONCLUSION

RT remains one of the key treatment options for lung cancer and central nervous system tumors in the era of the COVID-19 pandemic. To date, in June 2020, for central nervous system tumors there is no published RT expert group consensus as there is for lung cancer, with the exception of individual expert opinions. Since the postponement of RT may have detrimental impact on tumor control and OS, we suggest compliance with the recommendations of the expert consensus where available. Individual expert opinions are encouraged as guidelines where expert consensuses are not available. Moreover, in the absence of evidence-based safety about modified regimens, we can only recommend an individual approach to every patient taking into account all relevant factors. Whenever possible, standard treatment with all precaution measures for the prevention of COVID-19 should be applied.

Conflict of interest: None declared.

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Радиотерапија и пандемија *COVID*-19 – осврт на тренутне препоруке

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САЖЕТАК

Болесници оболели од рака су под великим ризиком од развијања тешке клиничке слике и високог морталитета услед инфекције *COVID*-19. Зрачна терапија је један од кључних начина лечења тумора централног нервног система и рака плућа. Радиотерапија се најчешће примењује у већем броју фракција, што захтева много долазака у радиотерапијски центар и самим тим већи ризик од изложености инфекцији *COVID*-19. Компромис између оптималног третмана рака уз смањену изложеност инфекцији *COVID*-19 је упитан. За сада, најчешће мере које се примењују у радиотерапијским центрима су класификација болесника у приоритетне групе и чешћа примена хипофракционих режима зрачења. Од почетка пандемије *COVID*-19 објављено је само неколико консензуса експертских група за радиотерапију. У овом раду смо укратко прегледали доступне практичне препоруке експертских група за зрачну терапију и онкологију за лечење тумора плућа и централног нервног система, али и појединачна експертска мишљења током трајања пандемије *COVID*-19.

Кључне речи: *COVID*-19; радиотерапија; тумори мозга; рак плућа