

## EDITORIAL

# Radiotherapy and gynaecological cancers during the pandemic: the role of hematologic toxicity

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(Giuseppe Carlo Iorio)**Abstract**

The COVID-19 pandemic has killed more than 6.8 million people worldwide since late 2019. A hyperinflammatory condition depending on interleukin-6 (IL-6) rise and hypercytokinemia have been linked with fatality rates. This condition can lead to lymphocyte-deficiency. Lymphopenia came up as a major prognosticator of severe infection cases. Cancer therapies can induce lymphopenia due to reservoir lymphoid organ damage. The principal cause of hematologic toxicity (HT) is usually chemotherapy (ChT). Nonetheless, also radiotherapy contributes to hematologic cell lines impairment, impacting mainly on lymphocytes. Radiation-induced lymphopenia (RIL) has been linked to unfavorable outcomes in various solid tumors. In pelvic cancers, bone marrow (BM) dose-volume metrics have been related to HT occurrence, particularly Gynaecological Cancers. The present times offer an unprecedented opportunity to broadly embrace treatment strategies, as BM sparing (BMS), that avoid reservoir lymphoid organs' suppression and the potential subsequent RIL.

**Keywords**

COVID-19; Lymphopenia; Cancer care; Radiotherapy

## 1. COVID-19, lymphopenia and cancer care

The COVID-19 pandemic has killed more than 6.8 million people worldwide since late 2019 [1].

During the outbreak, accumulating evidence suggested that a subgroup of patients with severe disease developed a cytokine storm syndrome linked to an increased mortality rate [2].

This hyperinflammatory state may lead to lymphocyte deficiency through apoptosis, IL-6 and other pro-inflammatory cytokines levels rise [3, 4]. Of interest, lymphocyte death can be caused by direct lymphocytes infection by the virus. Furthermore, the virus may directly enter lymphocytes by angiotensin-converting enzyme 2 (ACE2) receptors, possibly resulting in lymphatic organs' attack [3]. Low lymphocyte count emerged as a significant predictor of gravity in COVID-19 patients [3]. Lymphopenia, indeed, has been correlated to a three-fold increase in severity of COVID-19, with a significant lower lymphocyte count observed in critical infections than in non-critical ones [4, 5].

Cancer treatments commonly lead to lymphopenia as a side effect and can influence its incidence and severity [6]. Chemotherapy (ChT) is considered the main cause of hematologic toxicity (HT) [7]. Radiotherapy (RT) has its impact on hematologic cell lines' impairment, through a well-documented and extensively described reduction of lymphocytes count [7]. Lymphocytes are notably the most

radiosensitive cells within the hematopoietic system, with only 1.5 Gy considered to be the lethal dose required to reduce the surviving fraction of lymphocytes by 50% (LD50) [8, 9]. The interplay between RT and immunomodulation has been investigated by several pre-clinical and clinical studies. Lymphocytes have a pivotal role in the anti-neoplastic immunity. Furthermore, lymphopenia has been linked to an increased risk of opportunistic infections, poorer oncologic outcomes and decreased survival in several cancer types [6, 7].

In this regard, non-negligible HT and lymphopenia rates are observed in gynaecological cancer patients undergoing combined modality treatments with RT and ChT [7].

Thus, during the present Pandemic, clinicians involved in the gynaecological cancer arena should adopt specific treatment strategies to pursue the cure and simultaneously limit the COVID infection- risk.

## 2. Radiotherapy and lymphopenia, the biological underpinnings

Ionizing radiation has a crucial role in immune-regulation and cancer progression, as it upregulates Fas ligand (FasL), a ligand involved in the lymphocyte's apoptosis pathway. FasL upregulation has been linked to disease progression in solid tumors [10–12]. Furthermore, increased FasL level within the bone marrow stem-cells has been observed to impair lymphocyte function [10, 13]. RT can also lead to increased IL-6 serum levels, which can decrease lymphocytes levels [14–

16]. IL-6 also plays a role in tumorigenesis, and can favor tumor progression. Indeed, the Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) signaling hyperactivation is observed in different types of tumors and it is associated with worse outcomes [14–18]. An aberrant IL-6/JAK/STAT3 signaling pathway activation has been observed to influence tumor growth by either driving tumor cell proliferation or suppressing the antitumor response [17]. In addition, STAT3 signaling hyperactivation has been related to both ChT and RT resistance [19]. Thus, radiation-induced FasL upregulation and the pro-inflammatory cytokines increase, through lymphopenia, may enhance cancer progression. Therefore, targeting IL-6 may help enhancing tumor control [14–16]. Tocilizumab, a monoclonal antibody blocking IL-6 activity, may theoretically be efficient in limiting tumor progression [17]. Thereupon, some authors are currently investigating the potential benefit of a synergic effect of tocilizumab in addition to RT on improving treatment response and patients' survival in different solid cancers treatment scenarios [19–22].

### 3. Radiation-induced lymphopenia in gynaecological malignancies

Radiation induced lymphopenia (RIL) has been observed to worsen prognosis in different solid tumors, including non-small cell lung cancer (NSCLC), glioblastoma, pancreatic, esophageal, head and neck and pelvic cancers [7, 23].

The risk of RIL has been associated with unintentional dose to circulating immune cells (EDRIC—immune cells circulating in heart, lung, blood vessels, lymphatic system and blood reservoirs), particularly in thoracic cancers [7]. In the pelvic cancers scenario, incidental bone marrow (BM) irradiation has been identified as a RIL trigger due to myelosuppression [7].

In this regard, BM dose-volume metrics have been related to the risk of developing HT, especially in gynaecological cancer patients [7].

BM is only a part of the pelvic reservoir lymphoid organs [6]. However, radiation-induced pelvic BM suppression is a recognized predictor of leukopenia and lymphopenia [7].

This can be explained considering that almost half of the active BM (aBM) is estimated to be in the pelvic and lumbar vertebrae (in the adult population) [7].

Additionally, it is necessary to consider that the other pelvic reservoir lymphoid organs, such as lymph nodes, pelvic blood vessels and the dense-associated lymphoid tissue within the gut mucosa, are difficult to spare [6].

Flourishing literature is available regarding BM-related toxicity in gynaecological cancers, and data from cervical cancer suggest that limiting BM volumes receiving low radiation doses is essential to decrease/avoid grade 2–3 HT (*e.g.*, pelvic BM V10 <90–95% and V20 <76–80%) [7].

In a series of patients with cervical cancer undergoing ChT-RT, Albuquerque *et al.* [24] showed an increased risk of developing grade 2 or greater HT with the whole-pelvic BM (WPBM) V20 >80%. Three-dimensional conformal RT (3D-CRT) was employed in this series, and the authors advocated for pelvic intensity modulated RT (IMRT) as a strategy to decrease unintended BM radiation exposure [24].

RTOG-0418 included also endometrial cancers among oth-

ers. In this study, BM V40 and median BM dose have been linked to higher rates of grade 2 or worse HT [25].

Data from another series, analyzing data from 83 cervical cancer patients, showed a significant decrease in HT, mainly grade 3 or worse neutropenia, thanks to BM sparing (BMS) procedures *via* PET-guided identification of aBM components [26].

Similar dosimetric findings have also been observed for anal and rectal patients. Of interest, data in a series of a mixed population of pelvic cancers (including rectal, cervical, anal, vaginal and bladder) undergoing ChT-RT, McGuire *et al.* [27] reported lymphopenia as the most common toxicity recorded.

Among possible future approaches to address pelvic myelosuppression, proton therapy (PT) offers theoretical enormous advantages. Indeed, PT's steep dose fall-off allows optimal pelvic normal tissue sparing [28]. In this regard, Dinges *et al.* [28] investigated the use of intensity-modulated PT (IMPT) for BMS in cervical cancer patients. With IMPT plans a significant reduction of aBM volume receiving a dose between 5 and 40 Gy was reported (compared to IMRT plans).

### 4. Closing remarks

When utilizing large elective RT volumes in treating gynaecological cancer, radiation oncologists should be cautious during the pandemic. The present times offer an unprecedented opportunity to broadly embrace treatment strategies (*e.g.*, BMS) that avoid reservoir lymphoid organs suppression and the potential subsequent RIL.

#### AVAILABILITY OF DATA AND MATERIALS

Not applicable.

#### AUTHOR CONTRIBUTIONS

GCI and VC—gave the idea and wrote the main manuscript text. GCI, VC and UR—decided the method of the literature review. GCI, VC and UR—reviewed references. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

#### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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## CONFLICT OF INTEREST

The authors declare no conflict of interest. GCI served as one of the Guest editors of this journal. Nonetheless, GCI had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to EH.

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