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Author's reply

Risk of death of patients with cancer presenting with severe symptoms of infection, with or without documented COVID-19: In reply to van Dam *et al.*



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We would like to thank Dr van Dam and colleagues [1] for their letter and the careful attention they dedicated to our work [2].

We first want to express our full agreement to their conclusion stating that patients with cancer must « have maximal access to (adapted) treatment and if necessary maximal supportive care in times of SARS-CoV-2 pandemic ».

Indeed, the COVID-19 epidemic is affecting deeply the care of patients with cancer for at least three reasons.

The first one is the delay to treatment that had to be given at the spike of the COVID-19 outbreak (in our case, in the period of March to April 2020). These delays were 1) requested to cope with the concentration of health care resources on the epidemic and 2) also often at requests of patients who feared to come to the health care services.

Reports of delayed treatments were issued in many countries from known cancer patients already followed up by multidisciplinary services [3]. In the period

reported in our work, this effect was of limited magnitude in the centre from which the patients were recruited. There was an increase in the number of patients receiving cancer treatment at home (+452%, $n = 181$ vs $n = 40$ as compared with the 8 previous weeks of 2020), with an increase of teleconsultations (+24550%, $n = 5886$ vs $n = 24$ in the previous 8 weeks of 2020). The access to the ICU for patients with cancer was never limited in our region, which is in contrast with other regions of our country or in Europe. Although a longer follow-up will be needed to investigate the long-term outcome of cancer patients in this time period, such delays are unlikely to have affected the survival of the patients in our series.

The second one, delays to the access to initial diagnosis and initial treatment, reported also in several countries, are associated with a maximal risk of increased deaths for curable patients. Although the magnitude of increased risk of deaths varies considerably across cancer types, a 6–15% increase in risk of death related delay to diagnosis and treatment suggested by recent studies [3,4]. In 9 centres of the French Unicancer Federation (Ms in preparation), a mean reduction of 36% of new incident cancer diagnosis was observed in this period of 8 weeks leading to estimates

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similar to those in the work of Maringe *et al.* [3]. Here again, the impact on the long-term outcome of patients with cancer will require additional years of follow-up.

The third impact of COVID-19 on patients with cancer is of course the high risk of death in the weeks after infection for patients with cancer in the active phase of the disease. As rightly pointed out by van Dam *et al.*, prognostic factors are here crucial to distinguish different patient populations. Age, gender, metastasis and usual prognostic criteria such as Performance status (PS) and lymphopaenia were all correlated with an increased risk of death in our series, and others. Prognostic factors are however not consistent across reported series of patients with cancer [2,5,6]. Of note, the immune response of patients with cancer to COVID-19, as evaluated by seroconversion assays, may be less efficient in treated cancer patients than in previously healthy individuals [7], in line with the observation that lymphopaenia is a negative prognostic factor.

The striking observation of our series is the high risk of death (actuarial survival close to 20% at day 28) of patients with cancer who did not demonstrate detectable SARS-COV-2 using the standard cobas test. Most often, multiple testing were performed and no other possible aetiology was identified. It is here important to remember that the 30 days death rates of patients with cancer, hospitalised with seasonal flu and H1N1, is close to 9%–15% in large series close from that reported in our series of patients with no proven COVID-19 [8,9], and larger than that of historical series of patients with cancer treated with cytotoxics [10]. The high death rates of RT-PCR–negative patients with cancer observed in our series may result from a sensitivity of SARS-COV-2 diagnostic assays (false negativity), and also other undocumented infections in the context of patients with a progressive cancer.

From these different series and works, it can be concluded that patients with cancer under active treatment are at high risk of lethal complications when presenting with symptoms resembling those of COVID-19 and requiring hospitalisation even in the absence of documented SARS-COV-2 infection. These patients must be managed with the greatest attention, similar to that of COVID-19-documented patients, even if negative for SARS-COV-2 on RT-PCR testing.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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