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

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

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

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

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 tumours and lung cancer. Radiotherapy is often delivered in a number of fractions which applies many visits to the radiotherapy center and thus possible more exposure to the COVID-19. The convenient compromise between the exposure of the patients to 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 experts group consensus of radiotherapy treatment are published. In this paper we briefly reviewed available practical recommendation of the experts groups for radiation therapy and oncology as well as the experts opinions for radiotherapy of the central nervous system tumours and lung cancer during the COVID-19 pandemic.
Keywords: COVID-19, radiotherapy, brain tumors, lung cancer

САЖЕТАК
Пацијенти оболели од рака су под значајним ризиком од развијања тешке клиничке слике и високог морталитета услед инфекције *COVID*-19. Зрачна терапија је један од кључних модалитета 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 експозиције *COVID*-19. Компромис између оптималног третмана рака уз смањену експозицију *COVID*-19 је упитан. За сада, најчешће мере које се примењују у радиотерапијским центрима су класификација пацијената 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

INTRODUCTION

A novel RNA virus named Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) first was described in Wuhan City, Hubei Province, China in December 2019 [1]. SARS-CoV-2 (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) hold firm position 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 reduction exposure to COVID-19.

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

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

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

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

European Society for Medical Oncology (ESMO) divided priorities for radiotherapy during COVID-19 pandemic into high, medium and low priority [7]. ESMO high priority group for radiotherapy include 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. found that patients treated with hypofractionation radiotherapy had worse OS than the others with standard course RT [9]. On the other side, Row et al. found that there were no difference in OS among the groups [10]. The addition of the oral TMZ to hypofractionation RT of glioblastoma may improve survival than radiotherapy 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 lack of data about safety of hypofractionated regimens in younger patients with good PS. Meta analysis by Liao et al. showed that hypofractionated radiotherapy is efficacious for patients older than 70 years, while in younger and others with good prognostic factors is yet to be seen [12]. Balakrishnan et al. proposed treatment options for brain tumours during SARS-CoV-2 pandemic [13]. Among others 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 oncologists point of view, radiation with SIB technique may produce toxicity different than with standard fractionation, which is important in young patients. Although, Zhong et al. reported mild acute and late toxicities in patients with glioblastoma treated with SIB intensity-modulated radiotherapy (IMRT) and TMZ [14].

According to ESMO, high priority group for RT include lower WHO grade gliomas, *IDH*-mutant with relevant clinical manifestations [7]. Medium priority for radiotherapy of gliomas is lower WHO grade gliomas, *IDH*-mutant [7]. For low grade gliomas, Balakrishnan et al. suggested delaying RT or offering RT at progression [13]. Mohile et al. proposed delay of the diagnostic surgery and adjuvant therapy during COVID-19 pandemic in stable patients and if the adjournment will not compromise further complete resection [15]. For low grade astrocytoma and 1p/19q co-deleted tumors, delay of all therapies in asymptomatic patients should be considered [15]. Yung et al. found that patients treated with chemotherapy 4 weeks before symptoms of the COVID-19 were related with increased risk of mortality [16]. In general, hematological toxicities as well as the opportunistic infections are observed in patients with oral TMZ [17]. Patients with O-Methylguanine-DNA methyltransferase unmethylated promotor may have little of none benefit of oral TMZ, while there is the risk of hematological and other toxicities. Along with a toxicities and imunosupressive condition, patients with cancer are in the greater risks for severe COVID-19 manifestations [17].

For medulloblastoma, Balakrishnan et al. suggested the beginning of the treatment within 4-6 weeks after surgery with possible start of the posterior fossa boost and then craniospinal radiotherapy with IMRT or Volumetric Modulated Arc Therapy (VMAT) [13]. Also, they proposed the treatment for other brain tumours mostly regarding postponement of the treatment or hypofractionation regimens [13].

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

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

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

Experts groups for lung cancer radiotherapy as well as the single institutions gave their opinions on susceptible changes in radiotherapy 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 radiotherapy appliance [20].

An ESTRO-ASTRO statement presented by Guckenberger et al. revealed as a strong consensus, that in terms of the 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 [20]. In the phase of the risk reduction, they had consensus not to change standard RT regimens in favor of more hypofractionated schemes [20]. Although, hypofractionated radiotherapy may be change to more hypofractionationed schemes in palliative NSCLC [20]. When concurrent radiochemotherapy is planned for stage III NSCLC, it should not be applied hypofractionated radiotherapy [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 as 60-66 Gy in 22-30 fractions and 50 Gy in 20 fractions [20].

ESMO consider three groups of priority for lung cancer RT as high, medium and low priority group [21]. The high priority group for RT comprise 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 radiotherapy planned during the COVID-19 pandemic for stage III NSCLC is presented in Figure 2.

Faivre-Finn et al. proposed stereotactic ablative radiotherapy (SABR) for early stage NSCLC but with other specific limitations about tumor size and depending on the distance from the chest wall [22]. Fractionation and dose schedules vary from 30-34 Gy in 1 fraction to 48-54 Gy in 3 fractions [22]. For central tumours, 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 radiotherapy (SBRT) may be a solution for the treatment in the era of COVID-19 [23]. Aside from having a better outcome with surgical resection, Moore et al. concluded that definitive RT may be a feasible curative approach for stage II NSCLC [24].

Radiation pneumonitis (RP) is one of the toxicities that is observed in patients with lung cancer treated with RT. Mechanism of RP is correlated with treatment factors as radiation dosimetry, irradiated lung volume, radiation treatment technique as well as with patients characteristics [25]. Considering α/β ratio of normal lung parenchyma, there is a question about safety of hypofractionation and therefore possible toxicity. Barriger et al. reported 9.4% of RP in patients treated with SBRT [26]. Lung volume that received 20 Gy (V20) was predictor of toxicity rather than gross tumor volume (GTV) or planning tumor volume (PTV) [26]. Moreover, Jin et al. reported that hypofractionation may be a better option for smaller tumor volume [27]. It should be born 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. showed that elderly patients treated with concurrent chemoradiation with carboplatin-paclitaxel chemotherapy are at highest risk for appearance of symptomatic pneumonitis [28]. Similarity between symptoms of RP and SARS-CoV-2 may be fatal if remains unrecognized. Shaverdian et al. suggested that patients with symptoms of RP should be tested for COVID-19 infection, regarding different treatment with these conditions [29].

CONCLUSION

Radiation therapy remains one of the key treatment option for lung cancer and central nervous system tumours in the era of 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 except of the individual expert opinions. Since the postponement of radiotherapy may have bad impact on tumour control and OS, we suggest complianse of the recommendations of the experts consensus where are available. Individuals experts opinions are encouraged as a guide where expert consensus are not available. Moreover, in the absence of evidence-based safety about modified regimens, we only can recommend an individual approach to every patient taking into account all relevant factors. Whenever is possible, standard treatment with all precaution measures for prevention of COVID-19 may be applied.

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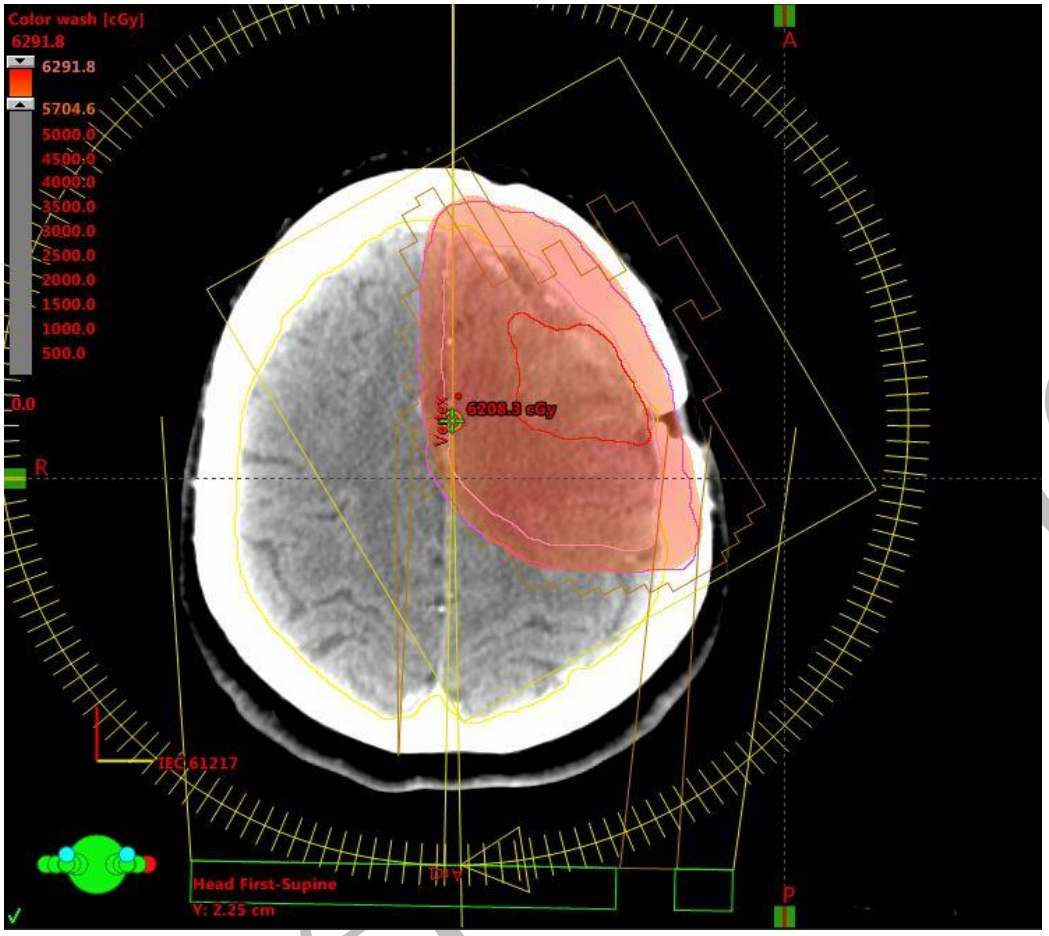

Figure 1. Example of postoperative radiotherapy plan in patient with glioblastoma planned with Volumetric Modulated Arc Therapy (VMAT) technique and standard fractionation scheme treated in the Institute for Oncology and Radiology of Serbia during the pandemic of COVID-19; the dose prescribed to the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

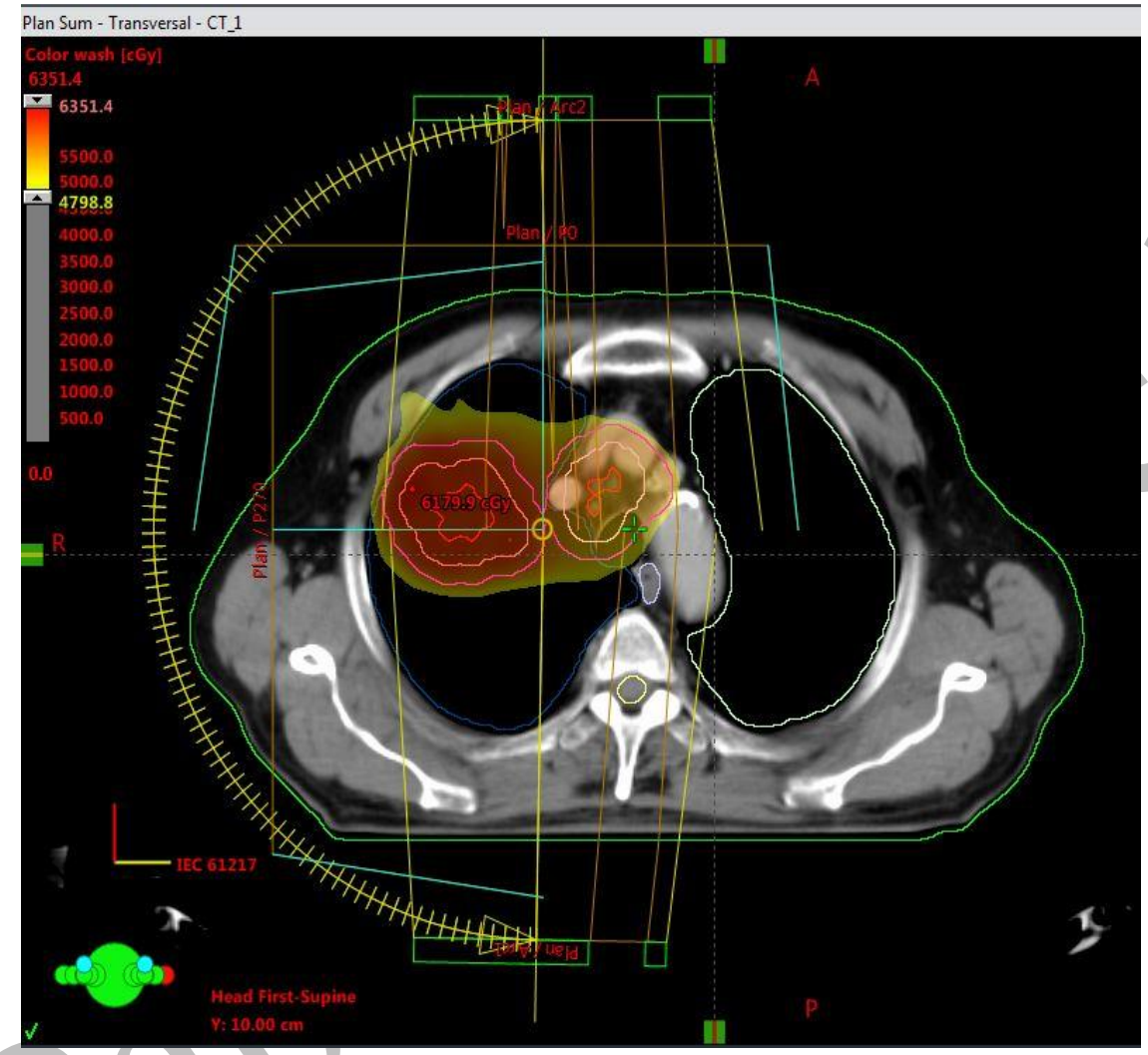

Figure 2. Example of dose distribution in Volumetric Modulated Arc Therapy (VMAT) plan for definitive radiotherapy in patient with stage III Non-small cell lung cancer (NSCLC) treated in the Institute for Oncology and Radiology of Serbia during the pandemic of COVID-19; the dose prescribed to the primary planning target volume (PTV1) (purple contour) is 50 Gy with a sequential boost of 10 Gy to the secondary planning target volume (PTV2) (light pink contour) conventionally fractionated; the VMAT field arrangements are presented with yellow arcs

