Dear Professor van Dam,

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High mortality of cancer patients in times of SARS-Cov-2: do not generalize!

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To the editor of the European Journal of Cancer,

Being heavily involved in the treatment of cancer patients in times of the SARS-Cov-2 pandemic,[1,2] we read with great interest the papers of Assaad et al[3] and Yarza et al[4] in the Eur J Cancer. Assaad et al performed an exciting retrospective analysis of 302 cancer patients presenting between March 1st to April 15th 2020 in the Comprehensive Cancer Center of Lyon with a suspicion of COVID-19.[3] In 55 (18.2%) of them the Cobas real time polymerase chain reaction (PCR, Roche, Neuilly) was positive for SARS-CoV-2, and in 247 (81.8%) it proved to be negative. Computed tomography scanning of the chest was suspect in respectively 27 (67.5%) and 59 (29.5%) of both groups. Thirty of the patients (9.9%) died during the observation period, the majority (24/30, 80%) with metastatic disease. Surprisingly mortality was not statistically different in the PCR-positive compared to the PCR-negative patients, respectively 8/55 (14.5%) versus 22/247 (8.9%) at 25 days. Although the authors are right to state that COVID-19 is underdiagnosed with current diagnostic test methods it is at least misleading to claim that cancer patients presenting with a cough, fever, muscle pain, diarrhea, anosmia or neurological problems have unrecognized COVID-19. These complains were also common in the pre SARS-CoV-2 era and can be caused by (advanced) cancer, cancer treatment and other medication, concomitant comorbidity, non-SARS-Cov-2 infections or allergic reactions. Particularly infectious morbidity is expected to be more frequent in autumn, when seasonal common colds, flues and bacterial infections will become more prevalent in patient populations and will likely cause diagnostic problems. Repetitive SARS-Cov-2 PCR testing is at this moment the only way to minimize false negative test results. Currently there are no generally accepted criteria to make a diagnosis of COVID-19 based on clinical symptoms only, although they can sometimes be highly suspicious. This is an important issue as in times limited of resources, the label "cancer with COVID-19" can compromise the access of intensive care (ICU) and outcome of patients dramatically in overwhelmed health care systems due to the outbreak of the SARS-CoV-2 pandemic. This was illustrated by the Thoracic Cancers International COVID-19 Collaboration (TERAVOLT), a multicenter observational registry on clinical data of 200 patients with PCR confirmed COVID19 and thoracic cancers, diagnosed between March 26 and April 2020. One hundred fifty two (76%) patients were hospitalized and 66 (33%) died. Strikingly only 13 (10%) of 134 patients who met criteria for intensive care unit (ICU) admission were admitted to ICU.[5] Prioritizing ICU admission implicated that many of these patients did not receive optimal ICU care. It also happened in Belgium although the limits of mechanical ventilation support and ICU bed capacity were far from reached, but beds were kept free "for future patients with a better long term prognosis". May this, besides the limited statistical power of the study explain (some of) the results of the Assaad et al paper?

It is of paramount importance that cancer patients should not be stigmatized to be too vulnerable to start or continue treatments of proven value, propending for delays or no

treatment at all.[1] Therefor one should be careful to reiterate and generalize in the literature that "cancer patients have a high mortality rate". The present data suggest that particularly patients with ongoing treatment for active locally advanced and metastatic solid cancers and hematological malignancies have a poorer outcome and higher mortality after a SARS-CoV-2 infection, but this seems not to be the case for other cancer settings.[1,5,7] In the paper of Yarza et al 82% of the patients had metastatic disease and mortality was particularly high in this group compared to the non-metastatic patients but not significantly different, again probably due to small numbers (respectively 29% vs 9%).[4] The OpenSAFELY study, looking at factors associated with 5683 COVID-19-related hospital deaths in the linked electronic health records of 17 million adult NHS patients clearly showed that male gender (HR 1.99; 95% CI 1.80-2.10), age (with a very strong gradient), ethnicity (adjusted HR 1.71; 95% CI 1.44-2.02), uncontrolled diabetes (HR 2.26 95% CI: 2.18-2.56), obesity (with a very strong gradient) and various other medical conditions often had a higher impact on the probability to die of SARS-CoV-2 then cancer.[6] This was confirmed in the study of Robilotti et al on the experiences of 423 cases of symptomatic COVID-19 in Memorial Sloan Kettering Cancer Center from 10 March to 7 April 2020.[7] Risk factors should all be taken into account in a balanced way making decisions for active treatment and ICU admission of COVID-19 patients if resources are limited, not discriminating cancer patients per se as many of them have an excellent prognosis. The rapidly expanding literature on COVID-19 should be interpreted with caution as it is often hampered by methodological and statistical flaws.[1] Many papers have a limited sample size, biased patient selection criteria, a retrospective design and several entangled cofactors involved which were often not corrected for. In addition the hospitalized cancer patients during the peak of the COVID-19 epidemic in general are at the worse end of the spectrum, having end stage metastatic disease, complications of surgery or systemic treatment, or other comorbidities requiring treatment, which make them more prone for fatal complications. Conclusions drawn from these patient groups should not be generalized for all cancer patients. Several adaptations in cancer care organization by means of protective measures, social distancing, minimizing the number of hospital attendances, aggressive testing for SARs-CoV-2 in patients and health care providers, telemonitoring, artificial intelligence and better knowledge of risk factors for severe morbidity proved to be helpful to provide cancer care safely in the majority of patients times of SARS-CoV-2 with a good outcome.[1,2,5,7] This letter is a plea for selection of cancer patients on an individual basis to give them maximal access to (adapted) treatment and if necessary maximal supportive care in times of SARS-CoV-2 pandemic.

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