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EDITORIAL

Balance on slack line; diagnostic intensity and patient safety during the SARS-CoV-2 pandemic

Henry Jensen[a] and Henrik Frederiksen[b,c]

[a]Research Unit for General Practice, Research Centre for Cancer Diagnosis in Primary Care (CaP), Aarhus, Denmark; [b]Department of Haematology, Odense University Hospital, Odense, Denmark; [c]Department of Clinical Research, University of Southern Denmark, Odense, Denmark

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A timely diagnosis and clinical management that minimizes the risk of complications and late effects are cornerstones in high-quality cancer care. These prerequisites are challenged during the SARS-CoV-2 pandemic. Patients with cancer are vulnerable to infections due to a compromised immune system from disease, treatment, frailty, comorbidity, and organ dysfunction. During the pandemic, patients with cancer have been particularly affected both by the direct health risk imposed by this new respiratory virus and by indirect effects imposed by changes in health care services and diagnostic procedures. Indeed, already in the first cohort studies cancer was mentioned as a risk factor for complications from COVID-19 [1].

Consequently, guidelines on how to ensure minimal immunosuppression and optimal shielding of patients with cancer soon emerged. Healthcare systems threatened to be overburdened by COVID-19 patients have reprioritized and struggled to keep up diagnostic capacity, avoiding patients' and doctors' delay, and ensuring timely and safe treatment, and adequate follow-up. Unfortunately, the multiple threats from the pandemic to cancer patients have proven to be real. In this issue, six articles provide examples of the effects of cancer management during the pandemic [2–7].

Several studies document that patients with cancer have a high risk of severe complications and mortality following SARS-CoV-2 infection. In this issue of Acta Oncologica, Larfors and colleagues performed a case-control study based on the nationwide Swedish Intensive Care Registry [5]. This approach enabled the identification of all cases with COVID-19 in Swedish intensive care units (ICUs) using the entire Swedish population as controls. The results are interesting. Patients with cancer had a higher risk of getting a COVID-19 diagnosis. This particularly applied to patients who had recently been treated with chemotherapy treatment, which was also associated with higher risks of ICU admission and COVID-19 related death. Compared to the general population patients who had no recent chemotherapy exposure had a similar to modestly increased risk of ICU admission or death [5]. Two meta-analyses show case fatality rates (CFR) following COVID-19 of approximately 21-22% in patients with cancer compared to 5.9% in non-cancer patients [8,9]. However, a notable exception is a study from two New York hospitals that included 585 COVID-19 patients and found a similarly high CFR of 25% for patients with cancer and a CFR of 21% for age-sex-comorbidity matched COVID-19 non-cancer patients [10]. These apparently conflicting results may be explained by the high median age (72 years) and comorbidities in the latter study [11,12].

A specific causal mechanism for the high CFR and other complications in patients with cancer and COVID-19 can, however, not be deduced from the study by Larfors *et al* [5]. The results may also reflect the effects of treatment, active cancer disease, frailty, cancer subtype, organ dysfunction or comorbidity. Their subgroup analyses provide some possible clues with the highest risk for patients with lung cancer and haematological cancer, that is, patients with either severe pulmonary disease or immune dysfunction [5]. From previous studies, patients with haematological cancers and COVID-19 has had high CFRs - mostly 30% or higher [9,13–18].

In another article in this issue, Höllein and colleagues report on poor outcomes with a CFR reaching 50% among haematological cancer patients with COVID-19 in a small cohort study [4]. In comparison to other patients (e.g., GI cancer patients or matched general population) with COVID-19, patients with haematological cancer have a twice as high risk of COVID-19 related death [14,16]. When comparing patients with haematological cancer with and without COVID-19, the standardized mortality ratio was up to 41 times higher in infected patients [14]. Similar, severe results have been seen for patients with lung cancer where the COVID-19 CFR is approximately 33% and highest in older patients and patients with the concurrent chronic obstructive pulmonary disease [9,16,19].

Intriguingly, this issue also includes results from a meta-analysis of 16 previous studies including 3,558 patients where Park and colleagues find that recent chemotherapy but not recent surgery, immunotherapy, targeted therapy, or chemo-immunotherapy is associated COVID-19 related mortality [7]. Although heterogeneity between the studies in the meta-analysis was considerable, and that effects of age,

CONTACT Henrik Frederiksen Henrik.Frederiksen@rsyd.dk

organ- and immune dysfunction, frailty, comorbidity, and the cancer disease in-itself cannot be separated, our overall interpretation is that immunosuppression and respiratory morbidity are two major underlying mechanisms for the high COVID-19 CFR among patients with cancer.

The indirect pandemic effects for patients with cancer is also addressed in the current issue. Skovlund and colleagues report that cancer diagnosis dropped with approximately 2800 (33%) cancers during the 2020 spring lockdown in Denmark [6], in line with the report of a 31% drop of preliminary cancer diagnosis in 2020 in Poland by Maluchnik and colleagues [2]. The impact of a drop in cancer diagnosis on long term survival is still not known, but modeling studies indicate that it will have a severe impact [20,21], although it may be smaller than modeled [22]. Additionally, the impact of these anticipated delayed cancer diagnoses could be long lasting for both patients and health care systems [23].

The reasons for the decline in cancer cases diagnosed are multifactorial, but a possibility often put forward is that patients refrain from seeking health care in fear of contracting SAR-CoV-2 [23,24]. This is parallel to the observation of how some patients with cancer refrain from consultations as reported by Jeppesen and colleagues in the current issue [3]. As the vast majority of patients with cancer are diagnosed following presenting of symptoms to a general practitioner (GP) [25–27], a valid starting point to counteract the negative impact of the SARS-CoV-2 pandemic on the diagnosis of cancer is to encourage to contact a GP when experiencing symptoms as advocated in the current issue [2,3,6]. However, encouraging patients to contact their GP when experiencing symptoms suggestive of cancer during a pandemic also raises questions related to optimal methods to ensure adequate health-seeking patterns. How should the risk of vulnerable people contracting SARS-CoV-2 during diagnostics vs the benefit of timely diagnosis of cancer be balanced? Will the effect of urging people to contact the GP be equal across socio-economic groups of patients?

Defining the optimal balance between the benefit of timely diagnosis of cancer and risk of contracting SARS-CoV-2 in the elderly and frail and in patients with comorbidities is difficult [22]. Increased use of virtual consultations (telemedicine) has been argued to counteract this [2,3,28], with an increased use already seen [24]. Virtual consultations are an important tool during a pandemic but should be adopted carefully, as it may decrease the use of pathology, radiology, and urgent referrals for suspected cancer [28]. Furthermore, increased use of virtual consultations may result in a reduced cancer suspicion owing to reduced physical examination findings, subtle cues from, for example, body language, and GP 'gut feeling' [23], which in turn may delay the diagnosis. In addition, the use of virtual consultations may be less suited for the elderly, vulnerable, and socio-economic deprived patients [23], who paradoxically have a high risk of having cancer diagnosed in an advanced stage.

Thus, although no single quick fix seems to exist to resolve the negative impact of SARS-CoV-2 pandemic on the number of cancers diagnosed, there is a reason [22,23,28], to strongly encourage that medical specialities, public health authorities, researchers, and patient representatives join forces to tackle this decline in cancer services.

The six studies in the current issue show that even during a relatively low incidence period of SARS-CoV-2 transmission, cancer incidence dropped dramatically and although a SARS-CoV-2 infection is a serious threat to patients with cancer, this tradeoff is debatable. Ensuring procedures to avoid nosocomial transmission of SARS-CoV-2 should be prioritized to ensure timely diagnoses and safe management – also in times of a pandemic.

Disclosure statement

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ORCID

Henrik Frederiksen http://orcid.org/0000-0001-8905-0220

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