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Editorial

Lymphocytopenia and Radiotherapy Treatment Volumes in the Time of COVID-19

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Cancer patients have a higher risk of developing 2019 novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Studies have also shown that these patients have a poorer prognosis, partly because they have a higher mean age than those without cancer [1,2]. However, immune suppression caused by the tumour and its treatment is also a plausible contributory factor [1]. This has meant that oncologists are carefully weighing the benefits of treatment offered to their patients against the risks posed by COVID-19.

Apart from the use of remote visits with telephone- and video-based assessment, some of the measures advocated include not offering treatment with modest or equivocal potential gains in survival, such as adjuvant whole breast radiotherapy in patients at very low risk of developing local recurrence, and treatments with a high risk of immune suppression, for example neoadjuvant chemotherapy in muscle-invasive bladder cancer [3,4]. Deferring treatment in patients with good prognostic tumours with a low risk of progression, such as low- and intermediate-risk prostate cancer, has also been recommended [3]. When the benefit of treatment unequivocally outweighs the potential risks, protocols that have minimal hospital visits, such as hypofractionated radiotherapy regimens, and the lowest risk of immune suppression, for instance avoidance of concurrent chemotherapy with postoperative radiotherapy in head and neck cancers, are preferred [3,5].

Coronaviruses like SARS, respiratory syncytial virus and Ebola virus have been linked with lymphocytopenia as a clinical feature [6]. There is clearly a connection between RNA viral infections and lymphocytopenia, but whether it is cause or effect is unknown [6]. The effect can be profound and prolonged, with one study showing that it can take 4–5 weeks to recover [6]. A number of hypotheses exist to explain this phenomenon, including a direct infection of the lymphocytes resulting in apoptosis, lymphocyte sequestration in the lung where the pathological response is most evident or altered trafficking mediated by a cytokine storm [6]. Immune suppression may predispose to secondary infection, increasing the risk of morbidity and mortality [6]. There is also some evidence to suggest that perturbations of T cell subsets, in particular impaired activity of CD4+ T cells and overactivation and exhaustion of CD8+ T cells, eventually lead to a diminished host antiviral immunity.

SARS-CoV-2 is a positive-sense, single-stranded RNA beta-coronavirus [7]. It contains a 30 kb genome encoding viral proteins in up to 14 open reading frames. Although a number of these proteins have been identified and work is being carried out looking at druggable targets, there is still much that is unknown about the mechanism and function of all the viral proteins that are produced [7]. Lymphocytopenia has been identified as an important adverse factor in COVID-19, as well as a negative prognostic biomarker in many malignancies [8,9]. COVID-19 patients with low lymphocyte counts have more severe disease and have a high risk of death from the infection [8]. It has been shown that a lymphocyte percentage of less than 5% of white cells by the second week of illness predicted death [8]. Although it has been shown that SARS-CoV-2 infects T lymphocytes, it is unclear if replication occurs within the lymphocytes [10]. As with some of the other coronavirus infections it is not definitively known whether lymphocytopenia in COVID-19 is a result of direct destruction of lymphocytes by the virus or a consequence of the cytokine storm that occurs in severe disease [8]. Nevertheless, it could be reasonably assumed that restoration of lymphocytes and their function

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would aid the immune response against COVID-19. As such, clinicians have been cautioned on the potential detrimental impact of the use of extracorporeal membrane oxygenation, even when it is used as a salvage option in patients with severe COVID-19 disease, as it could lead to significant depletion of circulating lymphocytes [11].

Although radiotherapy serves to enhance tumour immunogenicity and alters the tumour microenvironment to favour destruction by the immune system, it is also known to deplete circulating lymphocytes, as these cells are highly sensitive to radiotherapy-induced apoptosis. Pre-treatment lymphocytopenia, which has been identified as a poor prognostic factor in many malignancies, is probably a reflection of tumour-induced immune suppression [9]. In addition, it has been shown that post-treatment lymphocytopenia is associated with poorer outcomes in lung cancer patients treated with radical radiotherapy [12]. In this study, the dose delivered to the irradiated volume (described by the parameter integral body dose) was associated with lower post-treatment lymphocyte counts in lung cancer [12]. Therefore, radiation oncologists should be mindful of the possibility of radiotherapy-induced lymphocytopenia as a risk factor for severe COVID-19 disease in patients at risk of being exposed to the infection.

Although there has been much guidance on patient selection and choice of fractionation, the definition of the optimal clinical target volume (CTV) during the pandemic has received little attention. Radiation oncologists define a high-risk CTV as the volume that comprises the radiologically visible tumour together with other tissues highly likely to contain tumour cells. This often includes tissues surrounding the visible tumour and adjacent lymph nodes. In some instances, a low-risk CTV is also defined and this volume encompasses tissues (often lymph nodes) at a lower risk of containing tumour cells than those within the high-risk CTV, but of sufficient risk to need prophylactic irradiation. Although the dose delivered to the low-risk CTV is significantly lower than that prescribed to the high-risk CTV, this results in an expanded total CTV.

With this in mind, radiation oncologists should exercise caution when defining CTVs for radiotherapy during the time of the COVID-19 pandemic. Treatment strategies that result in an expanded CTV, especially where the evidence of benefit is uncertain, should be avoided, both to keep the risk of treatment-induced lymphocytopenia as low as possible and to reduce the risk of toxicity, which could result in additional hospital visits. During these extraordinary times, it may be wise to avoid prophylactic pelvic nodal radiotherapy in localised prostate and bladder cancer, as the evidence of benefit for such a practice in these tumours is fraught with controversy [13,14]. Careful consideration should be given to prophylactic irradiation of para-aortic lymph nodes in locally advanced cervical cancer as its benefit is equivocal [15]. In head and neck cancer, where there is some evidence of efficacy with prophylactic lymph node irradiation, we advocate careful evaluation of the potential risks and benefits on a patient by patient basis [16]. We also support the recommendation against radiotherapy to the axillary lymph nodes in early breast cancer patients treated with wide local excision and sentinel lymph node biopsy and found to have one or two macrometastases [4]. There is a more compelling rationale for continuing to offer prophylactic radiotherapy to the internal mammary lymph nodes in patients with high-risk breast cancer (T4 and/or N2-3 disease), as absolute gains in disease-free survival has been shown [17]. However, we suggest carefully weighing the risks and benefits of internal mammary lymph node irradiation in patients with intermediate-risk disease (T3 and/or N1) and central or medial tumours on an individual basis.

Another novel strategy that has been proposed to combat the cytokine storm associated with COVID-19 pneumonia is low-dose radiotherapy to lungs [18]. The rationale for this approach stems from data suggesting that at doses in the range of 0.3–1 Gy, irradiation of the lungs could result in a reduced inflammation relief of life-threatening symptoms in both bacterial and viral pneumonia. The published data suggest that the absolute risk of lymphocytopenia is associated with the pre-treatment lymphocyte count as well as the irradiated volume. Even though the prescribed dose is small, this would result in a large integral dose due to the large volume of irradiation and consequently would place patients at substantial risk of developing severe post-treatment lymphocytopenia, especially in a group of patients at high risk of pre-treatment lymphocytopenia. It is beholden to all radiation oncologists to follow the principle of ALARA and to use as low a dose and volume as is reasonably possible, if at all. If studies in this space are to go ahead, then it may be better to try partial lung irradiation or even splenic irradiation, as the spleen is a reservoir for the immune cells responsible for the cytokine storm associated with acute respiratory distress syndrome. Those of us who follow events on social media will have seen much discussion about the potential role of radiation for COVID-19 pneumonia. In unprecedented times, it is tempting to reach for the stars, but we must do so from a platform of science. Caution is also welcome in these challenging times.

Very little has been published on the long-term effects of coronavirus infections on the population, especially on cell-mediated or humoral immunity. We must seize this opportunity to collect robust data where possible of the effects of COVID-19 on patterns of care and long-term outcomes for oncology patients. This way we will be prepared for the future.

Declaration of Competing Interest

The authors declare no conflict of interest.

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